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# Air Quality Criteria for Lead

# Volume II of II

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# Air Quality Criteria for Lead

# Volume II

National Center for Environmental Assessment-RTP Division
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

## PREFACE

National Ambient Air Quality Standards (NAAQS) are promulgated by the United States Environmental Protection Agency (EPA) to meet requirements set forth in Sections 108 and 109 of the U.S. Clean Air Act. Those two Clean Air Act sections require the EPA Administrator (1) to list widespread air pollutants that reasonably may be expected to endanger public health or welfare; (2) to issue air quality criteria for them that assess the latest available scientific information on nature and effects of ambient exposure to them; (3) to set "primary" NAAQS to protect human health with adequate margin of safety and to set "secondary" NAAQS to protect against welfare effects (e.g., effects on vegetation, ecosystems, visibility, climate, manmade materials, etc); and (5) to periodically review and revise, as appropriate, the criteria and NAAQS for a given listed pollutant or class of pollutants.

Lead was first listed in the mid-1970's as a "criteria air pollutant" requiring NAAQS regulation. The scientific information pertinent to Pb NAAQS development available at the time was assessed in the EPA document *Air Quality Criteria for Lead*; published in 1977. Based on the scientific assessments contained in that 1977 lead air quality criteria document (1977 Lead AQCD), EPA established a 1.5 $\mu g/m^3$ (maximum quarterly calendar average) Pb NAAQS in 1978.

To meet Clean Air Act requirements noted above for periodic review of criteria and NAAQS, new scientific information published since the 1977 Lead AQCD was later assessed in a revised Lead AQCD and Addendum published in 1986 and in a Supplement to the 1986 AQCD/Addendum published by EPA in 1990. A 1990 Lead Staff Paper, prepared by EPA's Office of Air Quality Planning and Standards (OPQPS), drew upon key findings and conclusions from the 1986 Lead AQCD/Addendum and 1990 Supplement (as well as other OAQPS-sponsored lead exposure/risk analyses) in posing options for the EPA Administrator to consider with regard to possible revision of the Pb NAAQS. However, EPA chose not to revise the Pb NAAQS at that time. Rather, as part of implementing a broad 1991 U.S. EPA Strategy for Reducing Lead Exposure, the Agency focused primarily on regulatory and remedial clean-up efforts to reduce Pb exposure from a variety of non-air sources that posed more extensive public health risks, as well as other actions to reduce air emissions.

The purpose of this revised Lead AQCD is to critically assess the latest scientific information that has become available since the literature assessed in the 1986 Lead AQCD/Addendum and 1990 Supplement, with the main focus being on pertinent new information useful in evaluating health and environmental effects of ambient air lead exposures. This includes discussion in this document of information regarding: the nature, sources, distribution, measurement, and concentrations of lead in the environment; multimedia lead exposure (via air, food, water, etc.) and biokinetic modeling of contributions of such exposures to concentrations of lead in brain, kidney, and other tissues (e.g., blood and bone concentrations, as key indices of lead exposure).; characterization of lead health effects and associated exposure-response relationships; and delineation of environmental (ecological) effects of lead. This final version of the revised Lead AQCD mainly assesses pertinent literature published or accepted for publication through December 2005.

The First External Review Draft (dated December 2005) of the revised Lead AQCD underwent public comment and was reviewed by the Clean Air Scientific Advisory Committee (CASAC) at a public meeting held in Durham, NC on February 28-March 1, 2006. The public comments and CASAC recommendations received were taken into account in making appropriate revisions and incorporating them into a Second External Review Draft (dated May, 2006) which was released for further public comment and CASAC review at a public meeting held June 28-29, 2006. In addition, still further revised drafts of the Integrative Synthesis chapter and the Executive Summary were then issued and discussed during an August 15, 2006 CASAC teleconference call. Public comments and CASAC advice received on these latter materials, as well as Second External Review Draft materials, were taken into account in making and incorporating further revisions into this final version of this Lead AQCD, which is being issued to meet an October 1, 2006 court-ordered deadline. Evaluations contained in the present document provide inputs to an associated Lead Staff Paper prepared by EPA's Office of Air Quality Planning and Standards (OAQPS), which poses options for consideration by the EPA Administrator with regard to proposal and, ultimately, promulgation of decisions on potential retention or revision, as appropriate, of the current Pb NAAQS.

Preparation of this document has been coordinated by staff of EPA's National Center for Environmental Assessment in Research Triangle Park (NCEA-RTP). NCEA-RTP scientific staff, together with experts from academia, contributed to writing of document chapters. Earlier

drafts of document materials were reviewed by scientists from other EPA units and by non-EPA experts in several public peer consultation workshops held by EPA in July/August 2005.

NCEA acknowledges the valuable contributions provided by authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document. The constructive comments provided by public commenters and CASAC that served as valuable inputs contributing to improved scientific and editorial quality of the document are also acknowledged by NCEA.

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## Abbreviations and Acronyms

| | |
|---|---|
| αFGF | α-fibroblast growth factor |
| AA | arachidonic acid |
| AAL | active avoidance learning |
| AAS | atomic absorption spectroscopy |
| ABA | β-aminoisobutyric acid |
| ACBP | Achenbach Child Behavior Profile |
| ACE | angiotensin converting enzyme |
| ACh | acetylcholine |
| AChE | acetylcholinesterase |
| ACR | acute-chronic ratio |
| AD | adult |
| ADC | analog digital converter |
| ADP | adenosine diphosphate |
| AE | anion exchange |
| AEA | *N*-arachidonylethanolamine |
| AFC | antibody forming cells |
| 2-AG | 2-arachidonylglycerol |
| A horizon | uppermost layer of soil (litter and humus) |
| AHR | aryl hydrocarbon receptor |
| AI | angiotensin I |
| ALA | ∗-aminolevulinic acid |
| ALAD | ∗-aminolevulinic acid dehydratase |
| ALAS | aminolevulinic acid synthetase |
| ALAU | urinary δ-aminolevulinic acid |
| ALD | aldosterone |
| ALS | amyotrophic lateral sclerosis |
| ALT | alanine aminotransferase |
| ALWT | albumin weight |
| AMEM | Alpha Minimal Essential Medium |
| AMP | adenosine monophosphate |
| ANCOVA | analysis of covariance |
| ANF | atrial natriuretic factor |
| Ang II | angiotensin II |

| | |
|---|---|
| ANOVA | analysis of variance |
| ANP | atrial natriuretic peptide |
| AP | alkaline phosphatase |
| AP-1 | activated protein-1 |
| ApoE | apolipoprotein E |
| AQCD | Air Quality Criteria Document |
| Arg | arginine |
| AS52 | cells derived from the CHO cell line |
| ASGP-R | aceyl glycoprotein receptor |
| AST | aspartate aminotransferase |
| ASV | anode stripping voltammetry |
| 3-AT | 3-aminotriazole; 3-amino triazide |
| ATP | adenosine triphosphate |
| ATP1A2 | sodium-potassium adenosine triphosphase α2 |
| ATPase | adenosine triphosphatase |
| ATSDR | Agency for Toxic Substances and Disease Research |
| AVCD | atrioventricular conduction deficit |
| AVS | acid volatile sulfide |
| AWQC | ambient water quality criteria |
| ∃ | beta-coefficient; slope of an equation |
| ∃FGF | ∃-fibroblast growth factor |
| 17∃–HS | 17∃-hydroxysteriod |
| 3∃-HSD | 3∃-hydroxysteriod dehydrogenase |
| 17∃-HSDH | 17∃-hydroxysteriod dehydrogenase |
| 6∃-OH-cortisol | 6-∃-hydroxycortisol |
| B | both |
| BAEP | brainstem auditory-evoked potentials |
| BAER | brainstem auditory-evoked responses |
| BAF | bioaccumulation factor |
| B cell | B lymphocyte |
| BCFs | bioconcentration factors |
| BCS | bovine calf serum |
| BDNF | brain derived neurotrophic factor |
| BDWT | body weight changes |
| BEI | biological exposure index |

| | |
|---|---|
| BFU-E | blood erythroid progenitor |
| BLL | blood lead level |
| BLM | biotic ligand model |
| BM | basement membrane |
| BMI | body mass index |
| BDNF | brain-derived neurotrophic factor |
| BOTMP | Bruinicks-Oseretsky Test of Motor Proficiency |
| BP | blood pressure |
| BPb | blood lead concentration |
| BSA | bovine serum albumin |
| BSI | Brief Symptom Inventory |
| BTQ | Boston Teacher Questionnaire |
| BUN | blood urea nitrogen |
| bw, b. wt., BW | body weight |
| C3H10T/12 | mouse embryo cell line |
| C3, C4 | complement proteins |
| CA | chromosome aberration |
| CA3 | cornu ammonis 3 region of hippocampus |
| $^{45}Ca$ | calcium-45 radionuclide |
| Ca-ATP | calcium-dependent adenosine triphosphate |
| Ca-ATPase | calcium-dependent adenosine triphosphatase |
| $CaCO_3$ | calcium carbonate |
| CaEDTA | calcium disodium ethylenediaminetetraacetic acid |
| CAL | calcitonin |
| CaM | calmodulin |
| Ca-Mg-ATPase | calcium-magnesium-dependent adenosine triphosphatase |
| cAMP | cyclic adenosinemonophosphate |
| $CaNa_2$ EDTA | calcium disodium ethylenediaminetetraacetic acid |
| CANTAB | Cambridge Neuropsychological Testing Automated Battery |
| CAT | catalase; Cognitive Abilities Test |
| CBCL | Achenbach Child Behavior Checklist |
| CBCL-T | Total Behavior Problem Score |
| CBL | cumulative blood lead |
| CBLI | cumulative blood lead index |
| CCB | cytochalasin B |

| | |
|---|---|
| CCD | charge-coupled device |
| CCE | Coordination Center for Effects |
| CCL | carbon tetrachloride |
| CCS | cosmic calf serum |
| C-$CV_{RSA}$ | coefficient of component variance of respiratory sinus arrhythmia |
| Cd | cadmium |
| $^{109}Cd$ | cadmium-109 radionuclide |
| CdU | urinary cadmium |
| CEC | cation exchange capacity |
| CESD, CES-D | Center for Epidemiologic Studies Depression (scale) |
| GFAP | glial fibrillary acidic protein |
| CFU-E | colony forming unit blood-erythroid progenitor (cell count) |
| CFU-GEMM | colony forming unit blood-pluripotent progenitor (cell count) |
| CFU-GM | blood granulocyte/macrophage progenitor (cell count) |
| cGMP | cyclic guanosine-3',5'-monophosphate |
| ChAT | choline acetyltransferase |
| CHD | coronary heart disease |
| CHO | Chinese hamster ovary cell line |
| CI | confidence interval |
| CLE-SV | competitive ligand-exchange/stripping voltammetry |
| CLRTAP | Convention on Long-Range Transboundary of Air Pollution |
| CLS | Cincinnati Lead Study |
| CMC | criterion maximum concentration |
| CMI | cell-mediated immunity |
| CNS | central nervous system |
| COH | cation-osmotic hemolysis |
| ConA | concanavalin A |
| COR | cortisol |
| CoTx | cotreatment |
| COX-2 | cyclooxygenase-2 |
| CP | coproporphryn |
| CPT | current perception threshold |
| cr | creatinine |
| CRAC | calcium release activated calcium reflux |
| CREB | cyclic AMP-response element binding protein |

| | |
|---|---|
| CRF | chronic renal failure |
| CRI | chronic renal insufficiency |
| CSF | cerebrospinal fluid |
| CuZn-SOD | copper and zinc-dependent superoxide dismutase |
| CV | conduction velocity |
| CVLT | California Verbal Learning Test |
| $CV_{R-R}$ | coefficient of variation of the R-R interval |
| CYP | cytochrome (e.g., CYP1A, CYP-2A6, CYP3A4, CYP450) |
| CYP3a11 | cytochrome P450 3a11 |
| D | D-statistic |
| DA | dopamine; dopaminergic |
| dbcAMP | dibutyryl cyclic adenosine-3',5'-monophosphate |
| DCV | distribution of conduction velocities |
| DEAE | diethylaminoethyl (chromatography) |
| DET | diffusive equilibrium thin films |
| DEYO | death of young |
| DFS | decayed or filled surfaces, permanent teeth |
| dfs | covariate-adjusted number of caries |
| DG | dentate gyrus |
| DGT | diffusive gradient thin films |
| DL | DL-statistic |
| DMEM | Dulbecco's Minimal Essential Medium |
| DMEM/F12 | Dulbecco's Minimal Essential Medium/Ham's F12 |
| DMFS | decayed, missing, or filled surfaces, permanent teeth |
| DMPS | 2,3-dimercaptopropane 1-sulfonate |
| DMSA | 2,3-dimercaptosuccinic acid |
| DMT | Donnan membrane technique |
| DMTU | dimethylthiourea |
| DNA | deoxyribonucleic acid |
| DO | distraction osteogenesis |
| DOC | dissolved organic carbon |
| DOM | dissolved organic carbon |
| DOPAc | 3,4-dihydroxyphenylacetic acid |
| DPASV | differential pulse anodic stripping voltammetry |
| dp/dt | rate of left ventricular isovolumetric pressure |

| | |
|---|---|
| DPPD | *N*-*N*-diphenyl-*p*-phynylene-diamine |
| DR | drinking water |
| DSA | delayed spatial alternation |
| DTC | diethyl dithiocarbomate complex |
| DTH | delayed type hypersensitivity |
| DTPA | diethylenetriaminepentaacetic acid |
| DTT | dithiothreitol |
| dw | dry weight |
| E | embryonic day |
| $E_2$ | estradiol |
| EBE | early biological effect |
| EBV | Epstein-Barr virus |
| EC | European Community |
| $EC_{50}$ | effect concentration for 50% of test population |
| eCB | endocannabinoid |
| ECG | electrocardiogram |
| Eco-SSL | ecological soil screening level |
| EDS | energy dispersive spectrometers |
| EDTA | ethylenediaminetetraacetic acid |
| EEDQ | *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinone |
| EEG | electroencephalogram |
| EG | egg |
| EGF | epidermal growth factor |
| EGG | effects on eggs |
| EGPN | egg production |
| EKG | electrocardiogram |
| electro | electrophysiological stimulation |
| EM/CM | experimental medium-to-control medium (ratio) |
| EMEM | Eagle's Minimal Essential Medium |
| eNOS | endothelial nitric oxide synthase |
| EP | erythrocyte protoporphyrin |
| EPA | U.S. Environmental Protection Agency |
| Epi | epinephrine |
| EPMA | electron probe microanalysis |
| EPO | erythropoietin |

| | |
|---|---|
| EPSC | excitatory postsynaptic currents |
| EPT | macroinvertebrates from the Ephemeroptera (mayflies), Plecoptera (stoneflies), and Trichoptera (caddisflies) group |
| ERG | electroretinogram; electroretinographic |
| ERL | effects range – low |
| ERM | effects range – median |
| EROD | ethoxyresorufin-*O*-deethylase |
| ESCA | electron spectroscopy for chemical analysis |
| ESRD | end-stage renal disease |
| EST | estradiol |
| ESTH | eggshell thinning |
| ET | endothelein; essential tremor |
| ETOH | ethyl alcohol |
| EXAFS | extended X-ray absorption fine structure |
| EXANES | extended X-ray absorption near edge spectroscopy |
| F | F-statistic |
| F344 | Fischer 344 (rat) |
| FAV | final acute value |
| FBS | fetal bovine serum |
| FCS | fetal calf serum |
| FCV | final chronic value |
| FD | food |
| FEF | forced expiratory flow |
| FEP | free erythrocyte protoporphyrin |
| FERT | fertility |
| $FEV_1$ | forced expiratory volume in one second |
| FGF | fibroblast growth factor (e.g., βFGF, αFGF) |
| FI | fixed interval (operant conditioning) |
| FIAM | free ion activity model |
| FMLP | *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine |
| fMRI | functional magnetic resonance imaging |
| FR | fixed-ratio operant conditioning |
| FSH | follicle stimulating hormone |
| FT3 | free triiodothyronine |
| FT4 | free thyroxine |

| | |
|---|---|
| FTES | free testosterone |
| FTII | Fagan Test of Infant Intelligence |
| FTPLM | flow-through permeation liquid membranes |
| FURA-2 | 1-[6-amino-2-(5-carboxy-2-oxazolyl)-5-benzofuranyloxy]-2-(2-amino-5-methylphenoxy) ethane-*N*,*N*,*N'*,*N'*-tetraacetic acid |
| FVC | forced vital capacity |
| (-GT | (-glutamyl transferase |
| G | gestational day |
| GABA | gamma aminobutyric acid |
| GAG | glycosaminoglycan |
| G12 CHV79 | cells derived from the V79 cell line |
| GCI | General Cognitive Index |
| GD | gestational day |
| GDP | guanosine diphosphate |
| GEE | generalized estimating equations |
| GFAAS | graphite furnace atomic absorption spectroscopy |
| GFR | glomerular filtration rate |
| GGT | (-glutamyl transferase |
| GH | growth hormone |
| GI | gastrointestinal |
| GIME-VIP | gel integrated microelectrodes combined with voltammetric in situ profiling |
| GIS | geographic information system |
| GLU | glutamate |
| GMAV | genus mean acute value |
| GMCV | genus mean chronic value |
| GMP | guanosine monophosphate |
| GMPH | general morphology |
| GnRH | gonadotropin releasing hormone |
| GOT | aspartate aminotransferase |
| GP | gross productivity |
| G6PD, G6PDH | glucose-6-phosphate dehydrogenase |
| GPEI | glutathione *S*-transferase P enhancer element |
| $gp91^{phox}$ | NAD(P)H oxidase |
| GPT | glutamic-pyruvic transaminase |
| GPx | glutathione peroxidase |

| | |
|---|---|
| GRO | growth |
| GRP78 | glucose-regulated protein 78 |
| GSD | geometric standard deviation |
| GSH | reduced glutathione |
| GSIM | gill surface interaction model |
| GSSG | glutathione disulfide |
| GST | glutathione-*S*-transferase |
| GSTP | placental glutathione transferase |
| GTP | guanosine triphosphate |
| GV | gavage |
| $H^+$ | acidity |
| $^3H$ | hydrogen-3 radionuclide (tritium) |
| HA | humic acid; hydroxyapatite |
| Hb | hemoglobin |
| HBEF | Hubbard Brook Experimenatl Forest |
| HBSS | Hank's Balanced Salt Solution |
| HCG; hCG | human chorionic gonadotropin |
| Hct | hematocrit |
| HDL | high-density lipoprotein (cholesterol) |
| HEP | habitat evaluation procedure |
| HET | Binghamton heterogeneous stock |
| HFPLM | hollow fiber permeation liquid membranes |
| Hgb | hemoglobin |
| HGF | hepatocyte growth factor |
| HH | hydroxylamine hydrochloride |
| H-H | high-high |
| HHANES | Hispanic Health and Nutrition Examination Survey |
| H-L | high-low |
| HLA | human leukocyte antigen |
| H-MEM | minimum essential medium/nutrient mixture–F12-Ham |
| HMP | hexose monophosphate shunt pathway |
| $HNO_3$ | nitric acid |
| $H_2O_2$ | hydrogen peroxide |
| HOME | Home Observation for Measurement of Environment |
| HOS TE | human osteosarcoma cells |

| | |
|---|---|
| HPLC | high-pressure liquid chromatography |
| $H_3PO_4$ | phosphoric acid |
| HPRT | hypoxanthine phosphoribosyltransferase (gene) |
| HR | heart rate |
| HSI | habitat suitability indices |
| $H_2SO_4$ | sulfuric acid |
| HSPG | heparan sulfate proteoglycan |
| Ht | hematocrit |
| HTC | hepatoma cells |
| hTERT | catalytic subunit of human telomerase |
| HTN | hypertension |
| IBL | integrated blood lead index |
| IBL H WRAT-R | integrated blood lead index H Wide Range Achievement Test-Revised (interaction) |
| ICD | International Classification of Diseases |
| ICP | inductively coupled plasma |
| ICP-AES | inductively coupled plasma atomic emission spectroscopy |
| ICP-MS, ICPMS | inductively coupled plasma mass spectrometry |
| ID-MS | isotope dilution mass spectrometry |
| IFN | interferon (e.g., IFN-() |
| Ig | immunoglobulin (e.g., IgA, IgE, IgG, IgM) |
| IGF-1 | insulin-like growth factor 1 |
| IL | interleukin (e.g., IL-1, IL-1∃, IL-4, IL-6, IL-12) |
| ILL | incipient lethal level |
| immuno | immunohistochemical staining |
| IMP | inosine monophosphate |
| iNOS | inducible nitric oxide synthase |
| i.p., IP | intraperitoneal |
| IPSC | inhibitory postsynaptic currents |
| IQ | intelligence quotient |
| IRT | interresponse time |
| ISEL | in situ end labeling |
| ISI | interstimulus interval |
| i.v., IV | intravenous |
| IVCD | intraventricular conduction deficit |

| | |
|---|---|
| JV | juvenile |
| KABC | Kaufman Assessment Battery for Children |
| KTEA | Kaufman Test of Educational Achievement |
| KXRF, K-XRF | K-shell X-ray fluorescence |
| LA | lipoic acid |
| LB | laying bird |
| LC | lactation |
| $LC_{50}$ | lethal concentration at which 50% of exposed animals die |
| $LC_{74}$ | lethal concentration at which 74% of exposed animals die |
| $LD_{50}$ | lethal dose at which 50% of exposed animals die |
| LDH | lactate dehydrogenase |
| LDL | low-density lipoprotein (cholesterol) |
| L-dopa | 3,4-dihydroxyphenylalanine (precursor of dopamine) |
| LE | Long Evans (rat) |
| LET | linear energy transfer (radiation) |
| LH | luteinizing hormone |
| LHRH | luteinizing hormone releasing hormone |
| LN | lead nitrate |
| L-NAME | L-$N^G$-nitroarginine methyl ester |
| LOAEL | lowest-observed adverse effect level |
| LOEC | lowest-observed-effect concentration |
| LOWESS | locally weighted scatter plot smoother |
| LPO | lipoperoxide |
| LPP | lipid peroxidation potential |
| LPS | lipopolysaccharide |
| LT | leukotriene |
| $LT_{50}$ | time to kill 50% |
| LTER | Long-Term Ecological Research (sites) |
| LTP | long term potentiation |
| LVH | left ventricular hypertrophy |
| µPIXE | microfocused particle induced X-ray emission |
| µSXRF | microfocused synchrotron-based X-ray fluorescence |
| MA | mature |
| MA-10 | mouse Leydig tumor cell line |
| MANCOVA | multivariate analysis of covariance |

| | |
|---|---|
| MAO | monoamine oxidase |
| MATC | maximum acceptable threshold concentration |
| MDA | malondialdehyde |
| MDA-TBA | malondialdehyde-thiobarbituric acid |
| MDCK | kidney epithelial cell line |
| MDI | Mental Development Index (score) |
| MDRD | Modification of Diet in Renal Disease (study) |
| MEM | Minimal Essential Medium |
| MG | microglobulin |
| Mg-ATPase | magnesium-dependent adenosine triphosphatase |
| MiADMSA | monoisamyl dimercaptosuccinic acid |
| Mi-DMSA | mi monoisoamyl dimercaptosuccinic acid |
| MK-801 | NMDA receptor antagonist |
| MLR | mixed lymphocyte response |
| MMSE | Mini-Mental State Examination |
| MMTV | murine mammary tumor virus |
| MN | micronuclei formation |
| MND | motor neuron disease |
| MNNG | *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine |
| MPH | morphology |
| MRI | magnetic resonance imaging |
| mRNA | messenger ribonucleic acid |
| MROD | methoxyresorufin-*O*-demethylase |
| MRS | magnetic resonance spectroscopy |
| MS | mass spectrometry |
| MSCA | McCarthy Scales of Children's Abiltities |
| mSQGQs | mean sediment quality guideline quotients |
| MT | metallothionein |
| MVV | maximum voluntary ventilation |
| MW | molecular weight (e.g., high-MW, low-MW) |
| N, n | number of observations |
| N/A | not available |
| NAAQS | National Ambient Air Quality Standards |
| NAC | *N*-acetyl cysteine |
| NAD | nicotinamide adenine dinucleotide |

| | |
|---|---|
| NADH | reduced nicotinamide adenine dinucleotide |
| NADP | nicotinamide adenine dinucleotide phosphate |
| NAD(P)H, NADPH | reduced nicotinamide adenine dinucleotide phosphate |
| NADS | nicotinamide adenine dinucleotide synthase |
| NAF | nafenopin |
| NAG | *N*-acetyl-∃-D-glucosaminidase |
| Na-K-ATPase | sodium-potassium-dependent adenosine triphosphatase |
| NAWQA | National Water-Quality Assessment |
| NBT | nitro blue tetrazolium |
| NCBP | National Contaminant Biomonitoring Program |
| NCD | nuclear chromatin decondensation (rate) |
| NCS | newborn calf serum |
| NCTB | Neurobehavioral Core Test Battery |
| NCV | nerve conduction velocity |
| ND | non-detectable; not detected |
| NDI | nuclear divison index |
| NE | norepinephrine |
| NES | Neurobehavioral Evaluation System |
| NF-κB | nuclear transcription factor-κB |
| NGF | nerve growth factor |
| NHANES | National Health and Nutrition Examination Survey |
| NIOSH | National Institute for Occupational Safety and Health |
| NIST | National Institute for Standards and Technology |
| NK | natural killer |
| NMDA | *N*-methyl-D-aspartate |
| NMDAR | *N*-methyl-D-aspartate receptor |
| NMR | nuclear magnetic resonance |
| NO | nitric oxide |
| $NO_2$ | nitrogen dioxide |
| $NO_3$ | nitrate |
| NOAEC | no-observed-adverse-effect concentration |
| NOAEL | no-observed-adverse-effect level |
| NOEC | no-observed-effect concentration |
| NOEL | no-observed-effect level |
| NOM | natural organic matter |

| | |
|---|---|
| NORs | nucleolar organizing regions |
| NOS | nitric oxide synthase; not otherwise specified |
| $NO_x$ | nitrogen oxides |
| NP | net productivity |
| NPSH | nonprotein sulfhydryl |
| NR | not reported |
| NRC | National Research Council |
| NRK | normal rat kidney |
| NS | nonsignificant |
| NSAID | non-steroidal anti-inflammatory agent |
| NT | neurotrophin |
| NTA | nitrilotriacetic acid |
| $O_2$ | oxygen |
| ODVP | offspring development |
| OH | hydroxyl |
| 7-OH-coumarin | 7-hydroxy-coumarin |
| 1,25-OH-D, 1,25-OH $D_3$ | 1,25-dihydroxyvitamin D |
| 24,25-OH-$D_3$ | 24,25-dihydroxyvitamin D |
| 25-OH-$D_3$ | 25-hydroxyvitamin D |
| 8-OHdG | 8-hydroxy-2'-deoxyguanosine |
| O horizon | forest floor |
| OR | odds ratio; other oral |
| OSWER | Office of Solid Waste and Emergency Response |
| P, p | probability value |
| P300 | event-related potential |
| P450 1A1 | cytochrome P450 1A1 |
| P450 1A2 | cytochrome P450 1A2 |
| P450 CYP3a11 | cytochrome P450 3a11 |
| PAD | peripheral arterial disease |
| PAH | polycyclic aromatic hydrocarbon |
| PAI-1 | plasminogen activator inhibitor-1 |
| PAR | population attributable risk |
| Pb | lead |
| $^{203}Pb$ | lead-203 radionuclide |
| $^{204}Pb$, $^{206}Pb$, $^{207}Pb$, $^{208}Pb$ | stable isotopes of lead-204, -206, -207, -208, respectively |

| | |
|---|---|
| $^{210}Pb$ | lead-210 radionuclide |
| $Pb(Ac)_2$ | lead acetate |
| PbB | blood lead concentration |
| $PbCl_2$ | lead chloride |
| $Pb(ClO_4)_2$ | lead chlorate |
| PBG-S | porphobilinogen synthase |
| PBMC | peripheral blood mononuclear cells |
| $Pb(NO_3)_2$ | lead nitrate |
| PbO | lead oxides (or litharge) |
| PBP | progressive bulbar paresis |
| PbS | galena |
| PbU | urinary lead |
| PC12 | pheochromocytoma cell |
| PCR | polymerase chain reaction |
| PCV | packed cell volume |
| PDE | phosphodiesterase |
| PDGF | platelet-derived growth factor |
| PDI | Psychomotor Development Index |
| PEC | probable effect concentration |
| PEF | expiratory peak flow |
| PG | prostaglandin (e.g., $PGE_2$, $PGF_2$); prostate gland |
| PHA | phytohemagglutinin A |
| Pi | inorganic phosphate |
| PIXE | particle induced X-ray emission |
| PKC | protein kinase C |
| pl NEpi | plasma norepinephrine |
| PMA | progressive muscular atrophy |
| PMN | polymorphonuclear leucocyte |
| PMR | proportionate mortality ratio |
| PN | postnatal (day) |
| P5N | pyrimidine 5'-nucleotidase |
| PND | postnatal day |
| p.o., PO | per os (oral administration) |
| POMS | Profile of Mood States |
| ppb | parts per billion |

| | |
|---|---|
| ppm | parts per million |
| PPVT-R | Peabody Picture Vocabulary Test-Revised |
| PRA | plasma renin activity |
| PRL | prolactin |
| PROG | progeny counts or numbers |
| PRR | prevalence rate ratio |
| PRWT | progeny weight |
| PST | percent transferrin saturation |
| PTH | parathyroid hormone |
| PTHrP | parathyroid hormone-related protein |
| PVC | polyvinyl chloride |
| PWM | pokeweed mitogen |
| PRWT | progeny weight |
| QA/QC | quality assurance/quality control |
| Q/V | flux of air (Q) divided by volume of culture (V) |
| r | Pearson correlation coefficient |
| $R^2$ | multiple correlation coefficient |
| $r^2$ | correlation coefficient |
| $^{226}Ra$ | most stable isotope of radium |
| R/ALAD | ratio of ALAD activity before and after reactivation |
| RAVLT | Rey Auditory Verbal Learning Test |
| $^{86}Rb$ | rubidium-86 radionuclide |
| RBA | relative bioavailablity |
| RBC | red blood cell; erythrocyte |
| RBF | renal blood flow |
| RBP | retinol binding protein |
| RBPH | reproductive behavior |
| RCPM | Ravens Colored Progressive Matrices |
| REL | rat epithelial (cells) |
| REP | reproduction |
| RHIS | reproductive organ histology |
| $^{222}Rn$ | most stable isotope of radon |
| RNA | ribonucleic acid |
| ROS | reactive oxygen species |
| ROS 17.2.8 | rat osteosarcoma cell line |

| | |
|---|---|
| RPMI 1640 | Roswell Park Memorial Institute basic cell culture medium |
| RR | relative risk; rate ratio |
| RT | reaction time |
| RSEM | resorbed embryos |
| RSUC | reproductive success (general) |
| RT | reproductive tissue |
| ∑SEM | sum of the molar concentrations of simultaneously extracted metal |
| SA7 | simian adenovirus |
| SAB | Science Advisory Board |
| SAM | *S*-adenosyl-L-methionine |
| SBIS-4 | Stanford-Binet Intelligence Scale-4th edition |
| s.c., SC | subcutaneous |
| SCAN | Test for Auditory Processing Disorders |
| SCE | selective chemical extraction; sister chromatid exchange |
| SCP | stripping chronopotentiometry |
| SD | Spraque-Dawley (rat); standard deviation |
| SDH | succinic acid dehydrogenase |
| SDS | sodium dodecyl sulfate; Symbol Digit Substitution |
| SE | standard error; standard estimation |
| SEM | standard error of the mean |
| SES | socioeconomic status |
| sGC | soluble guanylate cyclase |
| SH | sulfhydryl |
| SHBG | sex hormone binding globulin |
| SHE | Syrian hamster embryo cell line |
| SIMS | secondary ion mass spectrometry |
| SIR | standardized incidence ratio |
| SLP | synthetic leaching procedure |
| SM | sexually mature |
| SMAV | species mean acute value |
| SMR | standardized mortality ratio |
| SNAP | Schneider Neonatal Assessment for Primates |
| SNP | sodium nitroprusside |
| $SO_2$ | sulfur dioxide |
| SOD | superoxide dismutase |

| | |
|---|---|
| SOPR | sperm-oocyte penetration rate |
| SPCL | sperm cell counts |
| SPCV | sperm cell viability |
| SQGs | sediment quality guidelines |
| SRA | Self Reported Antisocial Behavior scale |
| SRD | Self Report of Delinquent Behavior |
| SRIF | somatostatin |
| SRM | Standard Reference Material |
| SRT | simple reaction time |
| SSADMF | Social Security Administration Death Master File |
| SSB | single-strand breaks |
| SSEP | somatosensory-evoked potential |
| StAR | steroidogenic acute regulatory protein |
| STORET | STOrage and RETrieval |
| SVC | sensory conduction velocity |
| SVRT | simple visual reaction time |
| T | testosterone |
| TA | tail |
| TABL | time-averaged blood lead |
| T&E | threatened and endangered (species) |
| TAT | tyrosine aminotransferase |
| TB | tibia |
| TBARS | thiobarbituric acid-reactive species |
| TBPS | Total Behavior Problem Score |
| TCDD | methionine-choline-deficient diet |
| T cell | T lymphocyte |
| TCLP | toxic characteristic leaching procedure |
| TE | testes |
| TEC | threshold effect concentration |
| TEDG | testes degeneration |
| TEL | tetraethyl lead |
| TES | testosterone |
| TEWT | testes weight |
| TF | transferrin, translocation factor |
| TG | 6-thioguanine |

| | |
|---|---|
| TGF | transforming growth factor |
| TH | tyrosine hydroxylase |
| $^{232}Th$ | stable isotope of thorium-232 |
| TLC | Treatment of Lead-exposed Children (study) |
| TNF | tumor necrosis factor (e.g., TNF-α) |
| TOF | time-of-flight |
| tPA | plasminogen activator |
| TPRD | total production |
| TRH | thyroid releasing hormone |
| TRV | toxicity reference value |
| TSH | thyroid stimulating hormone |
| TSP | triple-super phosphate |
| TT3 | total triiodothyronine |
| TT4 | serum total thyroxine |
| TTES | total testosterone |
| TTR | transthyretin |
| TU | toxic unit |
| TWA | time-weighted average |
| TX | tromboxane (e.g., $TXB_2$) |
| U | uriniary |
| $^{235}U$, $^{238}U$ | uranium-234 and -238 radionuclides |
| UCP | urinary coproporphyrin |
| UDP | uridine diphosphate |
| UNECE | United Nations Economic Commission for Europe |
| Ur | urinary |
| USFWS | U.S. Fish and Wildlife Service |
| USGS | United States Geological Survey |
| UV | ultraviolet |
| V79 | Chinese hamster lung cell line |
| VA | Veterans Administration |
| VC | vital capacity; vitamin C |
| VDR | vitamin D receptor |
| VE | vitamin E |
| VEP | visual-evoked potential |
| VI | variable-interval |

| | |
|---|---|
| vit C | vitamin C |
| vit E | vitamin E |
| VMA | vanilmandelic acid |
| VMI | Visual-Motor Integration |
| VSM | vascular smooth muscle (cells) |
| VSMC | vascular smooth muscle cells |
| WAIS | Wechsler Adult Intelligence Scale |
| WDS | wavelength dispersive spectrometers |
| WHO | World Health Organization |
| WISC | Wechsler Intelligence Scale for Children |
| WISC-R | Wechsler Intelligence Scale for Children-Revised |
| WO | whole organism |
| WRAT-R | Wide Range Achievement Test-Revised |
| WT | wild type |
| WTHBF-6 | human liver cell line |
| ww | wet weight |
| XAFS | X-ray absorption fine structure |
| XANES | X-ray absorption near edge spectroscopy |
| XAS | X-ray absorption spectroscopy |
| XPS | X-ray photoelectron spectroscopy |
| X-rays | synchrotron radiation |
| XRD | X-ray diffraction |
| XRF | X-ray fluorescence |
| ZAF | correction in reference to three components of matrix effects: atomic number (Z), absorption (A), and fluorescence (F) |
| $ZnNa_2$ DTPA | zinc disodium diethylenetriaminepentaacetic acid |
| $ZnNa_2$ EDTA | zinc disodium ethylenediaminetetraacetic acid |
| ZPP | zinc protoporphyrin |

# AX6. CHAPTER 6 ANNEX

# ANNEX TABLES AX6-2

## Table AX6-2.1. Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Bellinger et al. (1992) U.S. | 148 subjects from the Boston Prospective Study were re-evaluated at 10 yrs of age. The WISCR was used to index intellectual status. Extensive assessment of medical and sociodemographic covariates. | Cord and serial postnatal blood Pb assessments<br>Cord blood Pb grouping <3, 6-7, >10 µg/dL<br>Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL | Increase of 10 µg/dL in blood Pb level at age two was associated with a decrement of ~6 IQ points. Relationship was stronger for verbal compared to performance IQ. Prenatal exposure to Pb as indexed by cord blood Pb levels was unrelated to psychometric intelligence. |
| Dietrich et al. (1991, 1992, 1993a); Ris et al. (2004) U.S. | 253-260 children followed since birth in the Cincinnati Pb Study were re-evaluated at 4, 5, and 6.5 yrs of age. At 4 and 5 yrs, the KABC was used to index intellectual status. At 6.5 yrs, the WISCR was administered. At 15-17 yrs of age, 195 Cincinnati Pb Study subjects were re-evaluated by use of a comprehensive neuropsychological battery that yielded a "Learning/IQ" factor in a principal components analysis. Extensive assessment of medical and sociodemographic covariates. | Prenatal (maternal) and serial postnatal blood Pb assessments<br>Prenatal blood Pb 8.3 (SD 3.7) µg/dL<br>Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL | Few statistically significant relationships between blood Pb indices and covariate-adjusted KABC scales at 4 and 5 yrs of age. One KABC subscale that assesses visual-spatial skills was associated with late postnatal blood Pb levels following covariate adjustment. After covariate adjustment, avg postnatal blood Pb level was significantly associated with WISCR performance IQ at 6.5 yrs. Blood Pb concentrations >20 µg/dL were associated with deficits in performance IQ on the order of 7 points compared with children with mean blood Pb concentrations <10 µg/dL. At 15-17 yrs, late childhood blood Pb levels were significantly associated with lower covariate-adjusted Learning/IQ factor scores. |
| Canfield et al. (2003a) U.S. | 172 predominantly African-American, lower socioeconomic status children in Rochester, NY followed since they were 5 to 7 mos were evaluated at 3 and 5 yrs. An abbreviated form of the Stanford-Binet Intelligence Scale-4 (SBIS-4) was used to index intellectual status. Extensive assessment of medical and sociodemographic covariates. | Serial postnatal blood Pb<br>Blood Pb at 2 yrs 9.7 µg/dL | Following covariate adjustment, there was a significant inverse relationship between blood Pb indices and IQ at all ages. Overall estimate indicated that an increase in avg lifetime blood Pb concentration of 1 µg/dL was associated with a loss of ½ IQ point. Effects were stronger for subjects whose blood Pb levels never exceeded 10 µg/dL. Semiparametric analysis indicated a decline in IQ of 7.4 points for a lifetime avg blood Pb concentration up to 10 µg/dL, while for levels between 10 and 30 µg/dL a more gradual decrease in IQ was estimated. Authors concluded that the most important aspect of their findings was that effects below 10 µg/dL observed in previous cross-sectional studies have now been confirmed by this rigorous prospective study. |

## Table AX6-2.1 (cont'd). Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Bellinger and Needleman (2003) U.S. | Reanalysis of data from the Boston Prospective Study focusing on 48 subjects at 10 yrs of age whose blood Pb levels never exceeded 10 µg/dL. WISCR was used to index intellectual status. See also Bellinger et al. (1992) | Serial postnatal blood Pb Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL | IQ was inversely related to two-yr blood Pb levels following covariate adjustment. Blood Pb coefficient (!1.56) was greater than that derived from analyses including children with concentrations above 10 µg/dL (!0.58). Authors conclude that children's IQ scores are reduced at Pb levels still prevalent in U.S. |
| Chen et al. (2005) U.S. | Repeat measure psychometric data on 780 children enrolled in Treatment of Pb-Exposed Children (TLC) clinical trial were analyzed to determine if blood Pb concentrations at 2 yrs of age constitute a critical period of exposure for expression of later neurodevelopmental deficits. Data for placebo and active drug groups were combined in these analyses, which spanned ~2 to 7 yrs of age. Measures of intellectual status included the Bayley Mental Development Index (MDI) and full scale IQ derived from age-appropriate Wechsler scales. | Blood Pb Range 20-44 µg/dL Baseline blood Pb 26 (SD 26.5) µg/dL in both drug and placebo groups Blood Pb at 7 yrs 8.0 (SD 4.0) µg/dL | Association between blood Pb and psychometric intelligence increased in strength as children became older, whereas the relation between baseline (2 yr) blood Pb and IQ attenuated. Peak blood Pb concentration thus does not fully account for the observed association in older children between their lower blood Pb concentrations and IQ. The effect of concurrent blood Pb on IQ may thusly be greater than currently believed. Authors conclude that these data (a) support the idea that Pb exposure continues to be toxic to children as they reach school age and (b) do not lend support to the interpretation that majority of the damage is done by the time the child reaches 2 to 3 yrs of age. |

## Table AX6-2.1 (cont'd). Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Wasserman et al. (1992, 1994, 2003); Factor-Litvak et al. (1999) Yugoslavia | Birth cohort of ~300-400 infants followed since birth residing in two towns in Kosovo, Yugoslavia, one group near a longstanding Pb smelter and battery manufacturing facility and another in a relatively unexposed location 25 miles away. Intellectual status was monitored from 2 to 10-12 yrs of age with the Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities, and WISCIII. Extensive assessment of medical and sociodemographic covariates. | Maternal prenatal, umbilical cord, and serial postnatal blood Pb<br><br>Maternal blood Pb in exposed area 19.9 (SD 7.7) µg/dL, unexposed area 5.6 (SD 2.0) µg/dL<br><br>Umbilical cord blood Pb in exposed area 22.2 (SD 8.1) µg/dL, unexposed area 5.5 (SD 3.3) µg/dL<br><br>Blood Pb at 2 yrs in exposed area 35.4 µg/dL, unexposed area 8.5 µg/dL | Postnatal blood Pb increment from 10 to 30 µg/dL at 2 yrs of age associated with covariate-adjusted decline of 2.5 points in Bayley MDI. Maternal and cord blood Pb not consistently associated with Bayley outcomes. Higher prenatal and cord blood Pb concentrations associated with lower McCarthy General Cognitive Index (GCI) scores at 4 yrs. Scores on the Perceptual-Performance subscale particularly affected. After covariate-adjustment, children of mothers with prenatal blood Pb levels >20 µg/dL scored a full standard deviation below children in the lowest exposure group (<5 µg/dL prenatal blood Pb). Postnatal blood Pb also associated with poorer performance. Increase in blood Pb level from 10 to 25 µg/dL associated with a reduction of 3.8 points in GCI after covariate-adjustment. Effects even more pronounced on the Perceptual-Performance subscale. At 7 yrs, significant inverse associations between lifetime avg blood Pb and WISCIII IQ were observed, including consistently stronger associations with Performance IQ and later blood Pb measures. Adjusted intellectual loss associated with an increase in lifetime avg blood Pb from 10 to 30 µg/dL was over 4 points in WISCIII Full-Scale and Performance IQ. At 10-12 yrs, subjects were again assessed with the WISCIII. Following covariate-adjustment, avg lifetime blood Pb was associated with all components of the WISCIII, with effect sizes similar to those observed at 7 yrs. In most instances, bone Pb-IQ relationships were stronger than those for blood Pb among subjects residing near the Pb smelter. |

## Table AX6-2.1 (cont'd). Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Schnaas et al. (2000) Mexico | 112 children followed since birth with complete psychometric data from the Mexico City Prospective Study were examined. Intellectual status indexed by General Cognitive Index (GCI) from McCarthy Scales of Children's Abilities (MSCA). Purpose of the study was to determine if magnitude of the effect of postnatal blood Pb levels on cognition varies with time between blood Pb and cognitive assessments. | Serial postnatal blood Pb<br>Avg blood Pb<br>24-36 mos 9.7<br>(range 3-48) µg/dL | A number of significant interactions observed between blood Pb levels and age of assessment. Greatest effect observed at 48 mos, when a 5.8 deficit in adjusted GCI scores was observed for each natural log increment in blood Pb. Authors concluded that four to five yrs of age appears to be a critical period for manifestation of earlier postnatal blood Pb level effects on cognition. |
| Schnaas et al. (2006) Mexico | From the Mexico City Prospective Study, 150 children followed since birth with complete data for all covariates were examined. Intelligence from age 6 to 10 yrs was assessed using the WISC-R. Blood Pb measurements from various time points, starting from maternal blood Pb levels during the 2nd trimester to postnatal Pb levels at age 10 yrs. | Serial prenatal (maternal) and postnatal blood Pb<br>Geometric mean blood Pb<br>During pregnancy 8.0<br>(range 1-33) µg/dL<br>Age 1-5 yrs 9.8<br>(range 2.8-36.4) µg/dL<br>Age 6-10 yrs 6.2<br>(range 2.2-18.6) µg/dL | Among all the Pb variables at the various time points, only log-transformed blood Pb levels during the 3rd trimester were significantly associated with full scale IQ at ages 6 to 10 yrs, after adjusting for potential confounders. A 3.44 point deficit in full scale IQ was observed for each natural log increment in blood Pb.<br>The authors note that, given the modest sample size and relatively low power of this study, they do not claim that Pb exposure from other developmental period has no effect on child IQ. |
| Gomaa et al. (2002) Mexico | 197 two yr-old children residing in Mexico City followed since birth. Bayley Scales of Infant Development Mental Development Index (MDI) used to index intellectual status. Extensive assessment of medical and sociodemographic covariates. | Umbilical cord and serial postnatal blood Pb<br>Umbilical cord blood Pb 6.7 (SD 3.4) µg/dL<br>Blood Pb at 2 yrs 8.4 (SD 4.6) µg/dL<br><br>Maternal tibial and patellar bone Pb<br>Patellar (trabecular) bone Pb 17.9 (SD 15.2) µg/g | Umbilical cord blood Pb and patellar (trabecular) bone Pb significantly associated with lower Bayley MDI scores. Maternal trabecular bone Pb levels predicted poorer sensorimotor functioning at two yrs independent of concentration Pb measured in cord blood. Increase in cord blood Pb level from 5 to 10 µg/dL was associated with a 3.1 point decrement in adjusted MDI scores. In relation to lowest quartile of trabecular bone Pb, the 2nd, 3rd, and 4th quartiles were associated with 5.4, 7.2, and 6.5 decrement in MDI following covariate adjustment. Authors concluded that higher maternal trabecular bone Pb levels constitute an independent risk factor for impaired mental development in infancy, likely due to the mobilization of maternal bone Pb stores over gestation. |

## Table AX6-2.1 (cont'd). Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America (cont'd)** | | | |
| Téllez-Rojo et al. (2006)<br>Mexico | 294 one and two yr-olds residing in Mexico City followed since birth. The Bayley Scales of Infant Development-II (MDI and PDI) were used to index developmental status. There was extensive assessment of medical and sociodemographic covariates. | Umbilical cord blood Pb and postnatal blood Pb at 12 and 24 mos<br>Umbilical cord blood Pb 4.8 (SD 3.0) µg/dL<br>Blood Pb at 1 yr 4.27 (SD 2.1) µg/dL<br>Blood Pb at 2 yrs 4.3 (SD 2.2) µg/dL | Blood Pb at 12 mos was not associated with MDI at either age. Blood Pb at 24 mos was significantly associated with 24 mo MDI. An increase of one logarithmic unit in 24 mo blood Pb level was associated with a reduction of ~5 points in MDI. Findings for PDI were similar. In comparison to a supplemental subsample of 90 subjects with blood Pb levels >10 µg/dL, the coefficient for blood Pb was significantly larger for infants never exceeding that level of internal dose. A steeper inverse slope was observed over the blood Pb range up to 5 µg/dL (!1.71 points per 1 µg/dL increase in blood Pb, $p = 0.01$) compared to the range between 5 and 10 µg/dL (!0.94 points, $p = 0.12$); however, these slopes were not significantly different ($p = 0.34$). In conclusion, a major finding of this prospective study was that a significant inverse relationship between blood Pb concentration and neurodevelopment was observed among children whose blood Pb levels did not exceed 10 µg/dL at any age. |
| **Australia** | | | |
| Baghurst et al. (1992); McMichael et al. (1994); Tong et al. (1996)<br>Australia | 400-500 subjects residing in and near Port Pirie, Australia and followed since birth were re-evaluated at 7 to 8 and 11-13 yrs of age. WISCR was used to index intellectual status at both ages. Extensive assessment of medical and sociodemographic covariates. | Maternal prenatal, umbilical cord and serial postnatal blood Pb<br>Antenatal avg blood Pb 10.1 (SD 3.9) µg/dL<br>Umbilical cord blood Pb 9.4 (SD 3.9) µg/dL<br>Blood Pb at 2 yrs geometric mean 21.3 (SD 1.2) µg/dL<br><br>Deciduous central incisor whole tooth Pb<br>Tooth Pb geometric 8.8 (SD 1.9) µg/g | Significant decrements in covariate-adjusted full scale IQ were observed in relationship to postnatal blood Pb levels at both ages. At 7 to 8 yrs of age a loss of 5.3 points was associated with an increase in blood Pb from 10 to 30 µg/dL. At 11-13 yrs, mean full scale IQ declined by 3.0 points for an increase in lifetime avg blood Pb concentrations from 10 to 20 µg/dL. Pb levels in central upper incisors were also associated with lower 7-8 yr IQ following covariate adjustment. Adjusted estimated decline in IQ across the range of tooth Pb from 3 to 22 ppm was 5.1 points. |

## Table AX6-2.1 (cont'd). Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Australia** (cont'd) | | | |
| Cooney et al. (1991)<br>Australia | 175 subjects from the Sydney, Australia Prospective Study were assessed at 7 yrs of age. The WISCR was used to index intellectual status. Extensive assessment of medical and sociodemographic characteristics. | Maternal and cord blood Pb<br>Cord blood Pb 8.4 µg/dL (SD not given)<br>Blood Pb at 2 yr 15.8 µg/dL (SD not given) | Blood indices of Pb exposure were not associated with any measure of psychometric intelligence. Authors conclude that the evidence from their study indicates that if developmental deficits do occur at blood Pb levels <25 µg/dL, the effect size is likely to be small (<5%). Sydney results are difficult to interpret from the statistical presentation in their report. It is not clear which covariates were entered into regression analyses nor is the empirical or substantive basis for their conclusion. |
| **Asia** | | | |
| Shen et al. (1998)<br>China | Pregnant women and newborns in Shanghai, China recruited from health care facilities in the community on the basis of cord blood Pb concentration percentiles (30th and 70th) yielding a total N of 173 subjects. The Bayley Scales of Infant Development Mental Development Index (MDI) and Psychomotor Development Index (PDI) were used to index sensorimotor/intellectual status at 3, 6, and 12 mos. Extensive assessment of medical and sociodemographic characteristics. | Cord blood Pb<br>"High group" 13.4 (SD 2.0) µg/dL<br>"Low group" 5.3 (SD 1.4) µg/dL<br><br>Blood Pb at 1 yr<br>"High group" 14.9 (SD 8.7) µg/dL<br>"Low group" 14.4 (SD 7.7) µg/dL | At all ages the Bayley MDI was associated with cord blood Pb groupings following adjustment for covariates. Postnatal blood Pb unrelated to any Bayley measures. Differences in MDI between prenatal blood Pb exposure groupings generally in accord with similar investigations in Boston, Cincinnati, and Cleveland. Authors conclude that the adverse effects of prenatal Pb exposure are readily discernible and stable over the first yr of life. |

## Table AX6-2.2. Meta- and Pooled-Analyses of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| Lanphear et al. (2005) | Pooled analysis of seven international prospective studies involving 1,333 school-age children. Primary outcome measure was full-scale IQ as assessed by age-appropriate Wechsler scale. Measures of exposure were concurrent, peak, avg lifetime and "early" blood Pb (i.e. mean blood Pb from 6-24 mos). Cord blood Pb was also investigated for those studies that collected these samples at birth. Multivariate regression models were developed adjusting for site as well as 10 common covariates. Blood Pb measure with the largest adjusted $R^2$ was nominated a priori as the preferred index for relating Pb exposure to IQ in subsequent analyses. Results evaluated by applying a random-effects model. | Umbilical cord blood Pb<br>Serial postnatal blood Pb<br>Lifetime avg blood Pb 12.4 (range 4.1-34.8) µg/dL | Concurrent blood Pb level exhibited the strongest relationship with IQ, although results of regression analyses for all blood Pb variables were similar. Steepest declines in IQ were at blood Pb concentrations below 10 µg/dL. For the entire pooled data set, a decline of 6.2 IQ points (95% CI: 3.8, 8.6) was estimated for an increment in blood Pb from 1 to 10 µg/dL. |
| Needleman and Gatsonis (1990) | Meta analysis of 12 studies chosen on the basis of quality—covariate assessment and application of multiple regression techniques. Studies weighted on basis of sample size. Studies divided according to tissue analyzed (blood or teeth). Joint p-values and avg effect sizes calculated using two different methods. | Blood Pb<br>Tooth Pb | Joint p-values for blood Pb studies were <0.0001 for both methods, whereas joint p-values of <0.0006 and <0.004 were obtained for teeth. Partial correlations ranged from –0.27 to –0.0003. No single study was responsible for the significance of the final findings. Authors concluded that the hypothesis that Pb lowers children's IQ at relatively low dose is strongly supported by results of this quantitative review. |
| Schwartz (1994) | Meta analysis of 7 recent studies relating blood Pb to IQ were reviewed, three longitudinal and four cross-sectional. Measure of effect was estimated decrease in IQ for an increase in blood Pb from 10 to 20 µg/dL. Studies were weighted by the inverse of the variances using random | Blood Pb | Estimated decrease in IQ per blood Pb increment from 10 to 20 µg/dL was –2.6 points (SE 0.41). Results were not determined by any individual study. Effect estimates were similar for longitudinal and cross-sectional studies.<br>For studies with mean blood Pb levels <15 µg/dL, estimated effect sizes were larger. When the study with the lowest exposures was examined alone using nonparametric smoothing (Boston), no evidence of a threshold was observed down to a blood Pb level of 1 µg/dL. Author concludes that these data provide further evidence of Pb effects on cognition at levels below 10 µg/dL. |

## Table AX6-2.2 (cont'd). Meta- and Pooled-Analyses of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| Pocock et al. (1994) | Meta-analysis of five prospective and fourteen cross-sectional studies (including tooth and blood tissues) were included. The fixed effect method of Thompson and Pocock (1992) was employed. Only blood Pb at or near two yrs of age was considered for the prospective studies. | Blood Pb<br>Tooth Pb | Overall conclusion was that a doubling of blood Pb levels from 10 to 20 µg/dL, or tooth Pb from 5 to 10 µg/g was associated with an avg estimated deficit in IQ of ~1-2 points. Authors caution interpretation of these results and Pb literature in general, citing questions about representativeness of the samples, residual confounding, selection bias, and reverse causality. |

## Table AX6-2.3. Cross-Sectional Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Lanphear et al. (2000) U.S. | 4,853 U.S. children ages six to 16 yrs enrolled in NHANES-III. Two subtests of the WISC-R (Block Design and Digit Span) used to assess intellectual status. Medical and sociodemographic covariates were assessed | Blood Pb at time of testing Geometric blood Pb 1.9 (SE 0.1) µg/dL 2.1% with blood Pb ∃10 µg/dL | Multivariate analyses revealed a significant association between blood Pb levels and both WISC-R subtests. Associations remained statistically significant when analyses were restricted to children with blood Pb levels below 10 µg/dL. Authors caution that lack of control for parental intelligence and variables like the HOME scale should temper any conclusions regarding observed effects. |
| Emory et al. (2003) U.S. | 77 healthy, lower-risk African-American infants age 7 mos. The Fagan Test of Infant Intelligence (FTII) was administered to assess intellectual status. Birth weight and gestational age examined as potential covariates/confounders. | Maternal blood Pb Blood Pb 0.72 (SD 0.86) µg/dL | Infants scoring in the upper 5th to 15th percentiles for the FTII had mother with significantly lower maternal blood Pb levels when compared to those scoring in the lower 5th or 15th percentile. Findings of this study should be considered preliminary due to small sample size and lack of covariate assessment or control. |
| Chiodo et al. (2004) U.S. | 237 African-American inner-city children assessed at 7.5 yrs of age. Cohort was derived from a larger study of the effects of prenatal alcohol exposure on child development. 83% of children in Pb study had little or no gestational exposure to alcohol. WISC-III was administered to assess intellectual status. Medical and sociodemographic covariates were assessed. | Blood Pb at time of testing Blood Pb 5.4 (SD 3.3) µg/dL | Following covariate adjustment statistically significant relationships between blood Pb and full-scale, verbal and performance IQ were observed. Significant effects of Pb on full-scale and performance IQ was evident at blood Pb concentrations below 7.5 µg/dL. |
| **Europe** | | | |
| Walkowiak et al. (1998) Germany | 384 six-yr-old children in three German cities. Two subtests of the WISC (Vocabulary and Block Design) used to estimate IQ. Both subscales were combined to form a "WISC Index." Medical and sociodemographic covariate covariates were assessed. | Blood Pb at time of testing Blood Pb 4.2 µg/dL 95th percentile 8.9 µg/dL | Following covariate-adjustment, WISC Vocabulary was significantly associated with blood Pb but combined WISC index was borderline. Authors conclude that findings roughly correspond with those of other studies that find effects below 10 µg/dL but caution that potentially important covariates such as HOME scores were not controlled. |
| Prpic-Majic et al. (2000) Croatia | 275 3rd and 4th grade students in Zagreb, Croatia. WISC-R was administered to assess intellectual status. Covariate factors limited to parents' educational status and gender of child. | Blood Pb at time of testing Blood Pb 7.1 (SD 1.8) µg/dL | Following covariate adjustment, no statistically significant associations were observed for Pb or other indicators of toxicity (ALAD, EP) on WISC-R. Authors argue that study had sufficient power and that the "no-effect" threshold for Pb must be in the upper part or above the study's range of exposures. |

## Table AX6-2.3 (cont'd). Cross-Sectional Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Kordas et al. (2004, 2006)<br>Mexico | 602 1st grade children in public schools in a highly industrialized area of northern Mexico. Premise of study was that effects of Pb could be explained by correlated nutritional factors such as iron status, anemia, and growth. Peabody Picture Vocabulary Test-Revised (PPVT-R), Cognitive Abilities Test (CAT), and an abbreviated form of the WISC-R were administered to assess intellectual status. Medical and sociodemographic covariates were assessed. | Blood Pb at time of testing<br>Blood Pb 11.5 (SD 6.1) µg/dL | Following covariate adjustment blood Pb levels were significantly associated with poorer performance on the PPVT-R, WISC-R Coding, and Number and Letter Sequencing, a Math Achievement Test, and the Sternberg Memory Test. Authors concluded that Pb's association with iron deficiency anemia or growth retardation could not explain relationship between Pb and cognitive performance. Non-linear analyses of selected neurocognitive outcomes revealed that dose-response curves were steeper at lower than at higher blood Pb levels. Moreover, the slopes appeared negative at blood Pb levels below 10 µg/dL, above which they tend to plateau. Effects of Pb on neurocognitive attainment appeared to be greatest among the least advantaged members of the cohort. |
| Counter et al. (1998)<br>Ecuador | 77 chronically Pb-exposed children living in Ecuadorian villages where Pb is used extensively in commercial ceramics production. Ravens Colored Progressive Matrices (RCPM) used to index intellectual status. Only half of the sample was assessed. No assessment of medical or sociodemographic covariates. | Blood Pb at time of testing<br>Blood Pb 47.4 (SD 22) µg/dL | Simple regression analysis revealed a correlation between blood Pb and RCPM of only borderline significance. Results difficult to interpret because there was no attempt to age-adjust. When analysis restricted to children 9 to 11 yrs of age, a highly significant negative correlation was obtained. Study has little relevance to the question of Pb hazards in the U.S. because of unusually high levels of exposure. |
| **Asia** | | | |
| Rabinowitz et al. (1991)<br>Taiwan | 443 children in grades one to three in Taipei City and three schools near Pb smelters. Ravens Colored Progressive Matrices (RCPM) used to index intellectual status. Medical and sociodemographic covariate factors were assessed. | Dentin tooth Pb<br>Taipei City 4.3 (SD 3.7) µg/g<br>Smelter areas 6.3 (SD 3.3) µg/g | Scores on the RCPM were negatively correlated with tooth Pb concentrations. In multivariate analyses, parental education was the most important predictor of RCPM scores, but tooth Pb concentrations still significantly predicted lower scores in females residing in low-income families. |
| Bellinger et al. (2005)<br>India | 74 four to fourteen yr-old children residing in Chennai, India were enrolled in the study, 31 of which were assessed with the Binet-Kamath Intelligence test. Data were collected on sociodemographic features of subjects' families. | Blood Pb at time of testing<br>Blood Pb 11.1 (SD 5.6) µg/dL | Covariate-adjusted blood Pb coefficient was negative but nonsignificant, perhaps due to small sample size and highly variable performance of subjects with the least elevated blood Pb concentrations. |

## Table AX6-2.3 (cont'd). Cross-Sectional Studies of Neurocognitive Ability in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Middle East** | | | |
| Al-Saleh et al. (2001) Saudi Arabia | 533 Riyadh, Saudi Arabian girls (6-12 yrs of age) were administered a variety of standardized tests including the TONI, and the Beery VMI. Extensive data were collected on potentially confounding variables including sociodemographic variables, early developmental milestones and child health status. | Blood Pb at time of testing Blood Pb 8.1 (SD 3.5) µg/dL | Blood Pb levels had no impact on TONI scores but this test has limited evidence of validity in this population. Significant negative associations were noted between blood Pb levels and the Beery VMI suggesting an association between impairment in visual-spatial skills in Saudi children with blood Pb levels in the range of 2.3 to 27.4 µg/dL. |

## Table AX6-2.4. Effects of Lead on Academic Achievement in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Lanphear et al. (2000) U.S. | Design: Cross-sectional. 4,853 U.S. children ages six to 16 yrs enrolled in NHANES-III. Subjects were administered the Arithmetic and Reading subtests of the Wide Range Achievement Test-Revised (WRATR). A number of medical and sociodemographic covariates were assessed and entered into multivariable models. | Blood Pb at time of testing<br>Geometric blood Pb 1.9 (SE 0.1) µg/dL<br>2.1% with blood Pb ∃10 µg/dL | Following covariate adjustment, a statistically significant relationship between blood Pb and WRATR performance was found. A 0.70 point decrement in Arithmetic scores and a 1 point decrement in Reading scores for each 1 µg/dL increase in blood Pb concentration was observed. Statistically significant inverse relationships between blood Pb levels and performance for both Reading and Arithmetic subtests were found for children with blood Pb concentrations <5 µg/dL. Authors concluded that results of these analyses suggest that deficits in academic skills are associated with blood Pb concentrations lower than 5 µg/dL. They cautioned, however, that two covariates that have been shown to be important in other Pb studies (i.e., parental IQ and HOME scores) were not available. This may have over or under estimated deficits in academic skills related to Pb. They further caution that, as with all cross-sectional studies utilizing blood Pb as the index of dose it is not clear whether deficits in academic skills were due to Pb exposure that occurred sometime during early childhood or due to concurrent exposure. Nevertheless, concurrent blood Pb levels reflect both ongoing exposure and preexisting body burden. |
| Needleman et al. (1990) U.S. | Design: Prospective cohort. Re-examination of the Chelsea and Somerville cohort recruited in the 1970's (Needleman et al., 1979). 132 adolescents were recalled. Large battery of tests was administered to examine neurobehavioral deficits and academic achievement in high school and shortly following graduation. Extensive assessment of medical and sociodemographic covariates. | Tooth (dentin) Pb<br>Tooth Pb median 8.2 µg/g | Subjects with dentin Pb levels >20 ppm were at higher risk of dropping out of high school (adjusted OR = 5.8 [95% CI: 1.4, 40.7]) and of having a reading disability (adjusted OR = 5.8 [95% CI: 1.7, 19.7]). Higher dentin Pb levels were also significantly associated with lower class standing, increased absenteeism, and lower vocabulary and grammatical reasoning scores on the Neurobehavioral Evaluation System (NES). Authors conclude that undue exposure to Pb has enduring and important effects on objective parameters of success in life. |

## Table AX6-2.4 (cont'd). Effects of Lead on Academic Achievement in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Bellinger et al. (1992) U.S. | Design: Prospective longitudinal. 148 children in the Boston Pb Study cohort were examined at 10 yrs of age. The short-form of the Kaufman Test of Educational Achievement (KTEA) was used to assess academic achievement. Primary outcome was the Battery Composite Score. Extensive assessment of medical and sociodemographic covariates. | Cord and serial postnatal blood Pb assessments. Cord blood Pb grouping <3, 6-7, >10 µg/dL Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL | After covariate-adjustment, blood Pb levels at 24 mos were significantly predictive of lower academic achievement (∃ = !0.51, SE 0.20). Battery Composite Scores declined by 8.9 points for each 10 µg/dL increase in blood Pb. This association was significant after adjustment for IQ. Authors conclude that Pb-sensitive neuropsychological processing and learning factors not reflected in measures of global intelligence may contribute to deficits in academic achievement. |
| Leviton et al. (1993) U.S. | Design: Prospective cohort. Teachers of ~2000 eight yr-old children born in 1 hospital in Boston between 1979 and 1980 filled out the Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior. Limited information is provided on the assessment of covariate factors but a number were considered and controlled for in multivariable analyses. | Cord blood Pb Cord blood Pb 6.8 µg/dL<br><br>Tooth (dentin) Pb Tooth Pb 2.8 µg/g | Following adjustment for potential confounding variables, elevated dentin Pb concentrations were associated with statistically significant reading and spelling difficulties as assessed by the BTQ among girls in the sample. Authors conclude that their findings support the case for Pb-associated learning problems at levels that were prevalent at that time in the general population. However, authors add that the inability to assess child-rearing quality in this study conducted by mail limits the inferences that can be drawn. |
| **Australia** | | | |
| Fergusson et al. (1993, 1997); Fergusson and Horwood (1993) New Zealand | Design: Prospective cohort. Academic performance was examined in a birth cohort of 1200 New Zealand children enrolled in the Christchurch Health and Development Study. Measures of academic performance at 12-13 yrs included the Brut Reading Test, Progressive Achievement Test, Test of Scholastic Abilities, and teacher ratings of classroom performance in the areas of reading, writing, and mathematics. The growth of word recognition skills from 8 to 12 yrs was also examined using growth curve modeling methods. Academic achievement in relationship to Pb was re-examined in this cohort at 18 yrs. Measures of academic achievement included the Burt Reading Test, number of yrs of secondary education, number of certificates passed (based on national examinations), and leaving school without formal qualifications (failing to graduate). Extensive assessment of medical and social covariates. | Tooth (dentin) Pb Tooth Pb 6.2 (SD 6.2) µg/g | Following covariate adjustment, dentin Pb levels were significantly associated with virtually every formal index of academic skills and teacher ratings of classroom performance in 12-13 yr-olds. After adjustment for covariates, tooth Pb levels greater than 8 µg/g were associated with significantly slow growth in word recognition abilities with no evidence of catch up. At 18 yrs, tooth Pb levels were significantly associated with lower reading test scores, having a reading level of less than 12 yrs, failing to complete three yrs of high school, leaving school without qualifications, and mean number of School Certificates passed. Authors conclude that early exposure to Pb is independently associated with detectable and enduring deficits in children's academic abilities. They further conclude that their findings are particularly significant in that they confirm the findings of Needleman (1990), albeit in a cohort with lower levels of exposure to environmental Pb. |

## Table AX6-2.4 (cont'd). Effects of Lead on Academic Achievement in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** | | | |
| Wang et al. (2002a)<br>Taiwan | Design: Cross-sectional. 934 3rd graders living in an urban industrial area of Taiwan. Outcome variables were grades for Chinese (reading, writing), mathematics, history, and natural science. Grades were converted into individual class rankings to avoid teacher bias. Limited data on medical and sociodemographic covariates. | Blood Pb at time of evaluation<br>Blood Pb 5.5 (SD 1.9) µg/dL | Following covariate adjustment, blood Pb was significantly associated with lower class ranking in all academic subjects. Major shortcoming of this study is lack of control for potentially important covariates such as parental IQ. However, the relatively low levels of exposure in this sample and strength and consistency of the reported relationships suggest that Pb may be playing some role in lowering academic performance. |
| Rabinowitz et al. (1992)<br>Taiwan | Design: Cross-sectional. Teachers of 493 children in grades 1-3 filled out the Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior. Sociodemographic and medical covariate factors were assessed. | Tooth (dentin) Pb<br>Tooth Pb 4.6 (SD 3.5) µg/g | Prior to adjustment for covariates, girls with higher exposures to Pb evinced a borderline significant trend for reading difficulties while byes displayed significantly increased difficulties with respect to activity levels and task attentiveness. In logistic regression models that include significant covariate factors, the tooth Pb terms failed to achieve statistical significance. Authors conclude that Pb levels found in the teeth of children in this Taiwanese sample are not associated with learning problems as assessed by the BTQ. |
| **Middle East** | | | |
| Al Saleh et al. (2001)<br>Saudi Arabia | Class rank, as assessed by the teacher, was examined in conjunction with blood Pb levels in 533 Riyadh, Saudi Arabian girls (6-12 yrs of age). Extensive data were collected on potentially confounding variables including sociodemographic variables, early developmental milestones and child health status. | Blood Pb at time of testing<br>Blood Pb 8.1 (SD 3.5) µg/dL | A significant inverse relationship between blood Pb levels and rank percentile scores was observed after adjusting for a number of demographic and socioeconomic variables. When multiple regression models were fitted to a subset of students with blood Pb levels below 10 µg/dL, class rank percentile continued to show a statistically significant association with blood Pb levels. |

## Table AX6-2.5. Effects of Lead on Specific Cognitive Abilities in Children — Attention/Executive Functions, Learning, and Visual-spatial Skills

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Bellinger et al. (1994a)<br>U.S. | Design: Prospective cohort. 79 subjects from the original Chelsea and Somerville, MA Pb study were re-evaluated at 19-20 yrs of age with the Mirsky battery of attentional measures. Extensive measures of medical and sociodemographic covariates. | Tooth (dentin) Pb<br>Tooth Pb 13.7 (SD 11.2) µg/g<br><br>KXRF Bone Pb<br>Tibial bone Pb<br>(range <1 - >10) µg/g<br>Patellar bone Pb<br>(range <1 - >15) µg/g | Higher tooth Pb concentrations were significantly associated with poorer scores on the Focus-Execute and Shift factors of the Mirsky battery. Few significant associations were observed between bone Pb levels and performance. Authors conclude that early Pb exposure may be associated with poorer performance on executive/regulatory functions, which are thought to depend on the frontal or prefrontal regions of the brain. |
| Stiles and Bellinger (1993)<br>U.S. | Design: Prospective longitudinal. 148 subjects from the Boston Pb Study were re-evaluated at 10 yrs of age with an extensive neuropsychological battery. Tests included the California Verbal Learning Test, Wisconsin Card Sorting Test, Test of Visual-Motor Integration, Rey-Osterieth Complex Figure, Story Recall, Finger Tapping, and Grooved Pegboard. Extensive measures of medical and sociodemographic covariates. | Cord and serial postnatal blood Pb assessments<br>Cord blood Pb grouping <3, 6-7, >10 µg/dL<br>Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL | Authors point out that the number of significant associations was about equal to those that would be expected by chance. However, tasks that assess attentional behaviors and executive functions tended to among those for which Pb was a significant predictor of performance. Following covariate adjustment, higher blood Pb concentrations at two yr were significantly associated with lower scores on Freedom from Distractibility factor of the Wechsler scales, increase in percentage of perseverative errors on the Wisconsin Card Sorting Test and the California Verbal Learning Test. |
| Canfield et al. (2003b, 2004)<br>U.S. | Design: Prospective longitudinal. 170-174 children from the Rochester Pb Study were administered a number of learning and neuropsychological functioning at 48, 54, and 66 mos of age. At 48 and 54 mos the Espy Shape School Task was administered while at 66 mos the Working Memory and Planning assessment protocols of the Cambridge Neuropsychological Test Automated Battery (CANTAB) was given. Extensive measures on medical and sociodemographic covariates. | Serial postnatal blood Pb<br>Blood Pb at 2 yrs 9.7 µg/dL<br>Lifetime avg blood Pb 7.2 (range 0-20) µg/dL | Following covariate adjustment, blood Pb level at 48 mos was negatively associated with children's focused attention while performing the Shape School Tasks, efficiency at naming colors, and inhibition of automatic responding. Children with higher blood Pb concentrations also completed fewer phases of the Espy tasks and knew fewer color and shape names. On the CANTAB battery, children with higher lifetime avg blood Pb levels showed impaired performance on spatial working memory, spatial memory span, and cognitive flexibility and planning. Authors conclude that the effects of pediatric Pb exposure are not restricted to global measures of intellectual functioning and executive processes may be at particular risk. |

## Table AX6-2.5 (cont'd). Effects of Lead on Specific Cognitive Abilities in Children — Attention/Executive Functions, Learning, and Visual-spatial Skills

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Ris et al. (2004)<br>U.S. | Design: Prospective longitudinal. 195 subjects from the Cincinnati Pb Study were administered an extensive and comprehensive neuropsychological battery at 16-17 yrs of age. Domains assessed included Executive Functions, Attention, Memory, Achievement, Verbal Skills, Visuoconstructional, and Fine Motor. Factor scores transformed to ranks derived from a principal components factor analysis of the neuropsychological test scores were the primary outcome variables. Extensive measures on medical and sociodemographic covariates. | Prenatal (maternal) and serial postnatal blood Pb assessments<br>Prenatal blood Pb 8.3 (SD 3.7) µg/dL<br>Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL | Following covariate adjustment, strongest associations between Pb exposure and performance were observed for factor scores derived from the Attention component, which included high loadings on variables from the Conners Continuous Performance Test. This relationship was strongest in males. Authors speculate that since the incidence of Attention Deficit/Hyperactivity Disorder is greater in males in general, early exposure to Pb may exacerbate a latent potential for such problems. |

## Table AX6-2.6. Effects of Lead on Disturbances in Behavior, Mood, and Social Conduct in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Sciarillo et al. (1992)<br>U.S. | Design: Cross-sectional. 150 2-5 yr-old children in Baltimore separated into "high" (2 consecutive blood Pb levels >15 µg/dL) and "low" groups. Mothers filled out the Achenbach Child Behavior Checklist (CBCL). The Center for Epidemiologic Studies Depression Scale (CESD) was administered to mothers as a control measure. | Screening blood Pbs at various times before assessment<br>High group 28.6 (SD 9.3) µg/dL<br>Low group 11.3 (SD 4.3) µg/dL | When compared to lower exposed group, children in the high group had a significantly higher CBCL Total Behavior Problems Score (TBPS) and Internalizing and Externalizing scores. After adjustment for maternal depression, blood Pb concentrations were still significantly associated with an increase in the TBPS. Children in high group were nearly 3 times more likely to have a TBPS in the clinical range. A significantly higher percentage of children in the high group scored in the clinical range for CBCL subscales measuring aggressive and destructive behavioral tendencies. |
| Bellinger et al. (1994b)<br>U.S. | Design: Prospective cohort: 1782 children born within a 1-yr period at a single Boston hospital were examined at 8 yrs of age. Teachers filled out the Achenbach Child Behavior Profile (ACBP). Medical and sociodemographic characteristics assessed by questionnaire and chart review. | Umbilical cord blood Pb<br>Cord blood Pb 6.8 (SD 3.1) µg/dL<br><br>Tooth (dentin) Pb<br>Tooth Pb 3.4 (SD 2.4) µg/g | Cord blood Pb levels were not associated with the prevalence or nature of behavioral problems reported by teachers. Tooth Pb levels were significantly associated with ACBP Total Problem Behavior Scores (TPBS). Statistically significant tooth Pb-associated increases in both Externalizing and Internalizing scores were observed. Each log unit increase in tooth Pb was associated with a 1.5-point increase in T scores for these scales. Authors caution that residual confounding cannot be ruled out because of the lack of information on parental psychopathology or observations of the family environment. However, these results are in accord with other studies that social and emotional dysfunction may be an important expression of elevated Pb levels during early childhood. |
| Denno (1990)<br>U.S. | Design: Prospective cohort. Survey of 987 Philadelphia African-American youths enrolled in the Collaborative Perinatal Project. Data available from birth through 22 yrs of age. Analysis considered 100 predictors of violent and chronic delinquent behavior. | Blood Pb<br>Values not provided | Repeat offenders presented consistent features such as low maternal education, prolonged male-provider unemployment, frequent moves, and higher Pb intoxication. In male subjects, a history of Pb poisoning was among the most significant predictors of delinquency and adult criminality. |

## Table AX6-2.6 (cont'd). Effects of Lead on Disturbances in Behavior, Mood, and Social Conduct in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Needleman et al. (1996)<br>U.S. | Design: Prospective cohort. 850 boys enrolled in the Pittsburgh Youth Study were prescreened to assess delinquent behavioral tendencies. Subjects who scored in the 30th percentile on the risk score and an equal number randomly selected from the remainder form the sample of 530 subjects. Measures of antisocial behavior were administered at 7 and 11 yrs of age including the Self Reported Antisocial Behavior scale (SRA), Self Report of Delinquent Behavior (SRD), and parents' and teachers' versions of the Achenbach Child Behavior Profile (CBCL). Extensive assessment of medical and sociodemographic covariates. | Bone Pb by K-XRF<br>Bone Pb (exact concentrations not reported)<br>Negative values treated categorically as 1 and positive values grouped into quintiles. | Following covariate-adjustment, parents of subjects with higher Pb levels in bone reported significantly more somatic complaints, more delinquent and aggressive behavior, and higher Internalizing and Externalizing scores. Teachers reported significant increase in scores on somatic complaints, anxious/depressed, social problems, attention problems, delinquent behavior, aggressive behavior, internalizing and externalizing problems in the higher bone Pb subjects. At 11 yrs, subject's SRD scores were also significantly related to bone Pb levels. More high Pb subjects had CBCL T scores in the clinical range for attention, aggression, and delinquency. Authors conclude that Pb exposure is associated with increased risk for antisocial and delinquent behavior. |
| Dietrich et al. (2001)<br>U.S. | Design: Prospective longitudinal. 195 subjects from the Cincinnati Pb Study were examined at 16-17 yrs of age. Parents were administered a questionnaire developed specifically for the study while CLS subjects were given the Self Report of Delinquent Behavior. Extensive assessment of medical and sociodemographic covariates. | Prenatal (maternal) and serial postnatal blood Pb assessments.<br>Prenatal blood Pb 8.3 (SD 3.7) µg/dL<br>Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL | Prenatal (maternal) blood Pb was significantly associated with a covariate-adjusted increase in the frequency of parent-reported delinquent and antisocial acts. Prenatal and measures of postnatal Pb exposure were significantly associated with self-reported delinquent and antisocial behaviors. Authors concluded that Pb might play a measurable role in the development of behavioral problems in inner-city children independent of other important social and biomedical cofactors. |
| Needleman et al. (2002)<br>U.S. | Design: Case-control. 194 adjudicated delinquents and 146 non-delinquent controls recruited from high schools in the City of Pittsburgh and Allegheny County, PA. Covariate assessments were not extensive but did include race, parental sociodemographic factors, and neighborhood crime rates. | Bone Pb by KXRF<br>Cases 11.0 (SD 32.7) µg/g<br>Controls 1.5 (SD 32.1) µg/g | Cases had significantly higher avg concentrations of Pb in tibia than controls. Following covariate adjustment, adjudicated delinquents were 4 times more likely to have bone Pb concentration >25 µg/g then controls. Bone Pb level was the second strongest factor in the logistic regression models, exceeded only by race. In models stratified by race, bone Pb was exceeded as a risk factor only by single parent status. Authors conclude that elevated body Pb burdens are associated with increased risk for adjudicated delinquency. |

## Table AX6-2.6 (cont'd). Effects of Lead on Disturbances in Behavior, Mood, and Social Conduct in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Wasserman et al. (1994)<br>Yugoslavia | Design: Prospective longitudinal. Birth cohort of ~300-400 infants followed since birth residing in two towns in Kosovo, Yugoslavia, one group near a longstanding Pb smelter and battery manufacturing facility and another in a relatively unexposed location 25 miles away. 379 children at 3 yrs of age were examined. Parents were interviewed with the Achenbach Child Behavior Checklist (CBCL). Extensive assessment of medical and sociodemographic covariates. | Maternal prenatal, umbilical cord and serial postnatal blood Pb<br><br>Maternal blood Pb in exposed area 19.9(SD 7.7) µg/dL, unexposed area 5.6 (SD 2.0) µg/dL<br><br>Umbilical cord blood Pb in exposed area 22.2 (SD 8.1) µg/dL, unexposed area 5.5 (SD 3.3) µg/dL<br><br>Blood Pb at 2 yrs in exposed area 35.4 µg/dL, unexposed area 8.5 µg/dL | Following covariate adjustment, concurrent blood Pb levels were associated with increased Destructive Behaviors on the CBCL subscale, although the variance accounted for by Pb was small compared to sociodemographic factors. As blood Pb increased from 10 to 20 µg/dL, subscale scores increased by 0.5 points. The authors conclude that while statistically significant, the contribution of Pb to social behavioral problems in this cohort was small compared to the effects of correlated social factors. |
| **Australia** | | | |
| Burns et al. (1999)<br>Australia | Design: Prospective longitudinal. 322 subjects residing in and near Port Pirie, Australia and followed since birth were re-evaluated at 11-13 yrs of age. Parents completed the Achenbach Child Behavior Checklist. Extensive assessment of medical and sociodemographic characteristics. | Maternal prenatal, umbilical cord and serial postnatal blood Pb<br>Antenatal avg blood Pb 10.1 (SD 3.9) µg/dL<br>Umbilical cord blood Pb 9.4 (SD 3.9) µg/dL<br>Blood Pb at 2 yrs geometric mean 21.3 (SD 1.2) µg/dL | After adjustment for covariates, regression models revealed that for an increase in avg lifetime blood Pb concentrations from 10 to 30 µg/dL, the Externalizing behavior problem T score increased by 3.5 points in boys (95% CI: 1.6, 5.4), but only 1.8 points (95% CI: !0.1, 11.1) in girls. Internalizing behavior problems were predicted to rise by 2.1 points (95% CI: 0.0, 4.2) in girls by only 0.8 (95% CI: !0.9, 2.4) in boys. Authors concluded that Pb exposure is associated with an increase in externalizing (undercontrolled) behaviors in boys. |
| Fergusson et al. (1993)<br>New Zealand | Design: Prospective cohort. 690-891 children ages 12 and 13 yrs from the Christchurch Child and Health Study, New Zealand were examined. Mothers and teachers were asked to respond to a series of items derived from the Rutter and Conners parental and teacher questionnaires. Extensive assessment of sociodemographic and medical covariates. | Tooth (dentine) Pb<br>Tooth Pb range 3–12 µg/g | Statistically significant dose-effect relationships were observed between tooth Pb levels and the inattention/restlessness variable at each age. Authors conclude that this evidence is consistent with the view that mildly elevated Pb levels are associated with small but long term deficits in attentional behaviors. |

## Table AX6-2.6 (cont'd). Effects of Lead on Disturbances in Behavior, Mood, and Social Conduct in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Australia** | | | |
| Silva et al. (1988) New Zealand | As part of the 11-yr follow-up of the Dunedin Multidisciplinary Health and Development Study, a longitudinal study of a birth cohort of children born in Dunedin's only obstetric hospital, blood Pb levels were measured in 579 children at age 11 yrs old. The study sample was over-representative of higher SES, but was found to be representative of Dunedin children in educational attainment. Blood Pb levels were examined in association with intelligence assessed using the WISC-R and behavioral problems as assessed by both parents and teachers. | Blood Pb at time of testing Blood Pb at age 11 yrs 11.1 (SD 4.91, range 4-50) µg/dL | Log blood Pb levels were significantly correlated with most measures of behavioral problems, including the Parents' and Teachers' Rutter Behavioral Scale, the Parents' and Teachers' Hyperactivity Scale, and the Teachers' Inattention Scale, after adjustment for various potential confounders. No associations were observed between log blood Pb levels and IQ. Authors concluded that exposure to Pb is associated with increases in children's' general behavioral problems, especially in inattention and hyperactivity. |

## Table AX6-2.7. Effects of Lead on Sensory Acuities in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Schwartz and Otto (1991)<br>U.S. | Design: Cross-sectional. 3545 subjects 6-19 yrs old who participated in the Hispanic Health and Nutrition Examination Survey. Pure tone audiometric evaluations were performed at 500 Hz, 2000 Hz, and 4000 Hz. Extensive measures on medical and sociodemographic covariates. | Blood Pb at the time of testing<br>Blood Pb 50th percentile 8 µg/dL | Following covariate adjustment, higher blood Pb concentrations were associated with an increased risk of hearing thresholds that were elevated above the standard reference level at all four frequencies. Blood Pb was also associated higher hearing threshold when treated as a continuous outcome. These relationships extended to blood Pb levels below 10 µg/dL. An increase in blood Pb from 6 to 18 µg/dL was associated with a 2-dB loss at all frequencies. Authors conclude that HHANES results those reported earlier for NHANES-II. |
| Dietrich et al. (1992)<br>U.S. | Design: Prospective/longitudinal. 215 subjects drawn from the Cincinnati Pb Study at the age of 5 yrs. Children were administered the SCAN-a standardized test of central auditory processing. Extensive measurement of medical and sociodemographic covariates | Prenatal (maternal) and serial postnatal blood Pb assessments<br>Prenatal blood Pb 8.3 (SD 3.7) µg/dL<br>Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL | Higher prenatal (maternal), neonatal and postnatal blood Pb concentrations were associated with more incorrect identification of common monosyllabic words presented under conditions of muffling. Following covariate adjustment, avg childhood blood Pb level remained significantly associated with impaired performance on the SCAN subtest. Authors conclude that Pb-related deficits in hearing and auditory processing may be one plausible mechanism by which an increased Pb burden might impede a child's learning. |
| **Europe** | | | |
| Osman et al. (1999)<br>Poland | Design: Cross-sectional. 155 children 4-14 yr-old living in an industrial region of Poland. Pure tone audiometric evaluations were performed at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 6000Hz, and 8000 Hz. Basic data on medical history, limited information on sociodemographic covariates such as family structure and income. | Blood Pb at the time of testing<br>Blood Pb median 7.2 (range 1.9-28) µg/dL | Higher blood Pb concentrations were significantly associated with increased hearing thresholds at all frequencies studied. This relationship remained significant when analyses were limited to subjects with blood Pb levels below 10 µg/dL. Authors conclude that auditory function in children is impaired at blood Pb concentrations below 10 µg/dL. |

## Table AX6-2.8. Effects of Lead on Neuromotor Function in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Dietrich et al. (1993b); Bhattacharya et al. (1995); Ris et al. (2004)<br>U.S. | Design: Prospective longitudinal. Relationship between Pb exposure and neuromotor function has been examined in several studies on the Cincinnati Pb Study Cohort from 6 to 17 yrs of age. At 6 yrs of age 245 subjects were administered the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP); at 6-10 yrs of age subjects were assessed for postural instability using a microprocessor-based strain gauge platform system and at 16-17 yrs of age the fine-motor skills of study subjects were assessed with the grooved pegboard and finger tapping tasks (part of a comprehensive neuropsychological battery). Extensive measurement of medical and sociodemographic factors. | Prenatal (maternal) and serial postnatal blood Pb assessments<br>Prenatal blood Pb 8.3 (SD 3.7) µg/dL<br>Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL | Following covariate adjustment, postnatal Pb exposure was significantly associated with poorer scores on BOTMP measures of bilateral coordination, visual-motor control, upper-limb speed and dexterity and the Fine Motor Composite score. Low-level neonatal blood Pb concentrations were also significantly associated with poorer scores on the aforementioned subtests, as well as measures of visual-motor control. Postnatal Pb exposure was significantly associated with greater postural instability in 6-10 yr-old subjects and poorer fine-motor coordination when examined at 16-17 yrs.<br>Authors conclude that effects of early Pb exposure extend into a number of dimensions of neuromotor development. |
| **Europe** | | | |
| Wasserman et al. (2000a)<br>Yugoslavia | Design: Prospective longitudinal. Birth cohort of ~300-400 infants followed since birth residing in two towns in Kosovo, Yugoslavia, one group near a longstanding Pb smelter and battery manufacturing facility and another in a relatively unexposed location 25 miles away. 283 children at age 54 mos were administered the Beery Developmental Test of Visual-Motor Integration (VMI) and the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP). Extensive measurement of medical and sociodemographic factors. | Maternal prenatal, umbilical cord and serial postnatal blood Pb<br><br>Maternal blood Pb in exposed area 19.9 (SD 7.7) µg/dL, unexposed area 5.6 (SD 2.0) µg/dL<br><br>Umbilical cord blood Pb in exposed area 22.2 (SD 8.1) µg/dL, unexposed area 5.5 (SD 3.3) µg/dL<br><br>Blood Pb at 2 yrs in exposed area 35.4 µg/dL, unexposed area 8.5 µg/dL | Following covariate-adjustment, the log avg of serial blood Pb assessments to 54 mos was associated with lower Fine Motor Composite and VMI scores. Pb exposure was unrelated to gross motor performance. With covariate adjustment, an increase in avg blood Pb from 10 to 20 µg/dL was associated with a loss of 0.62 and 0.42 points respectively, in Fine Motor Composite and VMI. Authors noted that other factors such as indicators of greater stimulation in the home make a larger contribution to motor development than Pb. |

## Table AX6-2.9. Effects of Lead on Direct Measures of Brain Anatomical Development and Activity in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Trope et al. (1998) U.S. | Design: Case-control. One 10 yr-old subject with history of Pb poisoning and unexposed 9 yr-old cousin. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) were used to assess differences in cortical structures and evidence of neuronal loss. This was the first study to attempt to determine in vivo structural and/or metabolic differences in the brain of a child exposed to Pb compared with a healthy control. | Blood Pb<br>Pb poisoned case 51 µg/dL at 38 mo<br>Unexposed control not reported. | Both children presented with normal volumetric MRI. MRS revealed a significant alteration in brain metabolites, with a reduction in N-acetylaspartate:creatine ratio for both gray and white matter compared to the subject's cousin. Authors conclude that results suggest neuronal loss related to earlier Pb exposure. |
| Trope et al. (2001) U.S. | Design: Case-control. 16 subjects with a history of elevated blood Pb levels before 5 yrs of age and 5 age-matched siblings or cousins were evaluated. Avg age at time of evaluation was 8 yrs. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) were used to assess differences in cortical structures and evidence of neuronal loss. | Blood Pb<br>Range in Pb-exposed 23 to 65 µg/dL<br>Controls <10 µg/dL | All children had normal MRI examinations, but Pb-exposed subjects exhibited a significant reduction in N-acetylaspartate:creatine and pohosphocreatine ratios in frontal gray matter compared to controls. Authors conclude that Pb has an effect on brain metabolites in cortical gray matter suggestive of neuronal loss. |
| Cecil et al. (2005) U.S. | Design: Prospective/longitudinal. 48 young adults ages 20 to 23 yrs were re-examined. Functional MRI (fMRI) was used to examine the influence of childhood Pb exposure on language function. Subjects performed a verb generation/finger-tapping paradigm. Extensive measurement of medical and sociodemographic covariates | Blood Pb<br>Avg childhood blood Pb 13.9 (SD 6.6, range 4.8-31.1) µg/dL | Higher avg childhood blood Pb levels was significantly associated with reduced activation in Broca's area in the left hemisphere and increased activation in the right temporal lobe, the homologue of Wernicke'a area in the left hemisphere. Authors conclude that elevated childhood Pb exposure strongly influences neural substrates of semantic language function on normal language areas with concomitant recruitment of contra-lateral regions resulting in a striking dose-dependent atypical organization of language function. |

## Table AX6-2.9 (cont'd). Effects of Lead on Direct Measures of Brain Anatomical Development and Activity in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Rothenberg et al. (2000) Mexico | Design: Prospective/longitudinal. 113 5-7 yr-old children from the Mexico City Prospective Study were re-examined. Brain stem auditory evoked potentials were recorded to assess the impact of prenatal and postnatal Pb exposure on development of auditory pathways. Results adjusted for gender and head circumference. | Blood Pb<br>Prenatal (20 wks) 8.1 (SD 4.1) µg/dL<br>Cord 8.7 (SD 4.3) µg/dL<br>Postnatal 18 mo 10.8 (SD 5.2) µg/dL | Prenatal blood Pb at 20 wks was associated with decreased interpeak intervals. After fitting a nonlinear model to these data, I-V and III-V interpeak intervals decreased as blood Pb rose from 1 to 8 µg/dL and increased as blood Pb rose from 8 to 30 µg/dL. Increased blood Pb at 12 and 48 mos was related to decreased conduction intervals for I-V and II-V across the entire blood Pb range suggesting pathway length effects. |
| **Asia** | | | |
| Meng et al. (2005) China | Design: Case-control. 6 subjects with blood Pb concentrations ∃27 µg/dL and 6 controls with blood Pb concentrations <10 µg/dL were evaluated with Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy to evaluate structural abnormalities and differences in N-acetylaspartate, creatine, and choline in frontal lobes and hippocampus of cases and controls. | Blood Pb<br>Cases 37.7 (SD 5.7) µg/dL<br>Controls 5.4 (SD 1.5) µg/dL | All children presented with normal MRI. Peak values of N-acetylaspartate, choline, and creatine in all four brain regions were reduced in Pb exposed children relative to controls. Authors conclude that reduced brain N-acetylaspartate in cases may be related to decreased neuronal density or loss. Reduced choline signal may indicate decreased cell membrane turnover or myelin alterations while lower creatine may indicate reduced neuronal cell viability. |

## Table AX6-2.10. Reversibility of Lead-related Deficits in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Ruff et al. (1993)<br>U.S. | Design: Intervention study, non-randomized. 126 children with complete data age 13 to 87 mos and with blood Pb levels between 25 and 55 µg/dL were given chelation with ETDA and/or therapeutic iron where indicated. At baseline and follow-up, patients were evaluated with the Bayley Scales of Infant Development, Mental Development Index, or Stanford Binet Scales of Intelligence depending upon age. | Blood Pb at time of treatment<br>Blood Pb 31.2 (SD 6.5) µg/dL | Without respect to treatment regimen, changes in performance on cognitive measures after 6 mos were significantly related to changes in blood Pb levels after control for confounding factors. Standardized scores on tests increased 1 point for every 3 µg/dL decrement in blood Pb. |
| Rogan et al. (2001); Dietrich et al. (2004)<br>U.S. | Design: Double blind, placebo-controlled randomized clinical trial. The Treatment of Pb-Exposed Children (TLC) clinical trial of 780 children in 4 centers was designed to determine if children with moderately elevated blood Pb concentrations given succimer would have better neuropsychological outcomes than children given placebo. Children between 12 and 33 mos of age were evaluated 3 yrs following treatments and again at 7 and 7.5 yrs of age. A wide range of neurological, neuropsychological, and behavioral tests was administered. Assessment of potentially confounding factors included sociodemographics and parental IQ. | Blood Pb<br>Baseline blood Pb 26 (SD 26.5) µg/dL in both drug and placebo groups | Succimer was effective in lowering blood Pb levels in subjects on active drug during the first 6 mos of the trial. However, after 1 yr differences in the blood Pb levels of succimer and placebo groups had virtually disappears. 3 yrs following treatment, no statistically significant differences between active drug and placebo groups were observed for IQ or other more focused neuropsychological and behavioral measures. When evaluated at 7 and 7.5 yrs of age, TLC could demonstrate no benefits of earlier treatment on an extensive battery of cognitive, neurological, behavioral and neuromotor endpoints. Authors conclude that the TLC regimen of chelation therapy is not associated with neurodevelopmental benefits in children with blood Pb levels between 20 and 44 µg/dL and that these results emphasize the importance of taking environmental measures to prevent exposure to Pb in light of the apparent irreversibility of Pb-associated neurodevelopmental deficits. |

## Table AX6-2.10 (cont'd). Reversibility of Lead-related Deficits in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Liu et al. (2002)<br>U.S. | Design: Prospective longitudinal clinical trial. Data from the Treatment of Pb-Exposed Children (TLC) used to examine prospective relationships between falling blood Pb levels and changes in cognitive functioning. 741 children recruited between 13 and 33 mos of age were assessed at baseline and 6 mos later with the Bayley Mental Development Index (MDI) and 36 mos post-randomization with the Wechsler Preschool and Primary Scales of Intelligence-Revised to obtain IQ. | Blood Pb<br>Baseline blood Pb 26.2 (SD 5.1) µg/dL<br>36 mos post-randomization blood Pb 12.2 (SD 5.2) µg/dL | TLC found no overall effect of changing blood Pb level on change in cognitive test scores from baseline to 6 mos. Slope estimated to be 0.0 points per 10 µg/dL change in blood Pb. From baseline to 36 mos and 6 mos to 36 mos, falling blood Pb levels were significantly associated with increased cognitive test scores, but only because of an association in the placebo group. Authors conclude that because improvements were not observed in all children, the data do not provide support that Pb-induced cognitive impairments are reversible. Although the possible neurotoxicity of succimer cannot be ruled out. |
| **Latin America** | | | |
| Kordas et al. (2005); Rico et al. (2006)<br>Mexico | Design: Double-blind, placebo-controlled nutritional supplementation clinical trial conducted among 602 1st grade children ages 6-8 yrs in Torreón, Mexico. Subjects received iron, zinc, both or placebo for 6 mos. Parents and teachers filled out the Conners Rating Scales at baseline and follow-up six mos following the end of supplementation to index behavioral changes following therapy. In addition, 11 cognitive tests of memory, attention, visual-spatial abilities, and learning were administered, including WISCR-M at baseline and follow-up 6 mos later. | Blood Pb<br>Baseline blood Pb 11.5 (SD 6.1) µg/dL | No significant effects of treatment on behavior or cognition could be detected with any consistency. Authors conclude that this regimen of supplementation does not result in improvements in ratings of behavior or cognitive performance. |
| **Australia** | | | |
| Tong et al. (1998)<br>Australia | Design: Prospective longitudinal. 375 children from the Port Pirie Prospective Study were followed from birth to the age of 11-13 yrs. Bayley Mental Development Index (MDI) at 2 yrs, the McCarthy Scales General Cognitive Index (GCI) and IQs from the Wechsler Intelligence Scale served as the primary indicators of intellectual status. The purpose of the study was to assess the reversibility of Pb effects on cognition in relationship to declines in blood Pb over time. | Postnatal blood Pb<br>Mean blood Pb at 2 yrs 21.2 µg/dL declining to 7.9 µg/dL at 11-13 yrs | Although blood Pb levels declined substantially, covariate adjusted scores on standardized measures of intellectual attainment administered at 2, 4, 7, and 11-13 yrs of age were unrelated to declining body burden. Authors conclude that effects of early exposure to Pb during childhood are not reversed by a subsequent decline in blood Pb concentration. |

# ANNEX TABLES AX6-3

## Table AX6-3.1. Neurobehavioral Effects Associated with Environmental Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Krieg et al. (2005)<br>1988-1994<br>U.S. | 4,937 adults aged 20-59 yrs from NHANES III completed three neurobehavioral tests. Regression analyses of neurobehaqvioral test and log of blood Pb concentration adjusted for sex, age education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase. | Mean blood Pb 3.3 µg/dL<br>Range 0.7 to 41.7 µg/dL | No statistically significant relationship between blood Pb concentration and mean simple reaction time, symbol-digit substitution latency and errors and serial digit learning trials to criterion and total score after adjustments for covariates. |
| Muldoon et al. (1996)<br>U.S. | 325 women from rural location (mean age 71) and 205 women from a city location (mean age 69) participants in the Study for Osteoporotic Fractures had the association of nonoccupational Pb exposure and cognitive function examined. Logistic regression determined effect of blood Pb on neuropsychological performance. | Rural group<br>Blood Pb 5 µg/dL<br>Urban group<br>Blood Pb 5 µg/dL | Groups were significantly different with the urban group more educated and smoked and drank more. Performance in each group stratified by exposure into three groups (low <4 µg/dL, medium 4-7 µg/dL, high >7 µg/dL rural and >8 µg/dL) — no significant associations were present in the urban group but the rural group had significantly poorer performance with increasing blood Pb for Trails B (OR = 2.6 [95% CI: 1.04, 6.49]), Digit Symbol (OR = 3.73 [95% CI: 1.57, 8.84]),and Reaction Time in the lower (OR = 2.84 [95% CI: 1.19, 6.74]) and upper extremities (OR = 2.43 [95% CI: 1.01, 5.83]). The fact that marked differences exist between the low Pb groups for rural and urban (the lowest 15th percentile) suggests the differences between the two groups are unrelated to Pb. Response time for reaction time across Pb groups increased for the rural group and decreased or remained the same for the urban group. As response time is sensitive to Pb effect, this raises question whether factors not measured accounted for difference. Namely MMSE for the whole population was 25 (15-26) with poorer performance in the rural group. The clinical cutoff score for MMSE is 24 suggesting the presence of clinical cognitive disorders. Even though this is a simple neuropsychological battery up to 9 were unable to perform some of the tests including 3 on the MMSE. |

## Table AX6-3.1 (cont'd). Neurobehavioral Effects Associated with Environmental Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Payton et al. (1998)<br>U.S. | 141 healthy men in VA normal aging study evaluated every 3 to 5 yrs with cognitive battery and blood Pb and once a measurement of patella and tibia bone Pb. Statistics are confusing as it is not clear when ANCOVA is used and how the groups are created. | Mean blood Pb 6 µg/dL<br>Mean patella bone Pb 32 µg/g<br>Mean tibia bone Pb 23 µg/g bone mineral | Regressions adjusted for age and education found significant relationship of blood Pb with Pattern Comparison (perceptual speed), Vocabulary, Word List Memory, Constructional Praxis, Boston Naming Test, and Verbal Fluency Test. Only for Constructional Praxis were bone Pb and blood Pb significantly associated. Mechanism most sensitive to low levels Pb exposure believed to be response speed. Vocabulary is significantly associated with blood Pb. Education is negatively correlated to bone and blood Pb. It is not clear how multiple comparisons were handled |
| Rhodes et al. (2003)<br>U.S. | 526 participants with mean age 67 yrs, 47% had education level of high school or less. Mood symptoms evaluated with Brief Symptom Inventory (BSI). Use of logistic regression adjusting for covariates examined association of BSI scales and blood Pb and bone Pb levels. | Mean blood Pb 6 µg/dL<br>Mean tibia Pb 22 µg/g<br>Mean patella Pb 32 µg/g | BSI found mood symptoms for anxiety and depression were potentially associated with bone Pb levels. Education was inversely related to bone Pb and high school graduates had significantly higher odds of Global Severity Index and Positive Symptom Total. |
| Wright et al. (2003)<br>U.S. | 736 healthy men (mean age 68) in Normative Aging Study examined every 3 to 5 yrs were administered the Mini-Mental State Exam (MMSE). Linear regression examined relationship of MMSE and blood Pb, patella and tibia bone Pb measurements after adjusting for covariates. | Mean blood Pb 5 µg/dL,<br>Mean patella bone Pb 30 µg/g<br>Mean tibia bone Pb 22 µg/g | Mean MMSE score 27. Relation of MMSE scores <24 (n = 41) and blood Pb by logistic regression found OR = 1.21 (95% CI: 1.07, 1.36) and for patella Pb OR = 1.21 (95% CI: 1.00, 1.03) and tibia Pb OR = 1.02 (95% CI: 1.00, 1.04). Risk of MMSE <24 when comparing the lowest and highest quartiles of patella Pb was 2.1 (95% CI: 1.1, 4.1), for tibia Pb was 2.2 (95% CI: 1.1, 3.8) and blood Pb was 3.4 (95% CI: 1.6, 7.2). Interaction between patella Pb and age, and blood Pb and age in predicting MMSE found steeper decrease in MMSE score relative to age in the higher quartiles of patella Pb and blood Pb.<br><br>MMSE very sensitive to yrs of education below 8 yrs. In this study 213 subjects had less than high school education. If the community dwelling population had older individuals with less education living in areas with higher past pollution the confounding may be impossible to sort out. Initially at beginning of NAS subjects were eliminated with chronic medical problems or blood pressure >140/90. It is not addressed how the development of medical conditions during the duration of the study are handled. |

## Table AX6-3.1 (cont'd). Neurobehavioral Effects Associated with Environmental Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Weisskopf et al. (2004b)<br>U.S. | 466 men, mean age 70 yrs, in the VA Normative Aging Study had 2 MMSE tests 3.5 yrs apart. | Mean blood Pb 4 µg/dL<br>Mean patella bone Pb 23 µg/g<br>Mean tibia bone Pb 19 µg/g | Baseline mean MMSE score was 27 and mean change in MMSE score over 3.5 yrs was 0.3. Change in MMSE associated with one interquartile range increment for bone Pb and blood Pb found relationship between patella Pb and change in MMSE was unstable when patella Pb is ∃90 µg/g bone mineral. Examination of patella Pb below this level found a greater inverse association with MMSE at lower Pb concentrations (∃ = !0.25 [95% CI: !0.45, !0.05]). A similar but weaker association existed for tibia Pb when values ∃67 µg/g bone mineral were removed (∃ = !0.19 [95% CI: !0.39, 0.02]). There was no association of MMSE change and blood Pb (∃ = !0.01 [95% CI: !0.13, 0.11]). There was no interaction of age and bone Pb. These are very high bone Pb levels for environmental exposure. The biological plausibility of change in the MMSE over 3.5 yrs would have been reinforced if the change by functional domain in the MMSE was provided. |
| **Europe** | | | |
| Nordberg et al. (2000)<br>Sweden | 762 participants, mean age 88 yrs, in a study of aging and dementia examined MMSE. Used blood Pb as dependent and examined contribution of covariates and MMSE. | Mean blood Pb 3.7 µg/dL | Mean MMSE 25 found no relation of blood Pb and MMSE. In this population was fairly homogenous, all elderly Swedes, and the likelihood of prior exposure to elevated Pb levels was low. |

## Table AX6-3.2. Symptoms Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** | | | |
| Lindgren et al. (1999) Canada | Smelter workers (n = 467) with a mean age of 40 yrs completed the Profile of Mood Scale. Factor structure of POMS validated in this occupational population. Regression analysis determined association with Pb exposure. | Mean (SD, range) blood Pb 28 (8.5, 4-62) µg/dL<br><br>Mean (SD, range) IBL 711 (415.5, 1-1537) µg·yr/dL | Factor analysis found one factor labeled "general distress" composed of POMS subscales anger, confusion, depression, fatigue and tension and a second factor labeled 'psychological adjustment.' IBL was significantly associated with 'general distress' after adjustment for the covariates ($\exists$ = 0.28 [SE 1.51 H $10^{14}$], p = 0.01) while there was no relation with blood Pb. The factor structure of POMS originally validated in a clinical population had six mood subscales however the factor structure in this occupational population was found to have only two subscales. |
| Holness et al. (1988) Canada | 47 demolition workers with acute Pb intoxication - Phase 1 - were followed with blood Pb and symptoms during engineering modifications to control exposure – Phases 2-4. Workers stratified by blood Pb and symptom frequency was analyzed. | Phase I - Mean blood Pb 59 µg/dL<br>Phase 2 - Mean blood Pb 30 µg/dL<br>Phase 3 - Mean blood Pb 19 µg/dL<br>Phase 4 - Mean blood Pb 17 µg/dL | Below blood Pb <50 µg/dL, workers reported symptoms of fatigue (25%), headache (14%), dizzy (9%), sleep (8%), abdominal cramps (8%), muscle ache (8%), paresthesiae (8%), appetite (7%), constipation (6%), and weakness (6%). All symptoms were significantly lower except for paresthesiae when compared to group with blood Pb >70 µg/dL. Of interest, at beginning of Phase 4 when mean blood Pb was 13 µg/dL, no symptoms were reported. At the end of Phase 4, mean blood Pb was 17 µg/dL and one worker complained of fatigue. |
| **Europe** | | | |
| Lucchini et al. (2000) Italy | 66 workers in Pb manufacturing, mean age 40 (8.7) yrs and 86 controls mean age 43 (8.8) yrs were administered a questionnaire with neuropsychological (14 items), sensory-motor (3 items), memory (4 items) and extrapyramidal (8 items), 10 Parkinson symptoms and the Mood Scale. Group comparisons and linear regression examined relationship of symptoms and Pb exposure. | Pb workers<br>Mean (SD, range) blood Pb 27 (11.0, 6-61) µg/dL<br>Mean (SD, range) TWA 32 (14.1, 6-61) µg/dL<br>Mean (SD, range) IBL 410 (360.8, 8-1315) µg·yr/dL<br><br>Controls<br>Mean (SD, range) blood Pb 8 (4.5, 2-21) µg/dL | Pb exposed worker reported confusion, somnolence, abnormal fatigue, irritability, and muscular pain more frequently (p < 0.04). There were no group differences for the parkinsonism symptoms or Mood Scale. Linear regression combing exposed and control group found neurological symptoms significantly associated with blood Pb r = 0.22, p = 0.006). Neuropsychological symptoms were significantly higher in the High-IBL compared to the Low-IBL group. The estimated threshold for a significant increase (prevalence of 5%) of a high score for neurological symptoms was at a blood Pb of 12 µg/dL. |

## Table AX6-3.2 (cont'd). Symptoms Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Maizlish et al. (1995)<br>Venezuela | 43 workers from a Pb smelter, mean age 34 (9) yrs and 47 nonexposed workers, mean age 35 (11) yrs completed the profile of mood states (POMS) questionnaire and a questionnaire of symptoms of the central and peripheral nervous system, and gastrointestinal. Prevalence ratios used to examine symptoms and Pb. ANCOVA and linear regression adjusting for potential confounders examined relationship of Pb exposure and POMS. | Pb workers<br>Mean (SD) blood Pb 43 (12.1) µg/dL<br>Mean (SD) peak blood Pb 60 (20.3) µg/dL<br>Mean (SD) TWA 48 (12.1) µg/dL<br><br>Controls<br>Mean (SD) blood Pb 15 (6) µg/dL<br>Mean (SD) peak blood Pb 15 (6) µg/dL<br>Mean (SD) TWA 15 (SD 6) µg/dL | Significantly increased relative risks found for difficulty concentrating (RR = 1.8 [95% CI: 1.0, 3.1]), often being angry or upset without reason (RR = 2.2 [95% CI: 1.2, 4.1]), feeling abnormally tired (RR = 2.2 [95% CI: 0.9, 5.3]) and joint pain (RR = 1.8 [95% CI: 1.0, 3.3]). The six subscales of the POMS were not significantly different between the exposed and control groups. However dose-related analysis found significantly poorer scores for tension-anxiety and blood Pb ($p = 0.009$), hostility and blood Pb ($p = 0.01$) and TWA ($p = 0.04$), and depression and blood Pb ($p = 0.003$) and peak Pb ($p = 0.003$) and TWA ($p = 0.004$). |
| **Asia** | | | |
| Schwartz et al. (2001a)<br>Korea | 803 Pb-exposed Korean workers, mean age 40 yrs completed the Center for Epidemiologic Studies Depression Scale. Linear regression examined for association of CES-D and Pb biomarkers after adjusting for the covariates. | Mean (SD) blood Pb 32 (15.0) µg/dL<br>Mean (SD) tibia Pb 37 (40.3) µg/g bone mineral | After adjustment for age, gender and education significant associations found for CES-D and tibia Pb ($\exists = 0.0021$ [SE 0.0008]; $p < 0.01$) but not with blood Pb. This occupational Pb-exposed populations had higher past Pb exposure compared to the current mean blood Pb of 32 µg/dL. |
| Lee et al. (2000)<br>Korea | 95 Korean Pb exposed workers, mean age 43 yrs, completed questionnaire of Pb-related symptoms present over last three mos. Relationship between symptom score and measures of Pb exposure assessed by linear regression. Logistic regression use to model presence or absence of symptoms for gastrointestinal, neuromuscular, and general. | DMSA-chelatable Pb Mean (SD) 289 (167.7) µg<br>Mean (SD) ZPP 108 (60.6) µg/dL<br>Mean (SD) ALAU3 (2.8) mg/L<br>Mean(SD) blood Pb 45 (SD 9.3) µg/dL | Workers with DMSA-chelatable Pb above the median of 261 µg were 6.2 (95% CI: 2.4, 17.8) times more likely to have tingling or numbness in their extremities, 3.3 (95% CI: 1.2, 10.5) times more likely to experience muscle pain and 3.2 (95% CI: 1.3, 7.9) times more likely to feel irritable. The workers with higher chelatable Pb were 7.8 (95% CI: 2.8, 24.5) times more likely to experience neuromuscular symptoms compared to workers with lower chelatable Pb. In this study ZPP predicted weakness of ankle and wrist (OR = 2.9 [95% CI: 1.1, 8.1]) and fatigue (OR = 2.9 [95% CI: 1.1, 8.7]) while ALAU predicted inability to sleep (OR = 5.4 [95% CI: 1.2, 33.2]) and blood Pb was not significantly associated with any symptoms. A measure of Pb in bioavailable storage pools was the strongest predictor of symptoms particularly neuromuscular. |

## Table AX6-3.2 (cont'd). Symptoms Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Niu et al. (2000)<br>China | 44 Pb-exposed workers (17 men, 27 women) from Pb printing houses, mean age 35 (4.9) and education 9.3 (no SD) yrs and 34 controls (19 men and 15 women), mean age 33 (7.4) yrs and education 9.5 (no SD) yrs completed the profile of mood state as part of the NCTB. ANCOVA controlling for age, sex and education examined group differences and linear regression for dose-response relationship. | Mean blood Pb 29 (SD 26.5) µg/dL (8 workers blood Pb exceeded 50 µg/dL)<br><br>Controls<br>Mean blood Pb 13 (SD 9.9) µg/dL (1 control blood Pb exceeded 50 µg/dL) | POMS subscales for confusion ($F = 3.02$, $p < 0.01$), fatigue ($F = 3.61$, $p < 0.01$), and tension ($F = 2.82$, $p < 0.01$) were significantly elevated in the Pb exposed group. Regression analyses found a dose response (data not shown). |

## Table AX6-3.3. Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Fiedler et al. (2003)<br>New Jersey | 40 workers with Pb exposure, mean age 48 (9.5) yrs completed a neurobehavioral battery and was compared to 45 Pb/solvent workers, mean age 47 (10.2), 39 solvent exposed workers, mean age 43 (9.4), and 33 controls, mean age 44 (10.2). Group differences and dose-effect relationships were assessed after adjusting for potential confounding. | Mean (SD) blood Pb µg/dL; mean (SD) bone Pb ppm (dry weight)<br>Pb workers<br>14 (11.7); 2.7 (0.7)<br>Pb/Solvent workers<br>12 (11.6); 2.8 (0.6)<br>Solvent workers<br>5 (4.1); !1.8 (1.8)<br>Controls<br>4 (1.4); !1.1 (1.6) | Of nineteen outcomes, significant differences found on the California verbal learning test (CVLT) ($p = 0.05$) and positive symptom distress index on the Symptom checklist-90-R. On the CVLT the controls performed significantly better on trials 2 and 3 demonstrating efficiency of verbal learning. Symbol digit substitution (SDS) approached significance ($p = 0.09$) with Pb and Pb/solvent group slower on latency of response but not accuracy. Bone Pb was a significant predictor of latency of response on SDS, total errors on paced auditory serial addition task and simple reaction time non-preferred hand. Bone Pb and SRT, preferred hand approached significance. This is a confusing study design as bone Pb is used as a predictor in workers both with and without occupational Pb exposure. |
| **Canada** | | | |
| Lindgren et al. (1996)<br>Canada | 467 Canadian former and current, French and English speaking Pb smelter workers, mean age 43 (11.0) yrs and education 10 (3.2) yrs were administered a neuropsychological battery in English or French. Data analyses used MANCOVA adjusting for age, education, measure of depressive symptoms and self reported alcohol use. | Mean (SD) yrs employment 18 (7.4)<br>Mean (SD) blood Pb 28 (8.4) µg/dL<br>Mean (SD) TWA 40 (4-66) µg/dL<br>Mean (SD) IBL 765 (1-1626) µg·yr/dL | Fourteen neuropsychological variables examined by MANCOVA with the grouping variable exposure (high, medium and low) and the covariates, age, education, CES-D, and alcohol use found no exposure term significant until yrs of employment, a suppressor term, was added as a covariate. IBL exposure groups differed significantly (df 2,417) on digit symbol ($F = 3.03$, $p = 0.05$), logical memory ($F = 3.29$, $P = 0.04$), Purdue dominant hand ($F = 4.89$, $p = 0.01$), and trails A ($F = 3.89$, $p = 0.02$) and B ($F = 3.2$, $p = 0.04$). This study showed a dose-effect relationship between cumulative Pb exposure (IBL) and neuropsychological performance at a time when there was no association with current blood Pb. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** (cont'd) | | | |
| Bleecker et al. (2002) Canada | 256 smelter workers from the above population were currently employed and took the test battery in English. Their mean age was 41 (7.9) yrs, and education 10 (2.8) yrs. The goal was to determine if educational achievement as measured by WRAT-R Reading modified performance on MMSE. Linear regression assessed the contribution of age, WRAT-R, education, alcohol intake, cigarette use, IBL and IBLHWRAT-R on MMSE performance. | Mean (SD) blood Pb 28 (8.8) µg/dL<br>Mean (SD) IBL 725 (434) µg·yr/dL | MMSE had a median (range) score of 29 (19-30). The most common errors were recall of 3 items (38%), spell world backwards (31%), repetition of "no ifs ands or buts" (21%) and copy a design to two intersecting pentagons (16%). WRAT-R reading used as an additional measure of educational achievement because it was a stronger predictor of MMSE performance than yrs of education. The significant interaction (♠$R^2$ = 2%, p = 0.01) explained by a dose-effect between IBL and MMSE only in the 78 workers with a WRAT-R reading grade level less than 6. The workers with higher reading grade levels and the same cumulative Pb exposure were able to compensate for the effects of Pb on the MMSE because of increased cognitive reserve. |
| Bleecker et al. (2005a) Canada | 256 smelter workers currently employed and took the test battery in English. Their mean age was 41 (7.9) yrs, and education 10 (2.8) yrs. The purpose was to determine whether components of verbal memory as measured on the Rey Auditory Verbal Learning Test (RAVLT) were differentially affected by Pb exposure. Linear regression and ANCOVA assessed the relationship of Pb and components of verbal learning and memory. | Mean (SD) blood Pb 28 (8.8) µg/dL<br>Mean (SD) TWA 39 (12.3) µg/dL<br>Mean (SD) IBL 725 (434) µg·yr/dL | Outcome variables RAVLT a word list test included measures of immediate memory span and attention (Trial 1), best learning (Trial V), incremental learning across the five trials (Total Score), and storage (Recognition) and retrieval (Delayed Recall) of verbal material. TWA significantly contributed to the explanation of variance for Trial V (♠$R^2$ = 1.4%, p < 0.03) and Delayed Recall (♠$R^2$ = 1.4%, p = 0.03) after adjusting for age and WRAT-R while IBL did the same with Recognition (♠$R^2$ = 2.0%, p = <0.02) and Delayed Recall (♠$R^2$ = 1.1%, p = 0.06). Workers stratified into 3 group by increasing clinical memory difficulties-Group1 had normal encoding, storage and retrieval; Group2 could encode and store verbal information but had difficulty with retrieval and Group 3 had abnormal encoding, storage and retrieval but was still able to learn new verbal information. ANCOVA adjusting for age and WRAT-R compared Pb exposure across the memory groups. Blood Pb showed no difference but TWA and IBL were significantly higher in Group 3 compared to Group 1 (p < 0.05 for both). Internal strategies used on the RAVLT over the five trials found that Groups 1 and 2 remembered more words from the beginning of the list while group 3 remembered more from the end. At a time when blood Pb was not associated with performance, cumulative Pb exposure resulted in poorer storage and retrieval of previously learned material. Alterations in the ability to organize materials in long term memory interferes with retrieval efficiency. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** (cont'd) | | | |
| Bleecker et al. (1997a)<br>New Brunswick<br>1992-1993 | The performance of the 467 current and retired smelter workers as described in Lindgren et al. (1996) administered a screening neuropsychological battery by testers blinded to the degree of Pb exposure of the worker had their performance compared to age matched norms. If performance on two or more tests in any functional domain was below 1.5 standard deviations the worker was invited for a complete clinical evaluation. Eighty current workers were identified by this criterion. Mean yrs - age 44 (8.4) yrs, education 8 (2.8) yrs and duration employed 20 (5.3) yrs. Five neuropsychological tests commonly associated with Pb exposure were examined for a differential association with blood Pb, IBL,TWA and bone Pb. | Mean (SD) blood Pb 26 (7.07) µg/dL<br>Mean (SD) TWA 42 (8.4) µg/dL<br>Mean (SD) IBL 903 (305.9) µg·yr/dL,<br>Mean (SD) tibial bone Pb 41 µg/g bone mineral | Relationship of 5 neuropsychological tests with 4 measures of Pb dose after adjusting for age age$^2$ and education, education$^2$ found RAVLT trial V and Verbal Paired Associates were associated with blood Pb (♠$R^2$ = 6.2%, p = 0.02; ♠$R^2$ = 5.5%, p = 0.07) and TWA (♠$R^2$ = 3.2%, p = 0.09; ♠$R^2$ = 13.9%; P = 0.00) while Digit Symbol and Grooved Pegboard were associated with TWA (♠$R^2$ = 6.1%, p = 0.00; ♠$R^2$ = 5.5%, p = 0.02) and IBL (♠$R^2$ = 4.8%, p = 0.01; ♠$R^2$ = 5.7%, p = 0.02). Only grooved pegboard was associated with bone Pb (♠$R^2$ = 4.2%, p = 0.05). Block design was not associated with any measures of Pb dose. Age was an effect modifier with grooved pegboard. There was enhanced slowing in older workers when compared to younger workers with the identical IBL. |
| Bleecker et al. (1997b)<br>New Brunswick<br>1992-1993 | Of the 80 current smelter workers described above 78 completed a simple visual reaction time (SRT) and had mean yrs age 44 (8.2) yrs, education 8 (7.2) yrs and duration employed 20 (5.6) yrs. | Mean (SD) blood Pb, 26 (7.2) µg/dL<br>Mean (SD) blood Pb from bone 7 (4.2) µg/dL<br>Mean (SD) blood Pb from environment 19 (7.0) µg/dL<br>Mean (SD) bone Pb 40 (25.2) µg/g bone mineral | SRT consisted of 44 responses to a visual stimulus at interstimulus intervals (ISI) varying between 1 through 10 seconds with a mean SRT (median) of 262 (179 to 387) ms. Blood Pb and median SRT had a curvilinear relationship $R^2$ = Pb + Pb$^2$, 13.7%, p < 0.01) after adjusting for age and education with slowing of SRT beginning at a blood Pb of ~30 µg/dL. No relationship existed between bone Pb and SRT. There was a stronger association between Pb and Pb$^2$ and SRT for the longer ISIs of 6 to 10 seconds ($R^2$ = 13.9%, p < 0.01), as age was significantly related to the shorter ISI = s but not the longer ones. In this population the contribution of bone Pb to blood Pb had been previously where estimated where for a bone Pb level of 100 µg Pb/g bone mineral, 17 µg Pb/dL of the blood Pb was derived from internal bone stores with the remainder from the environment. Blood Pb was fractionated to that from bone (blood Pb-bn) vs. blood Pb from the environment (blood Pb-en). Regression analysis to examine the relationship of blood Pb-bn and blood Pb-en and SRT after adjusting for the covariates found significant contribution to the variance of SRT only for blood Pb-en ($R^2$ for blood Pb-en + blood Pb-en$^2$ = 14.4%, p < 0.01). The absence of a contribution by age and more stable responses with ISIs of 6 to 10 sec supports using this component of SRT. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** (cont'd) | | | |
| Lindgren et al. (2003)<br>New Brunswick<br>1992-1993 | In an attempt to separate the effects of past high Pb exposure from a lower proximate exposure, examination of the pattern of Pb levels of the 467 Canadian Pb smelter workers found 40 workers who had high past exposure followed by yrs where 90% of blood Pb were above 40 µg/dL (High-High = H-H) while another group of 40 workers had similar past high Pb exposure followed by yrs where 90% of blood Pb were below 40 µg/dL (High-Low = H-L). The groups did not differ on age, education, yrs of employment or CES-D. Five outcomes examined-Purdue Pegboard assembly, Block Design, Digit Symbol, Rey Auditory Verbal Learning Test-total score, delayed Logical Memory. | Mean (SD) IBL for past exposure<br>H-H 633 (202.2) µg·yr/dL<br>H-L 557 (144.8) µg·yr/dL<br><br>Mean (SD) IBL for the proximate exposure<br>H-H 647 (58.7) µg·yr/dL<br>H-L 409 (46.4) µg·yr/dL<br><br>Mean (SD) blood Pb<br>H-H 37 (5.1) µg/dL<br>H-L 24 (5.2) µg/dL | Of the five neuropsychological measures examined only RAVLT (total score) and Logical Memory (delayed) were significantly different after adjusting for the covariates in the two pattern groups. Use of regression analyses found pattern group contributed significantly ($R^2$ = 4%, $p < 0.05$) to the explanation of variance in RAVLT after accounting for current blood Pb ($R^2$ = 3%, $p < 0.10$) and IBL measures ($R^2$ = 7%, $p < 0.01$). For past IBL, H-H pattern correlated more strongly with RAVLT (r = !0.21) while H-L pattern had no relationship with past exposure (r = 0.08). For proximate IBL the difference was maintained between H-H (r = !0.11) and H-L pattern (r = 0.00). The authors suggested that the absence of an association between past high Pb exposure and verbal memory in the H-L pattern group may reflect reversibility of function when blood Pb is maintained below 40 µg/dL. |
| Braun and Daigneault (1991)<br>Quebec | 41 workers from a secondary Pb smelter, mean age 35 (9.6) yrs and yrs of education 10 (2.1) were compared to a control group mean age 37 (10.1) yrs and yrs of education 11 (1.3) on tests of cognitive and motor function. MANCOVA and dose-effect relationships after adjusting for potential confounders were performed. | Mean (SD) TWA 53 (7.5) µg/dL<br>Mean (SD) maximum blood Pb 87 (22.4) µg/dL | None of the measures of cognitive executive function showed group differences. Partial correlation adjusting for age and education with dose related variables found no statistical significance. On motor function the exposed workers had significantly slower simple reaction time ($p = 0.05$). However partial correlations with measures of dose found dose-effect correlation in both negative and positive directions. Group of exposed workers was mixed for Pb exposure with 11 currently working and the remainder with no exposure up to 84 mos. Also two of the exposed workers had been treated with chelation. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| H≅nninen et al. (1998) Finland | Fifty-four Pb battery workers were stratified by those whose blood Pb never exceeded 50 µg/dL (n = 26) (group 1) and those who had higher exposure in the past (n = 28) (group 2) to examine the neuropsychological effects of current low level blood Pb from higher blood Pb in the past. Mean age group 1was 42 (9.3) yrs, education 8 (1.7) yrs and yrs of exposure 12 (6.7). Mean age group 2 was 47 (6.2) yrs, education 8 (1.0) yrs and yrs of exposure 21 (6.9). Analysis included partial correlations within the groups and ANCOVA within group 1 divided at the median TWA3 of 29 µg/dL. | Group 1<br>Mean IBL 330 µg·yr/dL<br>Maximum blood Pb 40 µg/dL<br>TWA 29 µg/dL<br>Tibial Pb 20 µg/g<br>Calcaneal Pb 79 µg/g<br><br>Group 2<br>Mean IBL 823 µg·yr/dL<br>Maximum blood Pb 69 µg/dL<br>TWA 40 µg/dL<br>Tibial Pb 35 µg/g<br>Calcaneal Pb 100 µg/g<br><br>IBL, TWA and maximum blood Pb were also calculated for the previous 3 yrs with a median TWA3 of 29 µg/dL | Partial correlations controlling for age, sex and education in group 1 found block design, digit symbol, digit span, similarities, Santa Ana 1 and memory for design significantly associated with recent measures of exposure and embedded figures with maximum blood Pb. In group 2 embedded figures, digit symbol, block design, and associative learning were associated with IBL and /or maximum blood Pb. Calcaneal Pb was weakly associated with digit symbol, digit symbol retention, and synonyms. There was no association with tibial Pb in either group. Group 1 divided at the median TWA3 of 29 µg/dL found the high group had lower scores for visuospatial and visuoperceptive tasks (digit symbol, embedded figures and memory for design). Overall past high exposure, blood Pb >50 µg/dL, had the greatest effect on tests requiring the encoding of complex visually presented stimuli. The authors conclude that the effect of Pb on brain function is better reflected by history of blood Pb than content of Pb in bone. |
| Lucchini et al. (2000) Italy | 66 workers in Pb manufacturing, mean age 40 (8.6) yrs, mean education 8 ( 2.4) yrs and mean exposure time 11 (9) yrs and a control group of 86 with mean age 43 (8.8) yrs, mean yrs of education 9 (2.7) yrs. Group differences examined and dose-effect relationship with correlation and ANOVA. | Pb workers<br>Mean (SD) blood Pb 28 (11) µg/dL<br>Mean (SD) IBL 410 (360.8) µg·yr/dL<br>Mean (SD) TWA 32 (14.1) µg/dL<br>Mean (SD) yrs exposed 11(8.1)<br><br>Control<br>Mean (SD) blood Pb 8 4.5) µg/dL | No association with neuropsychological tests (addition, digit span, finger tapping symbol digit and motor test from Luria) and blood Pb, TWA or IBL were found. Blood Pb and visual contrast sensitivities at the high frequencies were significantly associated for the entire group. Blood Pb and serum prolactin in the whole group was significantly associated. Increased prolactin secretion occurs with a variety of neurotoxins and reflects impaired dopamine function in the pituitary. The estimated threshold for a significant increase of high prolactin levels was at a blood Pb of 10 µg/dL. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| _sterberg et al. (1997) Sweden | 38 workers, median age 42 (no range) yrs at a secondary smelter stratified by finger bone Pb concentration and along with 19 controls matched triplets for age, education and job level. Median yrs employed 10 (2-35). | High bone Pb<br>Median (range) bone 32 (17-101) µg/g<br>Median (range) blood Pb 38 (19-50) µg/dL<br>Median (range) peak blood Pb 63 (46-90) µg/dL<br>Median (range) IBL 408 (129-1659) µg·yr/dL<br><br>Low bone Pb<br>Median (range) bone 16 (!7 to 49) µg/g<br>Median (range) blood Pb 34 (17-55) µg/dL<br>Median (range) peak blood Pb 57 (34-78) µg/dL<br>Median (range) IBL 250 (47-835) µg·yr/dL<br><br>Controls<br>Median (range) bone 4 (!19 to 18) µg/g<br>Median (range) blood Pb 4 (1-7) µg/dL | A cognitive test battery (36 tests) covering learning and memory, visuomotor function, visuospatial function, concentration and sustained attention found no impairment or dose-response relationships with any of the markers of Pb exposure. Deviating test scores (belong to 10% lowest reference norms) were less in high bone Pb (1 vs. 4 vs. 4). None of the deviating parameters were significantly correlated with any of the Pb indices. Even when age was taken into account the significant associations between outcome and Pb exposure metrics did not exceed chance in light of the numerous analyses performed. These were the most heavily Pb-exposed workers in Sweden. It was unusual that the 2 visuomotor tasks significantly different had better performance in the Pb-exposed workers compared to the controls. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Stollery et al. (1991)<br>England | Seventy Pb-exposed workers, mean age 41(no SD) yrs, grouped by blood Pb (<20 µg/dL, 21-40 µg/dL and 41-80 µg/dL) examined on three occasions each separated by four mos. Tested on a computer for syntactic reasoning, delayed five choice reaction time, visual spatial memory, and category search task. | Low blood Pb<br>Mean blood Pb 14 µg/dL<br>Mean ZPP 13 mg/dL<br>Mean urinary ALA 2 mg/L<br>Mean yrs exposed 7<br><br>Medium blood Pb<br>Mean blood Pb 31 µg/dL<br>Mean ZPP 33 mg/dL<br>Mean urinary ALA 3 mg/L<br>Mean yrs exposed 10<br><br>High blood Pb<br>Mean blood Pb 52 µg/dL<br>Mean ZPP 77 mg/dL<br>Mean urinary ALA 6 mg/L<br>Mean yrs exposed 11 | Pb exposure was stable over the 8 mos of testing. The low Pb group drank significantly less alcohol and rated their work as less demanding. Performance and exposure stable except in the high Pb group where decision time was slowed more than movement time along with concentration difficulties that remained stable across testing sessions. Movement and decision times were significantly correlated for each duration of waiting. On the memory test of recalled nouns, the memory deficit associated with Pb (r = !0.35, p = 0.003) was restricted to recall of nouns unrelated to task (distracters) (p = 0.04) that did not improve with repetition suggestive of difficulties with incidental learning. Workers with blood Pb >40 µg/dL had impairments that correlated best with avg blood Pb over the preceding 8 mos. Workers with blood Pb between 21 to 40 µg/dL had essentially no impairment. |
| Stollery (1996)<br>England | Same as above except this was a further analysis of the five choice reaction time. | Same as above | Movement and decision slowing was correlated with blood Pb. Slowed movement time was constant across response-stimulus intervals in contrast to decision time that was increasingly affected by Pb especially at the shortest response-stimulus intervals. This supported the finding that decision gaps, central in origin, as opposed to movement gaps are selectively affected by Pb exposure in this population. |
| Barth et al. (2002)<br>Austria | 47 Pb storage-battery workers, mean age 40 (9.7) yrs and 53 nonexposed controls, mean age 39 (8.4) yrs were matched for age and verbal intelligence. Group differences and dose-response relationship were explored. | Pb workers<br>Mean (SD) blood Pb 31 (11.2) µg/dL<br>Mean (SD) IBL 384 (349.0) µg·yr/dL<br>Mean (SD) yrs employed 12 (9.0)<br><br>Controls<br>Mean (SD) blood Pb 4 (2.0) µg/dL | Significant differences were found for block design (p # 0.01), visual recognition (p # 0.01) and Wisconsin card sorting (categories p = 0.0005, total errors p = 0.0025, perseverations p = 0.001, loss of sorting principle p = 0.003) but not SRT or digit symbol. In the exposed group partial correlation adjusting for age found no significant associations with IBL (n = 53). In the entire group the full correlation was significant for blood Pb and Wisconsin card sorting, block design and visual recognition (n = 100). Visuospatial abilities and executive function were better predicted by blood Pb than cumulative Pb exposure. It is unusual that a frontal lobe task is associated with blood Pb when SRT and digit symbol sensitive to the affects of Pb are not. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Winker et al. (2005)<br>Austria | 48 workers formerly Pb-exposed, mean duration since last exposure 5 (3.5) yrs, and mean age 40 (8.8) yrs were matched with 48 controls for age, verbal intelligence, yrs of education and number of alcoholic drinks. Group differences and dose-response relationship were explored. | Formerly Pb-exposed<br>Mean (SD, range) blood Pb 5.4 (2.7, 1.6-14.5) µg/dL<br>Mean (SD) IBL 4153.3 (36930.3) µg·yr/dL<br><br>Controls<br>Mean (SD, range) blood Pb 4.7 (2.5, 1.6-12.6) µg/dL | No significant differences on neurobehavioral battery were present when groups compared by t-tests for paired samples. When the groups were combined, partial correlation adjusting for age found significant negative correlation between blood Pb and Block Design, ($r = -0.28$, $p < 0.01$) Visual Recognition ($r = -0.21$, $p < 0.05$) and Digit Symbol Substitution ($r = -0.26$, $p < 0.01$). The authors conclude that the cognitive deficits associated with low-level Pb exposure are reversible. However there appears to be a residual effect primarily from those with the highest past Pb exposure. |
| Winker et al. (2006)<br>Austria | The same 48 workers formerly Pb-exposed described above were compared to the 47 exposed workers described by Barth et al. (2002). Both groups were comparable for age and verbal intelligence. Group differences and differences by duration of exposure and exposure absence were evaluated. | Exposed workers<br>Mean (SD, range) blood Pb 31 (11.2, 10.6-62.1) µg/dL<br>Mean (SD) IBL 4613 (4187.6) µg·yr/dL<br><br>Formerly Pb-exposed<br>Mean (SD, range) blood Pb 5.4 (2.7, 1.6-14.5) µg/dL<br>Mean (SD) IBL 4153.3 (36930.3) µg·yr/dL | Mann-Whitney test found significantly better performance in the formerly Pb-exposed workers for Block Design ($p = 0.005$) and Wisconsin Card Sorting Test (categories $p = 0.0005$, total errors $p = 0.005$, perseverations $p = 0.0095$ and loss of sorting principle $p = 0.02$). To further examine the reduction of cognitive impairment with absence of exposure, workers were stratified by duration of exposure and exposure absence – short exposure and long absence; long exposure and long absence; short exposure and short/no absence and long exposure and short/no absence. Linear contrasts for Block Design ($p = 0.003$) and Wisconsin Card Sorting Test (categories- $p < 0.001$, total errors $p = 0.001$, perseverations $p = 0.019$ and loss of sorting principle $p = 0.030$) were highly significant in the hypothesized direction. Results were believed to support reversibility of cognitive deficits related to occupational Pb exposure. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Maizlish et al. (1995)<br>Venezuela | 43 workers from a Pb smelter, mean age 34 (9) yrs and 47 nonexposed workers, mean age 35 (11) yrs completed the WHO neurobehavioral core test battery. ANCOVA and linear regression adjusting for potential confounders examined relationship of Pb exposure and NCTB. | Pb workers<br>Mean (SD) blood Pb 43 (12.1) µg/dL<br>Mean (SD) peak blood Pb 60 (20.3) µg/dL<br>Mean (SD) TWA 48 (12.1) µg/dL<br><br>Controls<br>Mean (SD) blood Pb 15 (6) µg/dL<br>Mean (SD) peak blood Pb 15 (6) µg/dL<br>Mean TWA 15 (6) µg/dL | Group comparison was significant for SRT ($p = 0.06$) but the Pb exposed workers performed faster. Linear regression found SRT poorer performance with blood Pb and TWA but not significant. With peak blood Pb SRT improved with increasing Pb exposure. In this study only symptoms were significantly different between the groups. |
| **Asia** | | | |
| Schwartz et al. (2001a)<br>South Korea | 803 Korean Pb-exposed workers, 80% men and 20% women, mean age 40 (10.1) yrs from a variety of industries, and 135 controls, 92% men and 8% women, mean age 35 (9.1) yrs. Educational levels Pb-exposed workers/controls #6 yrs = 23% / 7%, 7-9 yrs 23% / 11%, 10-12 yrs = 46% / 70%, and >12 yrs 8% / 12%. Group differences on neurobehavioral testing after controlling for covariates and linear regression controlling for covariates examined the presence of a dose-effect relationship. | Pb workers<br>Mean (SD) blood Pb 32 (15) µg/dL<br>Mean (SD) tibia bone Pb 37 (40.3) µg/g<br>Mean (SD) DMSA-chelatable Pb level 186 (208.1) µg<br><br>Controls<br>Mean (SD) blood Pb 5 (1.8) µg/dL<br>Mean (SD) Tibia bone Pb 6 (7) µg/g | Nineteen outcomes examined. Compared to controls Pb exposed workers performed significantly worse on SRT, Digit Span, Benton Visual Retention, Colored Progressive Matrices, Digit Symbol, and Purdue Pegboard after controlling for age, gender and education. The association of DMSA with test performance was lost by the addition of blood Pb. Bone Pb was not associated with neurobehavioral performance. Blood Pb was the best predictor for significant decrements in neurobehavioral performance on trails B ($\exists$ = !0.0025 [SE 0.0009], $p < 0.01$), Purdue Pegboard (dominant $\exists$ = !0.0159 [SE 0.0042], $p < 0.01$; non-dominant $\exists$ = 0.0169 [SE 0.0042], $p < 0.01$; both $\exists$ = !0.0142 [SE 0.0038], $p < 0.01$; assembly $\exists$ = !0.0493 [SE 0.0151], $p < 0.01$), and Pursuit Aiming (# correct $\exists$ = !0.1629 [SE 0.0473], $p < 0.01$; # incorrect $\exists$ = !0.0046 [SE 0.0023], $p < 0.05$). The magnitude of the effect for these eight tests significantly associated with blood Pb was an increase in blood Pb of 5 µg/dL was equivalent to an increase of 1.05 yrs in age. Use of Lowess lines for Purdue Pegboard (assembly) and Trails B suggested a threshold at blood Pb 18 µg/dL after which there is a decline of performance. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Schwartz et al. (2005)<br>South Korea<br>1997-2001 | Longitudinal decline in neurobehavioral performance examined in 576 of the above group of Pb exposed workers who completed 3 visits at one yr intervals.<br>Mean age at baseline was 41 (9.5) yrs and job duration 9 (6.3) yrs and 76% were men.<br><br>Compared to non-completers Pb workers who completed 3 visits were 3.3 yrs older, baseline mean blood Pb was 2.0µg/dL lower, on the job 1.6 yrs longer, 24% women vs. 10% of noncompleters, and usually had less than high school education. Models examined short-term vs. long-term effects. Final model had current blood Pb, tibia bone Pb and longitudinal blood Pb and covariates. | Baseline mean (SD) blood Pb 31 (14.2) µg/dL<br>Mean (SD) tibia Pb 38 (43) µg/g | Blood Pb from baseline correlated with those from visit 2 and 3 and baseline tibial Pb correlated with that measured at visit 2. Cross-sectional associations of blood Pb or short-term change occurred with Trails A (∃ = !0.0020 [95% CI: !0.0040, !0.0001]) and B (∃ = !0.0037 [95% CI: !0.0057, !0.0017]), Digit Symbol (∃ = !0.0697 [95% CI: !0.1375, !0.0019]) , Purdue Pegboard (dominant ∃ = !0.0131 [95% CI: !0.0231, !0.0031]; non-dominant ∃ = !0.0161 (95% CI: !0.0267, !0.0055); both (∃ = !0.0163, [95% CI: !0.0259, !0.0067]; assembly (∃ = !0.0536 [95% CI: !0.0897, !0.0175]), and Pursuit Aiming (# correct ∃ = 0.1526, [95% CI: !0.2631, !0.0421]) after covariates. However, longitudinal blood Pb was only associated with poorer performance on Purdue Pegboard (non-dominant ∃ = !0.0086 [95% CI: !0.0157, !0.0015]; both (∃ = !0.0063 [95% CI: !0.0122, 0.0004]; assembly (∃ = !0.0289 [95% CI: !0.0532, !0.0046]). Historical tibial bone Pb was associated with digit symbol (∃ = !0.0067 [95% CI: !0.0120, 0.0014]) and Purdue Pegboard (dominant ∃ = !0.0012, [95% CI: !0.0024, !0.0001]). Magnitude of Pb associations was expressed as the number of yrs of increased age at baseline that was equivalent to an increase of Pb from the 25th to 75th percentile. At baseline, these Pb associations were equivalent to 3.8 yrs of age for cross-sectional blood Pb, 0.9 yrs of age for historical tibial Pb and 4.8 yrs of age for longitudinal blood Pb. Analyses showed decline in performance over time related to tibia Pb. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Hwang et al. (2002)<br>South Korea | From the above cohort of 803 Korean Pb workers, 212 consecutively enrolled workers, were examined for protein kinase C (PKC) activity and the relations between blood Pb and neurobehavioral performance. PKC activity assessed by measuring levels of phosphorylation of three erythrocyte membrane proteins. Seventy-four percent of workers were men, mean age 36(0.8)yrs, duration of exposure 9 (0.6) and education 93% had high school or less. For the female workers, mean age 47 (0.9) yrs, duration of exposure 6 (0.5), and education 95% had high school or less. | Male workers<br>Mean (SD) blood Pb 32 (13.0) µg/dL<br>Mean (SD) tibia Pb 38 (39.6) µg/g<br>Mean (SD) ZPP 69 (47.8) µg/dL<br><br>Female workers<br>Mean (SD) blood Pb 20 (9.2) µg/dL<br>Mean (SD) tibia Pb 26 (14.7) µg/g<br>Mean (SD) ZPP 72 (29.7) µg/dL | Blood Pb was associated significantly with decrements in Trails B (∃ = !0.003 [SE 0.002], $p < 0.10$), SRT (∃ = !0.0005 [SE 0.0003], $p < 0.10$) and Purdue Pegboard (dominant ∃ = !0.21 [SE 0.010], $p < 0.05$); non-dominant (∃ = !0.021 [SE 0.010], $p < 0.05$); both (∃ = !0.021 [SE 0.009], $p < 0.05$). PKC activity as measured by back-phosphorylation of erythrocyte membrane proteins was not associated with neurobehavioral test scores. Addition of the interaction term of blood Pb by back-phosphorylation dichotomized at the median found significant effect modification with the association of higher blood Pb and poorer neurobehavioral performance occurring only among workers with lower back-phosphorylation levels that corresponds to higher in vivo PKC activity. Association of blood Pb and SRT for the 52 kDa subunit with high in vivo PKC activity (adjusted ∃ = !0.001, $p < 0.01$) and for low in vivo PKC (adjusted ∃ = !0.0001, $p = 0.92$). The authors suggest that PKC activity may identify a subpopulation at increase risk of neurobehavioral effects of Pb. |
| Chuang et al. (2005)<br>Taiwan | 27 workers from a glazing factory were administered a computerized neurobehavioral battery 3 times over 4 yrs. At yr 1, the mean age was 40 (9.6) yrs. In the first yr workers were compared to a referent group matched for age and education. Neurobehavioral performance compared in first yr to referent group with adjustment for age and Vocabulary. Generalized mixed linear mixed models analyzed relationship between blood Pb level and neurobehavioral test performance after adjusting for age and Vocabulary. | Pb workers<br>Yr 1<br>Mean (SD) blood Pb 26 (12)<br>Yr 3<br>Mean (SD) blood Pb 11 (6.4)<br>Yr 4<br>Mean (SD) blood Pb 8 (6.9)<br><br>Referent<br>Mean (SD) blood Pb 7 (4.2) | Referents scored significantly lower on questionnaire for chronic symptoms in yr 1. In the mixed model analyses finger tapping dominant ($p = 0.008$) and non-dominant ($p = 0.025$) were significantly inversely associated with blood Pb. Pattern comparison ($p < 0.001$) and Pattern memory ($p = 0.06$) improved significantly as blood Pb levels improved. Chronic symptoms and neurobehavioral performance appear to reverse when Pb exposure is decreased. However since the referent group was not tested in yr 3 and yr 4 it was not possible to control for practice effect known to occur with repeat neurobehavioral testing even at two yr intervals. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Tsai et al. (2000)<br>Taiwan | 19 Pb workers and 19 referents included in the above publication, mean age 39 yrs in both groups and mean education 10 (2.9) and 9 (3.2) yrs, respectively, were tested with a computerized neurobehavioral battery. Alcohol use was similar. Mean duration of Pb exposure 6 (2.5) yrs. Student's t compared neurobehavioral performance between the two groups. | Mean (SD) blood Pb 32 (12.2) µg/dL<br><br>Referent<br>Mean (SD) blood Pb 7 (2.7) µg/dL | Poorer performance in Pb workers for finger tapping, dominant and non-dominant, and continuous performance task but only finger tapping was significant. Pb workers performed better than referents on Associate Learning, Pattern Comparison Test, Pattern Memory Test, Visual Delay and Associate Learning Delayed that was attributed to higher mean education. |
| Chia et al. (2004)<br>Singapore | 120 workers from Pb stabilizer factories, mean age 40 (10.7) yrs, duration of exposure 10.2 (7.9) were given a neurobehavioral battery. Genotyping of ALAD polymorphisms was performed. ANCOVA used to test for differences in neurobehavioral performance among ALAD polymorphism types adjusting for age, exposure duration and blood Pb. | Mean (SD) blood Pb 22 (9.4) µg/dL<br>Mean (SD) ALAD0.6 (0.25) µm of porphobilinogen/h/ml of RBC<br>Mean (SD) ALAU0.9 (0.56) mg/g creatinine | Frequency of ALAD11, 87%, ALAD12, 12%, and ALAD22, 1%. Mean blood Pb adjusting for age and exposure duration was 20 µg/dL for ALAD11 (n = 107) and 20.4 µg/dL for ALAD12 and 22 (n = 13). However ALAU was significantly higher in ALAD11 (p = 0.023). After adjusting for the covariates significant differences for grooved pegboard dominant hand (p = 0.01), non-dominant hand (p = 0.04), and grooved pegboard mean time (p = 0.006) were found between ALAD11 and ALAD12 and 22. Considering cognitive tests were part of battery it is surprising education was ignored. As noted by the authors the study only had 13 in the group with better performance and the ALAD12 or 22 genotypes limiting the power. |
| Chia et al. (1997)<br>Singapore | 50 Pb battery manufacturing workers, mean age 36 (10.6) yrs, education 8.6 (2.1) yrs duration of employment 9 (7.4) yrs and 97 controls, mean age 34 (3.7) yrs, and education 12 (1.8) yrs were administered a neurobehavioral battery. ANCOVA and linear regression used to assess relationship of Pb dose and performance. | Pb workers<br>Median (range) blood Pb of 38 (13.2-64.6) µg/dL<br>Median (range) IBL 264 (10.0-1146.2) µg·yr/dL<br><br>Controls<br>Median (range) blood Pb 6 (2.4-12.4) µg/dL | Significant group differences for Santa Ana, grooved pegboard, digit symbol, pursuit aiming and Trails A and B after adjusting for age, education, smoking, ethnic group and alcohol use. When the exposed group was stratified by age, in the group >35 yrs the poorer performance on digit symbol and Trails A was significantly associated with cumulative Pb and not blood Pb after adjusting for age and education. |

## Table AX6-3.3 (cont'd). Neurobehavioral Effects Associated with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Niu et al. (2000)<br>China | 44 Pb-exposed workers (17 men, 27 women) from Pb printing houses, mean age 35 (4.9) and education 9.3 (no SD) yrs and 34 controls (19 men and 15 women), mean age 33 (7.4) yrs and education 9.5 (no SD) yrs completed the NCTB. ANCOVA controlling for age, sex and education examined group differences and linear regression for dose-response relationship. | Pb workers<br>Mean (SD) blood Pb 29 (26.5) µg/dL<br>(8 workers blood Pb exceeded 50 µg/dL)<br><br>Controls<br>Mean (SD) blood Pb 13 (9.9) µg/dL<br>(1 control blood Pb exceeded 50 µg/dL) | SRT ($F = 2.30$, $p < 0.05$), digit symbol ($F = 4.81$, $p < 0.01$) pursuit aiming # correct ($F = 7.186$, $p < 0.01$) and pursuit aiming total ($F = 6.576$, $p < 0.01$) had significantly poorer performance compared to controls. No repression analyses provided. |
| Boey and Jeyaratnam (1988)<br>Singapore | 49 Pb-exposed workers, mean age 26 (7.6) yrs and 36 controls, mean age 30 (6.4) yrs completed SRT and 8 psychological tests covering attention, vigilance, visual-motor speed, short-term memory, visuomotor tracking, visual scanning, and manual dexterity. Control group was matched for education level. Discriminate analysis of neurobehavioral tests performed to determine which best discriminate the groups. | Pb workers<br>Mean (SD) blood Pb 49 (15) µg/dL<br><br>Controls<br>Mean (SD) blood Pb 15 (3) µg/dL | Six tests were significantly different between the two groups-Digit Symbol, Bourdon-Wiersma, Trails A, Santa Ana dominant, Flicker Fusion and SRT. The group of tests that best differentiates Pb-exposed workers from nonexposed workers were Simple Reaction Time, Digit Symbol (WAIS) and Trail Making Test (Part A) with long latency in reaction time contributing three times more to the derived function than Digit Symbol (WAIS) or Trails A. |

## Table AX6-3.4. Meta-analyses of Neurobehavioral Effects with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| Balbus-Kornfeld et al. (1995) | Reviewed 21 studies from 28 publications; number of subjects ranged from 9-708. | Mean blood Pb in most exposed group 28-68 µg/dL. Only 5 studies used a measure of cumulative exposure or absorption of Pb, 2 studies used duration of exposure. | Dexterity (17/21 studies) and executive or psychomotor 11/21 studies were the functional domains most commonly associated with Pb. Age not adequately controlled in most studies, usually matching means or medians. Intellectual abilities prior to exposure usually adjusted for with education; however, Vocabulary, a measure of overall intellectual ability still different between the groups. The conclusion reached that evidence of effects from cumulative exposure or absorption of Pb was inadequate. |
| Davis and Svendsgaard (1990) | Meta-analysis of 32 studies of nerve conduction studies and Pb exposure. | | Presented 41 effect sizes with the overall effect size for all studies D = !0.369 (p # 0.001). All median nerves combined was D = !0.481 (p # 0.001) and for all ulnar nerves D = !0.211 (p # 0.001). The median motor was most sensitive with an effect size of D = !0.553 (p # 0.001). Overall blood Pb was a weak measure of exposure for the peripheral nervous system. Paradoxical association found effect size smaller with increasing blood Pb but increased with duration of exposure. |
| Meyer-Baron and Seeber (2000) | Meta-analysis of studies with blood Pb <70 µg/dL found 12 studies with comparable test procedure and sufficient documentation of results. Thirteen tests from the 12 studies examined. | Exposed group Range of mean blood Pb 31 to 49 µg/dL<br><br>Controls Range of mean blood Pb 6 to 18 µg/dL | Block Design, Logical Memory, and Santa Ana had performance deficits with small effect size. For Block Design the effect size was comparable to changes observed with 20 yrs of aging. Aiming, SRT, Trials A and B, Digit Span and Digit Symbol also had poorer performance but the large variance for effect sizes suggest other factors besides Pb exposure influenced performance. The authors conclude, "that the evidence of neurobehavioral deficits at a blood Pb of ~40 µg/dL is obvious." |
| Goodman et al. (2002) | Meta-analysis of 22 studies with median blood Pb <70 µg/dL, numbers of exposed and unexposed workers given with scores and dispersion on neurobehavioral tests. | Exposed group Range blood Pb 24 to 63 µg/dL<br><br>Unexposed group Range blood Pb 0 to 28 µg/dL | Digit symbol and D-2 errors significant effect for fixed effects, weighted random effects and unweighted random effects. Simple reaction time, grooved pegboard, Trails A and B, picture completion visual reproduction, eye-hand coordination and vocabulary had significant effects for the fixed effects model only. The authors conclude none of the individual studies were adequate or conclusive of subclinical neurobehavioral effects of exposure to Pb as the biological effects of blood Pb <70 µg/dL are inconsistent. (See Schwartz et al. (2002) for comments). |

## Table AX6-3.4 (cont'd). Meta-analyses of Neurobehavioral Effects with Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| Schwartz et al. (2002) | Letter to the Editor commenting on shortcomings in the Goodman et al. (2002) meta-analysis on studies of neurobehavioral testing in workers occupationally exposed to Pb. | | The six points regarding problems with the methodology included: (1) no evaluation of quality of study design or statistical methods, (2) data from poorly done and well done studies are combined, (3) included 6 studies with no age adjustment and 3 with no adjustment for education, (4) confounding of age and education when addressed the variation across studies not discussed, (5) main effect only examined exposed vs. nonexposed comparisons that are known to have the lowest power, cannot evaluated dose-effect relationships and have a tendency for selection bias, and (6) few of the 22 studies included contributed to effect size. |
| Seeber et al. (2002) | A comparison of the two meta-analyses Meyer-Baron and Goodman) performed to evaluate recommendations of a German BEI of 40 µg/dL. | | Effect size calculated for 12 tests in two meta-analyses and 10 tests from one meta-analyses found subtle impairments associated with blood Pb between37 µg/dL and 52 µg/dL for Logical Memory, Visual Reproduction, Simple Reaction Time, Attention Test d2, Block Design, and Picture Completion, Santa Ana, Grooved Pegboard and Eye-hand Coordination. Effect sizes related to age norms between ~40 to 50 yrs. For example, !3 score on Block Design = 10 to 15 yrs; !3.5 score on Digit Symbol = 10 yrs; !21 score on Cancellation d2 = 10 yrs; and +5 to +6 on Trails A = 10 to 20 yrs. This analyses concluded that both meta-analyses supported recommendation for German BEI of 40 µg/dL. |
| Graves et al. (1991) | A meta-analysis on 11 case-control studies of Alzheimer's disease for occupational exposure to solvents and Pb. | | Four studies had data for Pb exposure with a pooled analysis of relative risks for occupational Pb of 0.71 (95% CI: 0.36, 1.41). The exposure frequencies were 16/261 for the cases and 28/337 for the controls. |

## Table AX6-3.5. Neurophysiological Function and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** | | | |
| Bleecker et al. (2005b)<br>New Brunswick<br>1992-1993 | 74 current smelter workers, mean age 44 (8.4) yrs, education 8 (2.8) yrs and employment duration 20 (5.3) yr had current perception threshold (CPT) measured for large and small myelinated and unmyelinated nerve fibers in the finger. Linear regression modeled CPT on metrics of Pb dose after adjusting for covariates. Interaction of Pb dose and ergonomic stressor on peripheral nerve function was assessed. | Mean (SD) blood Pb 26 (7.1) µg/dL<br>Mean (SD) IBL 891 (298.8) µg·yr/dL<br>Mean (SD) TWA 42 (8.4)µg/dL<br>Mean (SD) tibia bone 40 (23.8) µg/g<br>5 metrics relating to IBL cumulated only exposure above increasing blood Pb ranging from 20 to 60 µg/dL | Blood Pb and tibial bone Pb were not associated with any of the three nerve fiber populations. IBL and TWA accounted for a significant percentage of the variance only for the large myelinated nerve fibers (♠$R^2$ = 3.9%, ♠$R^2$ = 8.7% respectively). The relationship of CPT and TWA was curvilinear with a minimum at a TWA of 28 µg/dL. Unique variance of CPT for large myelinated fibers explained by different thresholds of IBL were IBL – 3.9%, p = 0.08; IBL20 – 5.8%, p < 0.03, IBL30 – 7.8%, p < 0.02; IBL40, p < 0.005; IBL50, p < 0.005; and IBL60, p < 0.005. IBL60 also explained significant variance of CPT for small myelinated nerve fibers demonstrating an increased impairment in peripheral nerve function. This effect on myelinated sensory nerve fibers was enhanced when a measure of ergonomic stress was added to the model for IBL60. |
| **Europe** | | | |
| Kovala et al. (1997)<br>Finland | 60 workers in a Pb battery factory with a mean age of 43 (9) yrs and mean exposure duration of 16 (8) yrs. Nerve conduction studies, vibration thresholds, and quantitative EEG were performed. Relationship of Pb exposure with peripheral nerve function and quantitative EEG were examined by partial correlation and regression analyses adjusting for age. | Mean (SD) tibial Pb 26 (17) mg/kg<br>Mean (SD) calcaneal Pb 88 (54) mg/kg<br>Mean (SD) IBL 546 (399) µg·yr/dL<br>Mean (SD) TWA 34 (8.4) µg/dL<br>Mean (SD) maximum blood Pb 53 (19) µg/dL,<br>Mean (SD) blood Pb 27 (8.4) µg/dL | The sensory amplitude of the median and sural nerves had a negative correlation with IBL and duration of exposure that was not related to age. Vibration threshold at the ankle related significantly to IBL and duration of exposure after adjusting for age. Vibration threshold in the finger was associated with blood Pb and blood Pb avgs over the past three yrs. The alpha and beta frequencies were more present in workers with higher long term Pb exposure such as tibial and calcaneal, IBL and TWA. Overall historical blood Pb measures were more closely associated with peripheral nerve function than bone Pb concentrations. The study had no comparison group and did not account for the effect of smoking and alcohol use or give their usage in this population. |

## Table AX6-3.5 (cont'd). Neurophysiological Function and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** | | | |
| Schwartz et al. (2001a)<br>South Korea<br>1997-1999 | 804 workers from 26 different Pb using facilities and 135 controls with a mean age of 40 ( 10.1) and 35 (9.1) yrs respectively, job duration of 8 (6.5) and 9 (5.3) yrs respectively, and education level 42 % and 69% completed high school respectively had comparable alcohol and smoking use. Linear regression used to compare vibration threshold in Pb exposed and controls controlling for potential confounders. | Pb-exposed workers<br>Mean (SD) blood Pb 32 (15) µg/dL<br>Mean (SD) tibia bone Pb 37 (40.3) µg/g<br>Mean (SD) DMSA-chelatable Pb 186 (208.1) µg (4 h collection) | After adjustment for age, gender, education and height, tibia Pb but not blood Pb was significantly associated with poorer vibration threshold in the dominant great toe but not the finger (∃ = !0.0020 [SE 0.0007], $p < 0.01$). These results contrast with those for neurobehavioral measures (see above) performed in the same study where tibial Pb was not a predictor of performance. |
| Schwartz et al. (2005)<br>South Korea<br>1997-2001 | Longitudinal decline in neurobehavioral performance examined in 576 of the above group of Pb exposed workers who completed 3 visits at one yr intervals.<br>Mean age at baseline was 41 (9.5) yrs and job duration 9 (6.3) yrs and 76% were men.<br><br>Compared to non-completers Pb workers who completed 3 visits were 3.3 yrs older, baseline mean blood Pb was 2.0 µg/dL lower, on the job 1.6 yrs longer, 24% women vs. 10% of noncompleters, and usually had less than high school education. Models examined short-term vs. long-term effects. Final model had current blood Pb, tibia bone Pb and longitudinal blood Pb and covariates. | Baseline mean (SD) blood Pb 31 (14.2) µg/dL<br>Mean (SD) tibia Pb 38 (43) µg/g | After adjustment for age, visit number, education, gender, height (for vibration) and BMI (for grip strength and pinch) vibration threshold in the dominant great toe and not the finger was associated with tibia Pb (∃ = !0.0006 [95% CI: !0.0010, !0.0002]) and longitudinal blood Pb (∃ = !0.0051 [95% CI: !0.0078, !0.0024]) in one model and blood Pb (∃ = !0.0019 [95% CI: !0.0039, 0.0001]) in another model. |

## Table AX6-3.5 (cont'd). Neurophysiological Function and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Chuang et al. (2000) Taiwan | 206 Pb battery workers, mean age 41 yrs, with annual blood Pb for the previous five yrs had vibration perception measured in hand and foot. Relationship of Pb exposure term and vibration perception threshold assessed with multiple regressions, hockey stick regression analysis after adjusting for potential confounders. | Mean blood Pb 28 µg/dL<br>Mean blood Pb over past 5 yrs 32 µg/dL<br>Mean maximum blood Pb 39 µg/dL<br>Mean index of cumulative exposure 425 µg·yr/dL<br>Mean TWA 32 µg/dL<br>Mean working duration 13 yrs and life span in work 31% | After adjustment for age, sex, body height, smoking, alcohol consumption, and use of vibrating hand tools, significant association between mean blood Pb and mean TWA and vibration perception in the foot were found. After adjustment for the covariates, a hockey stick regression analysis of foot vibration threshold vs. mean blood Pb concentration for 5 yrs found an inflection point around 30 µg/dL with a positive linear relation above this point suggesting a potential threshold. |
| Chia et al. (1996a) Singapore | 72 workers in a Pb battery manufacturing factory with a mean age of 30 yrs and reference group of 82 workers had nerve conduction studies and blood Pb performed every 6 mos over the course of three yrs. Only 28 Pb battery workers completed the program. At the end of the first yr of the 82 workers in the comparison group only 26 remained and by yr 3 this had decreased to 4. Mean nerve conduction values examined by ANCOVA between the exposed and reference after adjustment for age, ethnic group, smoking and drinking habits. Analysis of serial nerve conduction values and blood Pb treated as a clustered sample had the within-cluster regression coefficient examined. The 28 exposed workers were stratified by blood Pb level and the relationship between nerve conduction values and blood tested within the cluster. | Geometric mean blood Pb concentrations for the 6 testing periods: 37, 41, 42, 40, 41, and 37 µg/dL<br><br>Overall range for blood Pb 16-73 µg/dL | The relationship between blood Pb levels and nerve conduction values for the 28 exposed workers was significant for all outcomes except median motor conduction velocity and ulnar sensory nerve conduction velocity and ulnar sensory amplitude. The regression correlation coefficients for blood Pb >40 µg/dL was significant for all parameters except the median sensory conduction velocity and for blood Pb <40 µg/dL there was no association with nerve conduction values. Therefore the blood Pb level associated with no change in nerve conduction studies was <40 µg/dL. |

## Table AX6-3.5 (cont'd). Neurophysiological Function and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Chia et al. (1996b)<br>Singapore | Extension of above study - 72 workers in Pb battery manufacturing and 82 controls. Mean duration of exposure 5.3 yrs. | Mean blood Pb 37 µg/dL<br>Mean cumulative blood Pb 137 µg·yr/dL | ANCOVA found significant differences for all nerve conduction parameters except three for the ulnar nerve, after adjusting for age, ethnic groups, smoking and drinking habits. There was no significant correlation between blood Pb and cumulative blood Pb with nerve conduction values after linear regression with adjustment for confounders. When cumulative blood Pb was stratified- 12 workers <40 µg·yr/dL, 28 workers 40-300 µg·yr/dL, 21 workers >300 µg·yr/dL ANCOVA found significant differences for 5 nerve conduction parameters. The strongest dose effect relationship was for sensory nerve conduction velocity. |
| Chuang et al. (2004)<br>Taiwan | 181 Pb battery manufacture workers were stratified by milk drinkers, n = 158 and non- or rare mild drinkers n = 23. Mean age in the two groups was 40 and 36 yrs and working duration 10/8 yrs respectively. Peripheral nerve evaluation was with current perception threshold at 3 frequencies 5Hz = C fibers, 250 Hz = A-delta fibers and 2000 Hz = A-beta fibers. Linear regression estimated the association of CPT and Pb exposure variable and adjustment of milk intake and potential confounders. | Blood Pb<br>Milk drinkers 25 µg/dL<br>Non or rare milk drinkers 30 µg/dL<br><br>TWA<br>Milk drinkers 28 µg/dL<br>Non or rare milk drinkers 32 µg/dL<br><br>IBL<br>Milk drinkers 316 µg·yr/dL<br>Non or rare mild drinkers 245 µg·yr/dL | Age was significantly different but distributions of gender, smoking, alcohol use, use of hand vibration tool, working history and height were not different. Linear regressions found association of 5 Hz CPT and 250 Hz CPT in hand and foot with blood Pb and TWA but not IBL. However the protective effects of drinking milk was present for all fiber populations only in the hands. This paper presents an unusual finding of subclinical Pb neuropathy involving the unmyelinated and small myelinated fibers. Toxic axonopathies classically involve the large nerve fibers. The main group difference may be related to other nutritional deficiencies associated with the malabsorption syndrome that lead to the non-milk drinking status. |
| Yokoyama et al. (1998)<br>Japan | 17 gun-metal workers, mean age 48 yrs and a 20 controls with a mean age of 45 yrs had distribution of conduction velocities (DCV) measured and the maximum median sensory conduction velocity (SVC) performed twice at a yr interval. Group differences controlling for confounders and dose-effect relationships were examined. | Mean blood Pb 40 µg/dL<br>Mean mobilized Pb (CaEDTA) in urine 1 mg/24 h | ANCOVA controlling for age and alcohol found mobilized Pb was associated with significant slowing in the large nerve fibers while blood Pb was not. Workers with increased change in mobilized Pb over 1 yr interval (mean 0.44 mg/24hr) had significant reduction in large fiber (V95) conduction velocity while those workers with less change in mobilized Pb (0.08 mg/24hr) did not have significant change in DCV or SVC. It appears that larger faster conducting nerve fibers are susceptible to Pb and a measure of body burden (readily mobilized Pb from soft tissue) is a stronger predictor of this change than blood Pb. |

## Table AX6-3.5 (cont'd). Neurophysiological Function and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| He et al. (1988)<br>China | 40 workers in a Pb smelter with age range 20 to 45 yrs (no mean provided) and duration of exposure 5.4 yrs. Fifty controls age 20 to 55 yrs. Nerve conduction studies examined 11 parameters. Student = s t-test examined for differences between exposed and controls. | Mean blood Pb 40 µg/dL<br>Mean urinary Pb 71 µg/dL<br>Mean ALAU5 µg/dL | There were no symptoms or signs of peripheral nerve disorder. Both motor and sensory conduction velocities were slowed in the Pb exposed groups. 10 nerve conduction parameters were significant in the group with blood Pb >40 µg/dL and 6 parameters were significant in the group with blood Pb <40 µg/dL. An unusual finding in this study was the lack of age association with nerve conduction values and therefore it was not controlled for in the analyses. |
| Niu et al. (2000)<br>China | 44 Pb-exposed workers (17 men, 27 women) from Pb printing houses, mean age 35 (4.9) and education 9.3 (no SD)yrs and 34 controls (19 men and 15 women), mean age 33 (7.4) yrs and education 9.5 (no SD) yrs had nerve conduction studies for maximal motor nerve conduction velocity. ANCOVA controlling for age, sex and education examined group differences and linear regression for dose-response relationship. | Pb workers<br>Mean blood Pb 29 (26.5) µg/dL<br>(8 workers blood Pb exceeded 50 µg/dL)<br><br>Controls<br>Mean blood Pb 13 (9.9) µg/dL<br>(1 control blood Pb exceeded 50 µg/dL) | Only 12 Pb exposed workers and 24 controls examined for NCV. Left ulnar nerve was significantly slower but the left median and right ulnar were faster in the Pb exposed and the right median was slightly slower. This appears to be a finding of chance due to the small n. For the Pb exposed group mean left ulnar CV was 52 while the mean right ulnar CV was 59 while for the controls left ulnar CV was 58 while the mean right ulnar CV was 55. |

## Table AX6-3.6. Evoked Potentials and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** | | | |
| Bleecker et al. (2003)<br>New Brunswick<br>1992-1993 | 359 currently employed smelter workers, mean age 41 yrs, had brainstem auditory evoked potentials (BAEP) measured. Relationship between absolute latencies and interpeak latencies assessed using linear regression after adjusting for potential confounders. Exposure was assessed in cases with clinical abnormalities in Wave I and I-V interpeak latency compared to those workers with normal BAEP using post-hoc analysis. | Mean blood Pb 28 µg/dL<br>Mean TWA 39 µg/dL<br>Mean IBL 719 µg·yr/dL | Linear regression after the contribution of age found blood Pb and TWA were significantly associated with Wave I while IBL was significantly associated with Wave III and I-III interpeak interval. Four groups created with increasing abnormalities based upon clinical cut-off scores for Wave I and I-V interpeak interval had similar age. blood Pb, TWA and IBL were all significantly higher in the group with prolonged Wave I and I-V interpeak interval compared to the group with normal BAEP = s. These findings support involvement of the brainstem and auditory nerve with Pb exposure. |
| **Europe** | | | |
| Abbate et al. (1995)<br>Italy | 300 Pb exposed men ages 30 to 40 yrs in good health with no other neurotoxic exposure had P100 latency measured for visual evoked potentials (VEP) for 15 and 30 minute of arc. Groups created based upon blood Pb had VEPS examined followed by linear regression for each group. | Blood Pb 17 to 60 µg/dL range<br><br>Mean blood Pb for 4 groups<br>n = 39 23 µg/dL<br>n = 113 30 µg/dL<br>n = 89 47 µg/dL<br>n = 59 56 µg/dL | ANOVA of the blood Pb and P100 latencies were significantly prolonged for 15 and 30 minutes of arc. Linear regression found the association of blood Pb and P100 were significant in each group but the relationship was not proportional (angular coefficient). Effect of blood Pb on VEP began at 17-20 µg/dL. With age limited to one decade, contribution from age was not a concern. Even though no comparison group, careful screening ruled out other medical and eye conditions and other potential exposures. |
| Discalzi et al. (1992)<br>Italy | 49 Pb exposed workers and 49 age and sex matched controls had BAEPs measured. Relationship of 6 BAEP outcome variables and Pb exposure examined with analysis of variance and linear regression. | Mean blood Pb 55 µg/dL<br>Mean TWA for previous 3 yrs 54 µg/dL | Latencies for waves I, III, V and interpeak latencies, I-V, I-III, and III-V were all significantly prolonged in the Pb-exposed workers ($p < 0.04$). No significant association found with linear regression between BAEP outcomes and exposure variables. In those workers with TWA >50 µg/dL, I-V latency was significantly prolonged compared to workers with TWA <50 µg/dL. |

## Table AX6-3.6 (cont'd). Evoked Potentials and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Discalzi et al. (1993)<br>Italy | 22 battery storage workers, mean age 35 yrs and 22 control group, age and sex matched, with normal hearing had BAEPs recorded. Latencies I and V and Pb exposure examined by ANOVA after stratifying blood Pb. | Mean blood Pb 48µg/dL | Interpeak latency I-V was significantly prolonged in Pb exposed workers ($p = 0.001$). No significant associations by linear regression between I-V and Pb exposure. Stratifying Pb exposed workers by blood Pb 50 µg/dL found I-V interpeak latency significantly prolonged ($p = 0.03$) in subgroup with higher blood Pb. |
| **Latin America** | | | |
| Counter and Buchanan (2002)<br>Ecuador | 30 Pb-glazing workers, median age 35 yrs, had pure-tone thresholds and BAEPs performed. Regression analyses examined relations between auditory outcomes and blood Pb. | Mean blood Pb 45 µg/dL (range 11 to 80 µg/dL) | Sixty percent of the men and 20 percent of the women had abnormal high-frequency thresholds, however there was no significant relationship with blood Pb and pure tone threshold at all frequencies. Analysis of BAEPs found agreement between latencies for Waves I, III and V and peripheral hearing status. Interpeak latencies were within normal limits but no analysis provided with Pb exposure. Workers lived in a Pb contaminated environment from discarded Pb-acid storage batteries. Therefore a measure of chronic Pb exposure may have been more appropriate. |
| **Asia** | | | |
| Holdstein et al. (1986)<br>Israel | 20 adults and 8 children (mean age 27 yrs, range 8 - 56 yrs) accidentally exposed to Pb through food until one yr prior to measurement of BAEP. | Mean blood Pb<br>Adult 31 µg/dL<br>Children 22 µg/dL<br><br>10 mo avg blood Pb Adults 43 µg/dL<br>Children 36 µg/dL | In adults, latencies I, III and I-III and I-V interpeak intervals were significantly longer than the control group ($p < 0.05$). When group stratified by 10 mo avg blood Pb I-III interpeak interval was longer in the high group. Age and blood Pb were not studied due to few subjects. The I-III interpeak interval reflects transmission in the lower brainstem and VIIIth nerve. |

## Table AX6-3.6 (cont'd). Evoked Potentials and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Hirata and Kosaka (1993)<br>Japan | 41 Pb-exposed men from Pb-glass-based colors manufacturing (n = 20), production of Pb electrode plates (n = 8), casting of Pb-bronze (n = 4) and casting of Pb pipes and plates (n = 9) had mean age 41 yrs, mean duration of exposure 13 yrs. A battery of tests administered including radial nerve conduction study, electroretinogram (ERG), visual evoked potential (VEP), brainstem auditory evoked potential (BAER), and short-latency somatosensory evoked potential (SSEP). Comparison group of 39 unexposed used only for BAER analysis by Student's t test. Correlation and linear regression controlling for age examined the relationship of Pb and the other variables. | Mean (range) blood Pb 43 µg/dL (13-70)<br>Mean (range) TWA (based upon previous 5 yrs) 43 µg/dL (13-70)<br>Mean (range) duration of exposure 13 (0.6-29) yrs | Significant partial correlation after adjusting for age included TWA and radial motor conduction velocity, blood Pb and sensory conduction velocity, exposure duration and VEP, blood Pb and SSEP-N20. Comparison of BAERs of 15 Pb exposed and 39 controls found interpeak interval III-V was prolonged significantly. It is not clear why comparison group only used for BAERs. Considering the large number of variables examined with three exposure terms some of the findings could be by chance alone. |
| Murata et al. (1993)<br>Japan | 22 gunmetal foundry workers with age range of 32 to 59 yrs and work duration of 1 to 19 yrs and control group matched for age, no chronic disease and no Pb exposure participated. No significant difference between groups for age, height, skin temperature, alcohol consumption, and yrs of schooling. The test battery consisted of visual evoked potential (VEP), brainstem auditory evoked potential (BAEP), short latency somatosensory-evoked potential (SSEP), event related potential (P300) and EKG R-R interval variability. Paired-sample t test examined for differences between the matched groups. Dose-effect relationships examined with partial correlation adjusting for age and stepwise linear regression. | Blood Pb 12 to 64 µg/dL (no mean provided) | For VEPs, N75 and N145 were significantly prolonged in the Pb exposed workers. N9-N13 interpeak latency of the SSEP was significantly prolonged. BAEP latencies showed no significant differences. P300 believed to reflect cognitive function was prolonged in the Pb workers and correlated with blood Pb, and PbU. Autonomic nervous system effects were significantly diminished for $CV_{R-R}$ and for a measure of parasympathetic activity C-$CV_{RSA}$. Fifty percent of the outcome variables showed significant group differences but there is limited dose effect for any outcome within the exposed group. Small sample size limited conclusions with 20 outcome variables and 8 biomarkers of Pb exposure. |

## Table AX6-3.7. Postural Stability, Autonomic Testing, Electroencephalogram, Hearing Thresholds, and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Dick et al. (1999)<br>U.S. | 145 workers from a secondary Pb smelter, mean age 33 (8.7) and duration of employment 5 (4.8) yrs and 84 comparison workers mean age 30 (9.3) and duration of employment 4 (4.3) yrs had postural sway testing performed. The analysis of exposure with test conditions and covariates used mixed models. | Pb workers<br>Mean (SD) blood Pb 39 (8.5) µg/dL<br>Mean (SD) ZPP 55 (42.2) µg/dL<br>Mean (SD) CBL 230 (217.9) µg·yr/dL<br>Mean (SD) TWA 35 9 (8.5) µg/dL<br>Comparison workers<br>Mean (SD) blood Pb 2 (1.7) µg/dL | The postural sway test had 6 conditions that varied the challenge to the vestibular and proprioceptive afferents and visual system. Only blood Pb had a significant effect primarily on the one leg condition after the effects of the covariates age, height, mass, and race. For the left leg, exposure slope estimate for area ($b = 0.0067$, $t = 3.88$, $p = 0.0001$) and length ($b = 0.0046$, $t = 4.11$, $p = 0.0001$) were significant. For the right leg only the exposure slope estimate for length ($b = 0.0033$, $t = 3.02$, $p = 0.0029$) was significant. Dose effect was only significant when Pb workers were combined with comparison workers. If comparison workers with blood Pb level below 12 µg/dL removed no significant exposure effect was found. |
| **Europe** | | | |
| Kovala et al. (1997)<br>Finland | 60 workers in a Pb battery factory with a mean age of 43 (9) yrs and mean exposure duration of 16 (8) yrs. Quantitative EEG were performed. Relationship of Pb exposure with quantitative EEG were examined by partial correlation and regression analyses adjusting for age. | Mean (SD) tibial Pb 26 (17) mg/kg<br>Mean (SD) calcaneal Pb 88 (54) mg/kg<br>Mean (SD) IBL 546 (399) µg·yr/dL,<br>Mean (SD) TWA 34 (8.4) µg/dL,<br>Mean (SD) maximum blood Pb 53 (19) µg/dL<br>Mean (SD) blood Pb 27 (8.4) µg/dL | The alpha and/or beta frequencies were more present in workers with higher long term Pb exposure such as tibial ($p < 0.05$) and calcaneal ($p < 0.05$), IBL ($p < 0.01$) and TWA ($p < 0.05$). Slow alpha in workers was believed to correlate with increased episodes of 'microdrowsiness'. The study had no comparison group and did not account for the effect of smoking and alcohol use or give their usage in this population. |

## Table AX6-3.7 (cont'd). Postural Stability, Autonomic Testing, Electroencephalogram, Hearing Thresholds, and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** | | | |
| Iwata et al. (2005)<br>Japan | 121 workers from a battery recycling plant and 60 age matched comparison group, mean age 46 (11) yrs. Height, body weight, body mass index, and alcohol use was similar in both groups. Pb group had significantly more smokers. ANCOVA used to evaluate postural sway after controlling for age, height, and smoking and drinking status. Benchmark dose level was calculated as the 95% lower confidence limit of the benchmark dose. | Mean (SD) blood Pb 40 (15) µg/dL<br><br>Referent<br>Not done | Except for sagittal sway, all postural sway parameters with eyes open were significantly larger in Pb workers. Blood Pb level in workers was significantly associated with to sagittal sway at 1-2 Hz and 2-4 Hz with eyes open, and sagittal and transversal sways at 1-2 Hz and 2-4 Hz with eyes closed. The mean benchmark dose level of current blood Pb level for postural sway was 14.3 µg/dL for the linear model and 14.6 µg/dL for the K power model. |
| Yokoyama et al. (1997)<br>Japan | 49 chemical workers exposed to Pb stearate, mean age 48 (1.3) yrs and 23 controls, mean age 47 (2.5) had postural sway evaluated. ANCOVA examined group differences after adjusting for covariates. | Mean (SD) blood Pb 18 (1.0) µg/dL<br>Mean (SD) maximum blood Pb 48 (3.8) µg/dL<br>Mean (SD) TWA 24 (1.3) µg/dL<br>Mean (SD) Cumulative blood Pb 391 (48.2) µg·yr/dL | There were significant increases in sway in all directions at high and low frequencies with eyes open and eyes closed ($p < 0.05$). Regression analysis found blood Pb associated with sway in the anterior-posterior direction, 0.5-1Hz (0.321, $p = 0.03$), 1-2Hz (0.313, $p = 0.04$) and TWA associated with right to left sway (0.326, $p = 0.02$) after adjustment for the covariates age, height, weight and alcohol consumption. The authors conclude that change in the vestibulo-cerebellum is affected by blood Pb while in the anterior cerebellar lobe is affected by past Pb exposure. |
| Chia et al. (1994a)<br>Singapore | 60 Pb storage workers, mean age 32 (7.7) yrs and 60 controls, mean age 35 (7.4) had postural sway parameters measured. ANCOVA used to examine group differences after adjusting for covariates. Linear regression examined relationship between Pb exposure and postural sway. | Pb workers<br>Mean (SD) blood Pb 36 (11.7) µg/dL<br><br>Controls<br>Mean (SD) blood Pb 6 (2.4) µg/dL | Computerized postural sway measurements found Pb workers have poorer postural stability that increased with eyes closed ($p < 0.01$). Regression analysis adjusting for age, height, and weight found no significant association with blood Pb. |
| Chia et al. (1996c)<br>Singapore | The same 60 Pb storage workers as above and 60 control had postural sway data examined for contribution of cumulative blood Pb fractionated over 10 yrs of exposure. | Pb workers<br>Mean (SD) blood Pb 36 (11.7) µg/dL<br><br>Controls<br>Mean (SD) blood Pb 6 (2.4) µg/dL | The Pb exposed group had significantly poorer performance on all postural sway parameters with eyes closed compared to controls after adjusting for height, weight, age and drinking habits ($p < 0.01$). All postural sway parameters with eyes closed were significantly associated with IBL for the 2 yrs prior to testing ($n = 23$, $p < 0.05$). |

## Table AX6-3.7 (cont'd). Postural Stability, Autonomic Testing, Electroencephalogram, Hearing Thresholds, and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Ratzon et al. (2000)<br>Israel | 63 Pb battery workers, mean age 39 (8.7) yrs and 48 controls mean age 36 (11.8) yrs, matched for age with similar sex and education, had postural control measured. Group differences examined with t test. Dose-effect relations assessed with Pearson = s correlation coefficients. Linear regression done with exposure category as major predictor. | Mean past blood Pb 38 µg/dL<br>Mean yrs employed 11<br>Cumulative Pb determined by avg blood Pb H yrs employed | Using a computerized sway measurement system the exposed workers had significantly increased mean body oscillations with eyes closed ($p < 0.01$) and head tilted forward ($p < 0.001$). Partial correlation adjusting for education, coffee consumption, hrs of sleep and estimate of health was significant only for total Pb exposure and increased body oscillations with head tilted forward ($\exists = 2.25$, $p = 0.0089$). In order to maintain balance Pb exposed workers required increased oscillations when visual and vestibular inputs were altered. |
| Teruya et al. (1991)<br>Japan | 172 Pb exposed workers, mean age 34 (18.4-57.4) yrs had cardiac autonomic nervous system evaluated by R-R intervals variation with respiration measured. | Mean (range) blood Pb 36 (5-76) µg/dL | Age adjustment controlled for by use of ratios of predicted to observed values. A significant dose related decrease of R-R interval variation during deep breathing was present in 132 workers with stable blood Pb over the past yr ($p < 0.01$). This finding was more prominent in younger workers with blood Pb ∃30 µg/dL but a mild decrease present at blood Pb ∃20 µg/dL. A decrease in R-R interval variation indicates decreased cardiac parasympathetic function. |
| Ishida et al. (1996)<br>Japan | 128 workers in the ceramic painting industry, 58 men, mean age 55 (11.7) yrs and 70 women, mean age 52 (9.2) yrs had measures of sympathetic function by variations in R-R interval on EKG and changes in finger blood flow with postural changes using Doppler flowmetry. Correlation analyses and linear regression examined relationship of finger blood flow and Pb exposure after adjusting for covariates. | Men<br>Mean (SD) blood Pb 17 (2.1) µg/dL<br>Mean (SD) ALAD% 61.6 (28.3)%<br><br>Women<br>Mean (SD) blood Pb 11 (1.7) µg/dL<br>Mean (SD) ALAD% 72.6 (20.8)% | 22% had blood Pb >20 µg/dL, and 43% had ALAD% <60%. The 46 workers in the lowest group with blood Pb <10 µg/dL had ALAD% >80% equivalent to nonoccupational exposure and therefore served as the control group. Blood Pb ($\exists = 0.205$, $p = 0.02$), smoking ($\exists = -0.464$, $p < 0.01$), and BMI ($\exists = 0.213$, $p = 0.01$) were significant predictors of change in finger blood flow with postural change. Decrease in change of finger blood flow is compatible with a peripheral sympathetic nerve impairment. |

## Table AX6-3.7 (cont'd). Postural Stability, Autonomic Testing, Electroencephalogram, Hearing Thresholds, and Occupational Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Niu et al. (2000)<br>China | 44 Pb-exposed workers (17 men, 27 women) from Pb printing houses, mean age 35 (4.9) and education 9.3 (no SD) yrs and 34 controls (19 men and 15 women), mean age 33 (7.4) yrs and education 9.5 (no SD) yrs had autonomic nervous system examined. ANCOVA controlling for age, sex and education examined group differences and linear regression for dose-response relationship. | Pb workers<br>Mean (SD) blood Pb 29 (26.5) µg/dL<br>(8 workers blood Pb exceeded 50 µg/dL)<br><br>Controls<br>Mean (SD) blood Pb 13 (9.9) µg/dL<br>(1 control blood Pb exceeded 50 µg/dL) | Niu et al. (2000) examined autonomic nervous system in 44 Pb exposed workers, mean blood Pb 29 µg/dL, and 34 controls, mean blood Pb, 13 µg/dL. Linear regression found association between blood Pb and decreased R-R interval with valsalva (F/T 2.349, $p < 0.05$) and duration of Pb exposure and decreased R-R interval with deep breathing (F/T 3.263, $p < 0.01$) after adjusting for age, sex, education, smoking and drinking. In the same study, quantitative EEG found significant abnormalities in the Pb-exposed workers, dominant low amplitude in 59%, dominant beta frequency in 42% and abnormalities in 81%. |

## Table AX6-3.8. Occupational Exposure to Organolead and Inorganic Lead in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Schwartz et al. (1993) U.S. | Two hundred and twenty-two current employees that manufactured tetraethyl Pb participated in a study to determine if there was impairment on a neurobehavioral battery associated with a measure of cumulative exposure to organic and inorganic Pb derived from 12 yrs of air sampling. Mean age was 44 (8.7) yrs, education 13 (1.7) yrs. | Mean (SD) cumulative Pb exposure (inorganic and organic) 869 (769) μg·yr/$m^3$<br><br>Mean (SD) yrs of exposure 13 (9.5) | Exposure was divided into 4 groups with the lowest for yrs of exposure and cumulative Pb exposure serving as the reference group. After adjustments for premorbid intellectual ability, age, race, and alcohol consumption, cumulative Pb exposure had differential association poorer performance in many cognitive domains but most often in manual dexterity and verbal memory/learning. Performance on tests associated with exposure was 5 to 22% lower in the highest groups when compared with the low exposure reference group. |
| Stewart et al. (1999) U.S. | 543 former organolead workers, mean yrs since last exposure18, examined for ongoing neurobehavioral impairment related to past Pb exposure. Thirty-eight % were age 60 or older, predominantly white, 93% had at least a high school degree. Linear regression assessed the relationship between Pb dose and neurobehavioral function adjusting for the covariates. | Mean (SD) tibial Pb 14 (9.3) μg/g<br><br>Mean (SD) peak tibial bone Pb (extrapolated back using a clearance half-time of Pb in tibia of 27 yrs) 24 (17.4) μg/g<br><br>Mean (SD) DMSA chelatable Pb 19 (17.2) μg (urine collected for 4 hrs) | Peak tibial Pb was a significant predictor of poorer performance on Vocabulary (∃ = !0.063, p = 0.02), serial digit learning (∃ = !0.043, p = 0.04), RAVLT trial 1 (∃ = !0.054, p = 0.03), RAVLT recognition (∃ = !0.019, p = 0.03), Trails B (∃ = !0.002, p = 0.03), finger tapping nondominant (∃ = !0.042, p = 0.02), Purdue pegboard dominant (∃ = !0.043, p = 0.00), nondominant (∃ = !0.49, p = 0.00), both (∃ = !0.038, p = 0.00), assembly (∃ = !0.133, p = 0.00), and Stroop (∃ = !0.014, p = 0.00).<br>Current tibial Pb had similar associations – Vocabulary (∃ = 0.103, p = 0.04), Digit Symbol (∃ = !0.095, p = 0.05), finger tapping dominant (∃ = !0.87, p = 0.02), finger tapping nondominant (∃ = 0.102, p = 0.00), Purdue Pegboard dominant (∃ = !0.065, p = 0.01), nondominant (∃ = !0.091, p = 0.00), both (∃ = !0.068, p = 0.00), assembly (∃ = !0.197, p = 0.03 ), and Stroop (∃ = 0.017, p = 0.01).<br>DMSA-chelatable Pb was only significantly associated with choice reaction time (∃ = !0.001, p = 0.01). |

## Table AX6-3.8 (cont'd). Occupational Exposure to Organolead and Inorganic Lead in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Stewart et al. (2002)<br>U.S. | From the above group of former organolead workers 535 were re-examined twice or four times over a four yr period. Also a nonexposed control group of 118 had repeat examinations. Mean age at first visit exposed/controls 56 (7.4)/59 (7.0), percentage with at least a high school education 66/71.2. | 1st examination<br>Mean (SD) blood Pb 5 (2.7) µg/dL<br>Mean (SD) tibia Pb 14 (9.3) µg/g<br>Mean (SD) peak tibia Pb 23 (16.5) µg/g<br>Mean (SD) exposure duration 8 (9.7) yrs<br>Mean (SD) duration since last exposure 16 (11.7) yrs | On 17 of 19 neurobehavioral tests, former organolead workers demonstrated greater annual decline in adjusted test scores compared to controls with significant differences for Rey complex Figure copy, RAVLT Trial 1 and RAVLT recognition. Annual declines in performance showed greater age-related change in Pb workers compared to controls for block design, digit symbol, serial digit learning, finger tapping and Trails A. Blood Pb did not predict annual change scores but peak tibial Pb did for symbol digit, Rey Complex Figure delayed recall, RAVLT trial 1, RAVLT delayed recall, Purdue pegboard (1 measure) and the Stroop. For these 6 tests it was determined that an increase of 15.7 µg/g bone mineral of peak tibia Pb was equivalent in its effect on annual test decline to 5 more yrs of age at baseline. Authors conclude that data supports ongoing cognitive decline associated with past occupational exposure to Pb. |
| Balbus et al. (1997)<br>U.S. | 222 organolead manufacturing workers, mean age 44 (8.7) yrs and 62 nonexposed referents, mean age 43 (10) yrs performed simple visual reaction time (SVRT). Linear regression examined relationship between Pb exposure and mean RT, median RT and standard deviation of RT after controlling for covariates. | Mean (SD) blood Pb 20 (9.5) µg/dL<br>Mean (SD) peak urine Pb level 143 (130) µg/L | |
| Balbus et al. (1998)<br>U.S. | A second publication further examined the above data for relationship of interstimulus interval (ISI) and Pb exposure. | Same as above | Short ISIs of 1-3 seconds had no relationship with Pb exposure while ISIs of 4-6 seconds were significantly associated with blood Pb ($\exists$ = 0.06 [SE 0.02], p = 0.02 along with ISIs of 7-10 seconds ($\exists$ = 0.05 [SE 0.02], p = 0.03). ISIs 7-10 seconds with peak urine Pb levels ($\exists$ = 64.29 [SE 21.86], p < 0.01). |

## Table AX6-3.8 (cont'd). Occupational Exposure to Organolead and Inorganic Lead in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Stewart et al. (2002) U.S. | Population as described in Stewart et al. (1999) and Schwartz et al. (2000b). Data on 20 neurobehavioral tests from 529 former organolead workers were evaluated to determine if the previously described relationship with bone Pb levels is influenced by the apolipoprotein E (ApoE) genotype. | | In 20 linear regression models, coefficients for the ApoE and tibia Pb interaction term were negative in 19 with significance reached for digit symbol (∃ = !0.109 [SE 0.054], p # 0.05), Purdue pegboard dominant (∃ = 0.068 [SE 0.028], p # 0.05) and complex reaction time (∃ = !0.003 [SE 0.001], p#0.05) and borderline significance existed for symbol digit (∃ = !0.046 [SE 0.026], p # 0.10), Trails A (∃ = !0.303, [SE 0.164] p # 0.10) and Stroop (∃ = !0.013 [SE 0.008], p # 0.10). The slope of the relation between tibia Pb and neurobehavioral outcome was more negative in those individuals with at least one ε4 allele than individuals without this allele. It is suggested that the presence of one Apo-ε-4 allele increases the risk of persistent central nervous system effects of Pb. |
| Tassler et al. (2001) U.S. | 490 former organolead workers, mean age 58 (7.5) yrs. The peripheral nervous system was examined with sensory pressure thresholds, and pinch and grip strength. | Mean (SD) blood Pb 5 (2.6) µg/dL<br>Mean (SD) DMSA-chelatable Pb 19 (16.3) µg<br>Mean (SD) current tibia Pb 15 (9.4) µg/g<br>Mean (SD) peak tibia Pb 24 (17.6) µg/g | No strong association was found between Pb biomarkers and measures of sensory and motor function after adjusting for age. The authors attributed the findings to decreased sensitivity of the peripheral nerves in this dose range of inorganic Pb or the possibility of differential repair in the peripheral nervous system compared to the central nervous system. |
| Bolla et al. (1995) U.S. | 190 current workers in organolead manufacturing (from the 222 described in Schwartz et al., 1993) mean age 45 (8) yrs compared to 52 referents, mean age 45 (8) yrs and 144 solvent exposed workers, mean age 42 (8) yrs. | IH found organic Pb was 65 to 70% of exposure in production area.<br>Mean (SD) weighted avg blood Pb 24 (9.4) µg/dL | Pb and solvent exposure associated with adverse effects on tests of manual dexterity. When compared to the solvent group Pb exposure had greater impairment on memory and learning and less on executive/motor tests. An elevated neuropsychiatric score was present in 43% of the Pb group, 15% of the solvent and 7% of the referent group. |
| Mitchell et al. (1996) U.S. | 58 organolead workers, self-selected for a clinical evaluation. Mean age 45 (7.1) yrs. | Mean (SD) blood Pb 19 (6.5) µg/dL<br>Mean (SD) lifetime blood Pb 26 (9.1) µg/dL<br>Mean (SD) lifetime urine Pb 51 (18.8) µg/L | The most common symptoms were memory loss 74%, joint pain 56%, trouble sleeping 54%, irritability 51%, paresthesia 49%, fatigue 49%, nightmares 35%, moodiness 28%, headaches 21% and depression 21%. Of the 31 workers receiving nerve conduction studies, 29% were normal, carpal tunnel syndrome 36%, cubital tunnel syndrome 3%, median neuropathy 3%, ulnar neuropathy 23%, mononeuropathy in lower extremity 5%, tarsal tunnel syndrome 7% and sensorimotor polyneuropathy 36%. 39 workers had neurobehavioral evaluation with 64% had abnormal tests of which 46% were considered to be consistent with a toxic exposure. |

## Table AX6-3.9. Other Neurological Outcomes Associated with Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Louis et al. (2005)<br>New York | 63 cases of essential tremor (ET) and 101 controls, similar for age, 67 (16.6) and 65 (11.1) yrs, education, gender and ethnicity were examined for interaction of blood Pb and ALAD gene polymorphisms and increased odds of ET. | ET<br>Mean (SD) blood Pb 4 (2.2) µg/dL<br><br>Controls<br>Mean (SD) blood Pb 3 (1.5) µg/dL<br><br>2 ET cases but no controls had blood Pb >10 µg/dL | Of the 63 ET cases 18 (29%) vs. 17 (17%) of 101 controls had an ALAD2 allele (OR = 1.98 [95% CI: 0.93, 4.21]; p = 0.077). When log blood Pb was examined by presence of ALAD2 allele in ET, log blood Pb was highest in ET cases with and ALAD2 allele, intermediate in ET cases without an ALAD2 allele and lowest in controls (test for trend, ∃ = 0.10; p = 0.001). When ALAD2 allele was present, blood Pb was significantly associated with odds of ET (OR = 80.29 [95% CI: 3.08, 2.096]; p = 0.008). This increased odds of ET with an ALAD2 allele was 30 times greater than in an individual with only an ALAD1 alleles. In the highest log blood Pb tertile, ALAD2 allele was present in 22% of ET cases and 5% of controls. It was proposed that increased blood Pb along with the ALAD2 allele could affect the cerebellum and thereby increase the risk of tremor. |
| Louis et al. (2003)<br>New York | 100 cases of ET and 143 controls matched for age, sex, and ethnicity.<br>The relationship between blood Pb and ET was examined. | ET<br>Mean blood Pb 3 µg/dL<br><br>Controls<br>Mean blood Pb 2 µg/dL | Ten cases and 7 controls had bone Pb levels measured that were significantly correlated with blood Pb suggesting that higher blood Pb may have occurred in the past. Total tremor score was correlated with blood Pb (r = 0.14, p = 0.03). Logistic regression adjusting for age and current cigarette smoking found the odds ratio for ET was 1.19 (95% CI: 1.03, 1.37) per unit increase in blood Pb. Blood Pb was higher in those 39 ET cases with no family history. Both current and lifetime prevalence of occupational Pb exposure was the same in ET cases and controls but those with history of occupational exposure did have a higher blood Pb than those without this history (median, 3.1 µg/dL vs. 2.4 µg/dL, p = 0.004). |
| Kamel et al. (2002)<br>Massachusetts | 109 cases of ALS and 256 controls matched for age, sex and region of residence examined the relation of Pb and ALS. | Cases/controls<br>Mean (SD) blood Pb 5 (0.4) / 3 (0.4) µg/dL<br>3 cases and no controls had blood Pb >10 µg/dL<br>Mean (SD) patella Pb 21 (2.1) / 17 (2.0) µg/g<br>5 cases and 1 control had patella Pb levels >50 µg/g<br>Mean (SD) tibia Pb 15 (1.6) / 11 (1.6) µg/g<br>2 cases and no controls had tibia Pb >50 µg/g. | Increased risk of ALS was found for history of occupational Pb exposure (adjusted OR = 1.9 [95% CI: 1.1, 3.3]) increased lifetime days of exposure (adjusted OR = 2.3 [95% CI: 1.1, 4.9]). Association of blood Pb and ALS (adjusted OR = 1.9 [95% CI: 1.4, 2.6]). Elevation in both blood Pb and patella and tibia bone Pb was found in ALS cases though the precision of these measurements was questioned (Patella Pb adjusted OR = 3.6 [95% CI: 0.6, 20.6] and tibia Pb adjusted OR = 2.3 [95% CI: 0.4, 14.5]). Therefore, this study found Pb exposure from historical questionnaire data and biological markers associated with ALS. |

## Table AX6-3.9 (cont'd). Other Neurological Outcomes Associated with Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Kamel et al. (2003)<br>Massachusetts | As above, the same data was used to determine the associations of ALS with polymorphism in ALAD and the vitamin D receptor (VDR) and the influence of genotype. | Same as above | The ALAD2 allele was associated with a 2-fold increase risk of ALS after adjustment for the covariates, age, sex, region, education and physical activity adjusted (OR = 1.9 [95% CI: 0.60, 6.3]). Additionally adjusting for blood Pb strengthened the association of ALAD2 and ALS risk adjusted (OR = 3.6 [95% CI: 0.9, 15]). This was not found for bone Pb or occupational history of Pb exposure (patella-adjusted OR = 2.1 [95% CI: 0.61, 6.9]; tibial-adjusted (OR = 2.2 [95% CI: 0.66, 7.3]; occupational history-adjusted (OR = 2.4 [95% CI: 0.67, 8.7]). VDR was not associated with Pb or ALS risk. |
| Armon et al. (1991)<br>Minnesota | A case-control design with 47 ALS patients, mean age 61 with involvement of upper and lower motor neurons and 201 controls, mean age 62. For the Pb exposure analysis 45 male matched pairs were examined. | Lifetime exposure to Pb of 200 hrs or more (yrs on job x hrs spent per wk) | Of 13 discordant pairs for Pb exposure, 11 were in ALS patient. The relative risk was 5.5 (95% CI: 1.44, 21.0). A dose-response was weakened by 3 controls with highest lifetime exposure. Men with ALS worked more often at blue collar jobs and significantly more time welding ($p < 0.01$). These results expanded a prior pilot study that found a higher incidence of heavy metal exposure in ALS cases. |
| **Europe** | | | |
| Chancellor et al. (1993)<br>Scotland<br>1990-1991 | A case-control design 103 ALS patients from the Scottish Motor Neuron Disease Register and matched community controls. Differences in potential occupational exposures were determined between cases and controls. | Exposure to Pb obtained by lifetime employment history from Office of Population and Censuses and Surveys. Physician's record review and direct interview questionnaire. | Odds ratio for manual labor in ALS patients was 2.6 (95% CI: 1.1, 6.3). Occupational exposure to Pb was more common in ALS patients (OR = 5.7 [95% CI: 1.6, 30]). |
| Gunnarsson et al. (1992)<br>Sweden<br>1990 | A case-control study of 92 cases of MND and 372 controls. MND included ALS, progressive bulbar paresis (PBP), and progressive muscular atrophy (PMA). Relation of MND to risk factors including occupational exposure examined. | Exposure information obtained by self-administered questionnaire. | Exposure to heavy metals primarily from welding had an increased Mantel-Haenszel OR = 3.7 [95% CI: 1.1, 13.0]. |

## Table AX6-3.9 (cont'd). Other Neurological Outcomes Associated with Lead Exposure in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Guidetti et al. (1996) Italy | A retrospective incidence, prevalence, and mortality survey of ALS in northern Italy was performed. | Mean air Pb 3 μg/$m^3$ in 1975 to 1 μg/$m^3$ in 1985; blood Pb in monitored children decreased 18, 14, and 11 μg/dL in same time period. | The area studied had documented Pb pollution for yrs. Based upon 79 cases incidence and prevalence rate were comparable to the surrounding area. |
| Vinceti et al. (1997) Italy | 19 ALS cases, mean age 66 (14) yrs and 39 controls, mean age 64 (12.9) yrs. | Sporadic ALS<br>Mean (SD) blood Pb 13 (6.8) μg/dL<br><br>Controls<br>Mean (SD) blood Pb 11 (4.4) μg/dL | There were no cases familial ALS. Blood Pb between ALS cases and controls was not significantly different. Blood Pb was associated with disability due to ALS but no support was found for involvement of Pb in the etiology of sporadic ALS. |

# ANNEX TABLES AX6-4

## Table AX6-4.1. Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Kim et al. (1996)<br>Boston, MA<br>1979-1994 | 459 men in the Normative Aging Study; periodic exams every 3-5 yrs.<br><br>Mean serum creatinine at baseline<br>1.2 mg/dL<br><br>Random effects modeling, adjusting for baseline age, time since initial visit, body mass index, smoking status, alcohol ingestion, education level, hypertension (defined as blood pressure ≥160 or 95 mm Hg or anti-hypertensive medication use), and, in longitudinal analysis, baseline serum creatinine and time between visits. | Mean (SD) blood Pb at baseline<br>9.9 (6.1) µg/dL<br><br>Blood Pb levels from stored red blood cells were adjusted for hematocrit; the assay and adjustment procedure were validated against freshly collected samples. Storage tubes were shown to be Pb free. | Cross-sectional<br>Positive association between log transformed blood Pb and concurrent serum creatinine. 10-fold higher blood Pb level associated with 0.08 mg/dL higher serum creatinine (95% CI: 0.02, 0.13).<br><br>Association stronger in participants with lower peak blood Pb levels. ∃ coefficient (95% CI) in the 141 participants whose peak blood Pb #10 µg/dL: 0.06 (95% CI: 0.023, 0.097).<br><br>Longitudinal<br>Positive association between log transformed blood Pb and change in serum creatinine over subsequent follow-up period in participants whose peak blood Pb was #25 µg/dL ∃ coefficient 0.027 (95% CI: 0.0, 0.054)<br><br>Slope of age-related increase in serum creatinine steeper in group with highest quartile of time weighted avg Pb exposure compared to the lowest quartile. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Muntner et al. (2003)<br>U.S.<br>1988-1994 | Blood Pb levels measured in 15,211 adult subjects enrolled in the NHANES III study.<br><br>Study cohort representative of U.S. population; non-Hispanic African Americans, Mexican Americans, the elderly and children over-sampled to allow stable estimates in these groups.<br><br>Hypertension defined as blood pressure ∃140 and/or 90 mm Hg and/or current antihypertensive medication use. Based on evidence of interaction between blood Pb and hypertension, the population was stratified by hypertension for further analysis.<br><br>4,813 hypertensives; 10,398 normotensives.<br><br>Elevated serum creatinine (%)<br>Defined as ∃99th percentile of each race-gender specific distribution for healthy young adults [age 20-39 without hypertension or diabetes].<br><br>11.5 % (hypertensives)<br>1.8 % (normotensives)<br><br>Chronic kidney disease (%)<br>Chronic kidney disease defined as GFR <60 mL/min/1.73 $m^2$; estimated by MDRD equation (Levey et al. [1999]).<br><br>10 % (hypertensives)<br>1.1% (normotensives)<br><br>Multiple logistic regression.<br><br>Age, race, gender, diabetes, systolic blood pressure, smoking status, history of cardiovascular disease, body mass index, alcohol consumption, household income, marital status, and health insurance. | Mean (SD) blood Pb<br>4.21 (0.14) µg/dL (hypertensives)<br>3.30 (0.10) µg/dL (normotensives) | Higher odds ratios of both increased serum creatinine and chronic kidney disease by quartile of blood Pb in hypertensives but not in normotensives.<br><br>Hypertensives<br>Odds ratios for elevated serum creatinine after full adjustment:<br>Blood Pb (range, µg/dL) % Odds ratio (95% CI)<br>Quartile 1 (0.7 to 2.4) 7.2 1.00<br>Quartile 2 (2.5 to 3.8) 12.1 1.47 (1.03, 2.10)<br>Quartile 3 (3.9 to 5.9) 12.4 1.80 (1.34, 2.42)<br>Quartile 4 (6.0 to 56.0) 16.3 2.41 (1.46, 3.97)<br><br>$p < 0.001$ for chi-squared test for trend.<br><br>Odds ratios for chronic kidney disease after full adjustment:<br>Blood Pb % Odds ratio (95% CI)<br>Quartile 1 6.1 1.00<br>Quartile 2 10.4 1.44 (1.00, 2.09)<br>Quartile 3 10.8 1.85 (1.32, 2.59)<br>Quartile 4 14.1 2.60 (1.52, 4.45)<br><br>$p < 0.001$ for chi-squared test for trend.<br><br>Associations were similar when Pb was entered as a log transformed continuous variable.<br><br>In non-hypertensives, higher blood Pb was associated with a higher prevalence of chronic kidney disease, but not elevated serum creatinine, in diabetics. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Payton et al. (1994)<br>Boston, MA<br>1988-1991 | Blood Pb levels measured in 744 men enrolled in the Normative Aging Study.<br><br>Serum creatinine<br>1.3 mg/dL<br><br>Measured creatinine clearance<br>88.2 mL/min<br><br>Calculated creatinine clearance<br>71 mL/min<br><br>Multiple linear regression adjusting for age, body mass index, analgesic and diuretic use, alcohol consumption, smoking status, systolic/ diastolic blood pressure. | Mean blood Pb<br>8.1 µg/dL<br><br>Blood Pb levels below the limit of detection of 5 µg/dL were recoded as 4 µg/dL (n not stated). | In blood Pb negatively associated with ln measured creatinine clearance (∃ = !0.04 [95% CI: !0.079, !0.001]).<br><br>10 µg/dL higher blood Pb associated with a 10.4 mL/min lower creatinine clearance.<br><br>Borderline significant associations ($p < 0.1$) between blood Pb and both serum creatinine (∃ = 0.027; neither SE nor CI provided) and estimated creatinine clearance (∃ = !0.022; neither SE nor CI provided). |
| Shadick et al. (2000)<br>Boston, MA<br>1991-1996 | 777 participants in all male Normative Aging Study. | Mean blood Pb<br>5.9 µg/dL<br><br>Mean tibia Pb<br>20.8 µg/g bone mineral<br><br>Mean patella Pb<br>30.2 µg/g bone mineral | A significant association between patella Pb and uric acid (∃ = 0.0007 [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 increases uric acid. Fifty-two participants had gout; Pb dose was not associated with risk for gout. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Tsaih et al. (2004)<br>Boston, MA<br>1991-~2001 | 448 men enrolled in the Normative Aging Study.<br><br>Baseline Serum Creatinine<br>1.3 mg/dL<br><br>Longitudinal analysis of data from 2 evaluations a mean of 6 yrs apart.<br><br>Annual change in serum creatinine = (follow-up serum creatinine – baseline serum creatinine) / yrs of follow-up.<br><br>Covariates assessed = age, age squared, body mass index, hypertension (defined as blood pressure ∃160 or 95 mm Hg or physician diagnosis with use of antihypertensive medication), diabetes (defined as use of oral hypoglycemic drugs or insulin or reported physician diagnosis), smoking status, alcohol consumption, analgesic use, and, in longitudinal models, baseline serum creatinine and its square.<br><br>Six percent and 26% of subjects had diabetes and hypertension, at baseline, respectively. | Mean (SD) baseline blood Pb<br>6.5 (4.2) µg/dL<br><br>Mean (SD) baseline tibia Pb<br>21.5 (13.5) µg/g bone mineral<br><br>Mean (SD) baseline patella Pb<br>32.4 (20.5) µg/g | Mean blood Pb levels and serum creatinine decreased significantly over the follow-up period in the group. Pb dose not associated with change in creatinine overall.<br><br>Significant interaction of blood and tibia Pb with diabetes in predicting annual change in serum creatinine.<br><br>∃ (95% CI) for natural ln baseline blood Pb 0.076 (0.031, 0.121) compared to 0.006 (!0.004, 0.016) for non-diabetics.<br><br>∃ (95% CI) for natural ln baseline tibia Pb 0.082 (0.029, 0.135) compared to 0.005 (!0.005, 0.015) for non-diabetics.<br><br>Significant interaction of tibia Pb with hypertensive status in predicting annual change in serum creatinine.<br><br>∃ (95% CI) for natural ln baseline tibia Pb 0.023 (0.003, 0.019) compared to 0.0004 (!0.001, 0.002) for non-hypertensives.<br><br>Follow-up serum creatinine was also modeled separately in longitudinal analyses; diabetes modified the association between baseline tibia Pb and follow-up serum creatinine. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Wu et al. (2003a)<br>Boston, MA<br>1991-1995 | 709 men enrolled in the Normative Aging Study.<br><br>Serum creatinine<br>1.2 mg/dL<br><br>Calculated creatinine clearance<br>71.3 mL/min<br><br>Serum uric acid<br>6.5 mg/dL<br><br>Multiple linear regression, adjusting for age, body mass index, blood pressure or HTN (depending on model), and alcohol ingestion. Uric acid models also adjusted for serum creatinine, other outcome models adjusted for smoking status and analgesic medication use. | Mean (SD) blood Pb<br>6.2 (4.2) µg/dL<br>Mean (SD) tibia Pb<br>22 (13.4) µg/g bone mineral<br>Mean (SD) patella Pb<br>32.1 (19.5) µg/g bone mineral | Significant inverse association between patella Pb and creatinine clearance.<br><br>∃ = !0.069, SE not provided<br><br>Borderline significant (p = 0.08) inverse association between tibia Pb and creatinine clearance. Borderline significant (p = 0.08) positive associations between tibia and patella Pb and uric acid. No Pb measure significantly associated with serum creatinine.<br><br>ALAD gene polymorphism also assessed. 114 participants had the ALAD2 variant allele (7 were homozygous). None of the three renal outcomes differed by genotype. Effect modification by genotype on the association between tibia Pb and serum creatinine was observed; the beta coefficient (and slope) was greater in the group with the variant allele (∃ = 0.002 [SE not provided]; p = 0.03).<br><br>Effect modification of borderline significance (p < 0.1) on relations between of patella and tibia Pb with uric acid was observed; this was significant in participants whose patella Pb levels were above 15 µg/g bone mineral (∃ = 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. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Alfven et al. (2002)<br>Sweden<br>OSCAR Study<br>Date not provided | N = 479 men, 542 women. All resided near two battery plants, 117 participants were current or former workers from plants.<br><br>Renal outcome = urinary $\alpha_1$ microglobulin.<br><br>Multiple linear regression.<br><br>Age, smoking status, gender (by stratification), blood cadmium. | Mean blood Pb<br>0.16 µmolg/L men<br>0.11 µmolg/L women | Blood Pb not associated with urinary $\alpha_1$ microglobulin (regression performed separately in men and women). |
| Akesson et al. (2005)<br>Women's Health in the Lund Area Study, 1999-2000 | N = 820 women<br>Renal outcomes = GFR (estimated with cystatin C), estimated creatinine clearance, urinary NAG and $\alpha_1$ microglobulin.<br><br>Multiple linear regression.<br><br>Age, body mass index, diabetes, hypertension, and regular use of nephrotoxic drug, blood and urinary cadmium (in separate models), smoking status (by stratification). | Mean blood Pb<br>2.2 µg/dL | Blood Pb negatively associated with estimated GFR and creatinine clearance. No associations with NAG or $\alpha_1$ microglobulin.<br><br>∃ (95% CI) for association between blood Pb (µg/dL) and estimated creatinine clearance (mL/min) is !1.8 (!3.0, !0.7). |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| De Burbure et al. (2003)<br>France<br>Study date not provided | 600 adults (399 exposed, 201 age and gender matched controls).<br>400 children (200 exposed, 200 age and gender matched controls).<br>Age ranged from 8.5 to 12.3 yrs.<br>Exposure from residence near smelters.<br>Exclusion criteria for children included obesity, diabetes, and puberty; for adults included pregnancy, cancer, diabetes, and kidney disease.<br><br>Serum creatinine<br>1.43 mg/dL (adult male controls)<br>1.38 mg/dL (exposed adult males)<br>1.33 mg/dL (adult female controls)<br>1.26 mg/dL (exposed adult females)<br><br>Urinary $\exists_2$-microglobulin<br>68.16 µg/g creatinine (adult male controls)<br>76.29 µg/g creatinine (exposed adult males)<br>63.79 µg/g creatinine (adult female controls)<br>71.98 µg/g creatinine (exposed adult females)<br>87.8 µg/g creatinine (boy controls)<br>97.3 µg/g creatinine (exposed boys)<br>88.2 µg/g creatinine (girl controls)<br>94.8 µg/g creatinine (exposed girls)<br><br>Urinary NAG<br>1.12 IU/g creatinine (adult male controls)<br>1.24 IU/g creatinine (exposed adult males)<br>0.98 IU/g creatinine (adult female controls)<br>1.28 IU/g creatinine (exposed adult females)<br>2.29 IU/g creatinine (boy controls)<br>1.70 IU/g creatinine (exposed boys)<br>2.21 IU/g creatinine (girl controls)<br>1.07 IU/g creatinine (exposed girls)<br><br>Urinary RBP<br>82.8 µg/g creatinine (adult male controls)<br>85.8 µg/g creatinine (exposed adult males)<br>83.42 µg/g creatinine (adult female controls)<br>95.81 µg/g creatinine (exposed adult females)<br>94 µg/g creatinine (boy controls) 99 µg/g creatinine (exposed boys)<br>110 µg/g creatinine (girl controls) 109 µg/g creatinine (exposed girls)<br>Renal outcome measures also included urinary total protein, albumin, transferrin, and brush border antigens.<br>Multiple linear regression adjusting for age, sex, body mass index, area of residence, smoking, alcohol ingestion, mercury, cadmium and urinary creatinine level. | Geometric mean blood Pb<br>7.13 µg/dL (adult male controls)<br>6.78 µg/dL (exposed adult males)<br>4.17 µg/dL (adult female controls)<br>5.25 µg/dL (exposed adult females)<br><br>3.42 µg/dL (boy controls)<br>4.22 µg/dL (exposed boys)<br>2.74 µg/dL (girl controls)<br>3.69 µg/dL (exposed girls) | Adults<br>Mean blood Pb level higher in exposed women but not men. None of the renal outcomes analyzed showed any significant difference between exposed and unexposed groups. After adjustment for covariates, blood Pb was not associated with any renal outcomes.<br><br>Children<br>Mean blood Pb levels higher in exposed. The highest geometric mean blood cadmium was 0.52 µg/L. None of the renal outcomes were significantly higher in exposed. After adjustment for covariates, blood Pb was not associated with any renal outcomes, however, blood cadmium was positively associated with NAG. This association was present in both control and exposed areas.<br><br>Participants with extremes of urinary creatinine excluded from data analyses. As a result, number of subjects in data tables substantially less than in study. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Factor-Litvak et al. (1993)<br>Kosovo, Yugoslavia<br>1985-1986 | 1447 Yugoslavian women in prospective study of environmental Pb exposure and pregnancy.<br><br>Exposure from Kosovska Mitrovica with a Pb smelter, refinery, and battery plant. Controls from Pristina, 25 miles away.<br><br>Renal outcome = Proteinuria assessed with a dipstick.<br><br>Exclusionary criteria included HTN (n = 37 excluded, similar blood Pb levels to remaining participants).<br><br>Multiple logistic regression adjusting for age (linear and quadratic), height (linear and quadratic), cigarette smoking, gestational age (linear and quadratic), daily milk consumption, number of previous live births, avg weekly meat consumption, hemoglobin level and ethnic group. | Mean blood Pb<br>17.1 µg/dL (582 exposed)<br>5.1 µg/dL (865 controls) | Proteinuria (negative, trace, or ∃1+)<br>Exposed = 16.2% negative, 74.1% trace and 9.7% with ∃1+ proteinuria. Controls = 32.4% negative, 60.6% trace and 7.1% with ∃1+ proteinuria. Authors attributed overall high proportion of proteinuria to pregnancy.<br><br>Higher blood Pb associated with increased odds ratio for trace and ∃1+ proteinuria.<br><br>Comparing women in upper 10th percentile of exposure to lower 10th percentile of exposure, adjusted odds ratios (95% CI) for trace and ∃1+ proteinuria was 2.3 (1.3, 4.1) and 4.5 (1.5, 13.6), respectively.<br><br>Limitations = limited renal outcomes assessed. |
| Staessen et al. (1990)<br>London, England<br>Study date not provided | 531 London civil servants (398 male, 133 female).<br><br>Exclusionary criteria = occupational exposure to heavy metals.<br><br>Serum creatinine<br>1.10 mg/dL (men)<br>0.88 mg/dL (women) | Mean blood Pb<br>12.4 µg/dL (men)<br>10.2 µg/dL (women) | After removal of 2 outliers, the study found no significant correlation between serum creatinine and log blood Pb in men.<br><br>No correlation between serum creatinine and log blood Pb in women.<br><br>Limitations = lack of adjustment in data analysis, limited Pb dose and renal outcome assessment, loss of power by analyzing gender in separate models. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Staessen et al. (1992)<br>Belgium<br>1985-1989 | Blood Pb levels were measured in 1981 adult subjects (965 males, 1016 females) enrolled in the Cadmibel study of general Belgian population in four cadmium polluted and unpolluted areas.<br><br>Inclusion criteria included age ∃20 yrs and residence in one of four study areas for ∃8 yrs. Participants were randomly selected from the study areas; participation rates were 78% in the two rural areas but only 39% in the urban areas (one area from each category was known to be cadmium polluted).<br><br>Measured creatinine clearance<br>99 mL/min (males)<br>80 mL/min (females)<br><br>Calculated creatinine clearance<br>80 mL/min (males)<br>69 mL/min (females)<br><br>Multiple linear regression.<br><br>Covariates assessed included age, age squared, gender (by stratifying), body mass index, blood pressure, ferritin level, smoking status, alcohol ingestion, rural vs. urban residence, analgesic and diuretic use, blood and urinary cadmium, diabetes, occupational exposure to heavy metals, and gamma glutamyl transpeptidase. | Blood Pb<br>11.4 µg/dL (males)<br>7.5 µg/dL (females)<br><br>Zinc protoporphyrin also assessed. | After adjustment, log transformed blood Pb negatively associated with measured creatinine clearance.<br>∃ coefficient (95% CI)<br>!9.5 (!0.9, !18.1) males<br>!12.6 (!5.0, !20.3) females<br><br>A 10 fold increase in blood Pb associated with a decrease in creatinine clearance of 10 and 13 mL/min in men and women, respectively.<br><br>Log transformed blood Pb also negatively associated with calculated creatinine clearance.<br>∃ coefficient (95% CI)<br>!13.1 (!5.3, !20.9) males<br>!30.1 (!23.4, !36.8) females<br><br>Log transformed zinc protoporphyrin negatively associated with measured and calculated creatinine clearances and positively associated with serum $\exists_2$-microglobulin in both sexes and with serum creatinine in men.<br><br>Blood Pb positively associated with serum $\exists_2$-microglobulin in men. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** | | | |
| Lin et al. (1993)<br>Taiwan<br>Study date not provided | 123 adults living near a Pb battery factory for more than 10 yrs.<br><br>Divided into 3 groups by proximity to the factory.<br>Group 1 ≤500 m (n = 49)<br>Group 2 1000-1500 m (n = 47)<br>Group 3 farther away (n = 27)<br><br>Exclusionary criteria included history of exposure to nephrotoxicants and nephrotoxicant medications, such as NSAIDs.<br><br>24 h urinary NAG excretion<br>3.3 U/day (Group 1)<br>2.4 U/day (Group 3)<br><br>Multiple linear regression with adjustment for age. | Mean blood Pb<br>16.6 µg/dL (Group 1)<br>13.5 µg/dL (Group 2)<br>7.9 µg/dL (Group 3)<br><br>EDTA diagnostic chelation (done in Group 1)<br>126.1 µg/24 hrs | Significantly higher prevalence of abnormal urinary NAG found in the exposed group 1 compared to the control group 3 (55.6% compared to 11.1%; $p < 0.001$). However, mean NAG not significantly higher in Group 1.<br><br>In all 45 participants in whom both measures were obtained, EDTA chelatable Pb was not correlated with urinary NAG excretion. However, a significant correlation between EDTA chelatable Pb #200 µg/24 hrs and urinary NAG excretion was observed in the 39 participants in this group. Further evaluation with multiple linear regression, adjusting for age, revealed a ∃ = 0.034 (95% CI: 0.009, 0.059); $p = 0.01$.<br><br>No correlation noted between blood Pb level and urinary NAG.<br><br>Limitations = small sample size, plots indicate potential for influential outliers. |
| Satarug et al. (2004)<br>Bangkok, Thailand<br>Study date not provided | 118 Thai adults (53 men, 65 women).<br><br>Renal outcome measures noted below, also include BUN and total urinary protein.<br><br>Serum creatinine<br>0.94 mg/dL (males)<br>0.66 mg/dL (females)<br><br>Urinary NAG<br>4.4 U/g creatinine (males)<br>4.6 U/g creatinine (females)<br><br>Urinary $\exists_2$-microglobulin<br>51 µg/g creatinine (males)<br>29 µg/g creatinine (females) | Mean "serum" Pb<br>0.42 µg/dL (males) 0.3 µg/dL (females)<br><br>Note – cannot determine from article if actually serum Pb (much less commonly used) or blood Pb.<br><br>Mean urinary Pb<br>1.3 µg/g creatinine (males)<br>2.4 µg/g creatinine (females)<br><br>Urinary cadmium also assessed. | In men, urinary Pb excretion correlated only with urinary protein at borderline significance ($r = 0.22$, $p < 0.06$).<br><br>In women, urinary Pb excretion correlated with urinary NAG ($r = 0.5$, $p < 0.001$), protein ($r = 0.31$, $p = 0.01$) and $\exists_2$-microglobulin ($r = 0.36$, $p = 0.002$) excretion.<br><br>After adjustment for urinary cadmium, only association between urinary Pb and NAG remained significant.<br><br>Three urinary renal biomarkers correlated with urinary cadmium, although only at borderline significance ($p = 0.06$) for $\exists_2$-microglobulin.<br><br>Limitations = small sample size, Pb dose assessment since only urine Pb used in renal analyses, limited data analysis. |

## Table AX6-4.1 (cont'd). Renal Effects of Lead in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Satarug et al. (2004)<br>Bangkok, Thailand<br>Study date not provided | 96 Thai men.<br><br>Subjects subdivided into nonsmokers (n = 53), current smokers (n = 27), and ex-smokers (n = 16).<br><br>Renal outcome measures noted below, also include BUN and total urinary protein.<br><br><u>Serum creatinine</u><br>0.94 mg/dL (nonsmokers)<br>0.93 mg/dL (smokers)<br>0.96 mg/dL (ex-smokers)<br><br><u>Urinary NAG</u><br>4.4 U/g creatinine (nonsmokers)<br>4.2 U/g creatinine (smokers)<br>3.8 U/g creatinine (ex-smokers)<br><br><u>Urinary $\exists_2$-microglobulin</u><br>51 µg/g creatinine (nonsmokers)<br>95 µg/g creatinine (smokers)<br>98 µg/g creatinine (ex-smokers) | <u>Mean "serum" Pb</u><br>0.42 µg/dL (nonsmokers)<br>0.9 µg/dL (smokers)<br>0.61 µg/dL (ex-smokers)<br><br><u>Mean urinary Pb</u><br>1.3 µg/g creatinine (nonsmokers)<br>1.4 µg/g creatinine (smokers)<br>1.4 µg/g creatinine (ex-smokers)<br><br>Urinary cadmium also assessed. | Urinary Pb correlated with urinary protein ($r = 0.49$, $p < 0.01$) in smokers and at borderline significance ($r = 0.22$; $p = 0.06$) in never smokers. Also correlated with $\exists_2$-microglobulin in ex-smokers at borderline significance ($r = 0.39$; $p = 0.06$).<br><br>Urinary cadmium correlated with urinary NAG in current and never smokers and at borderline significance ($p = 0.07$) in ex-smokers. Also correlated with urinary protein and $\exists_2$-microglobulin in current smokers and, at borderline significance, in never smokers.<br><br>Limitations = small sample size, Pb dose assessment since only urine Pb used in renal analyses, limited data analysis. |
| **Middle East** | | | |
| Mortada et al. (2004)<br>Egypt<br>Study date not provided | 68 Egyptian men (35 smokers, 33).<br><br>Renal outcomes included serum creatinine, BUN, and $\exists_2$- microglobulin and urinary albumin, NAG, $\exists_2$-microglobulin, alkaline phosphatase, and γ-glutamyl transferase. | <u>Mean blood Pb</u><br>14.4 µg/dL (smokers)<br>10.2 µg/dL (nonsmokers)<br><br>Pb also measured in urine, hair, and nails.<br><br>Also measured cadmium, and mercury. | Blood and hair Pb levels significantly higher in smokers as compared to nonsmokers.<br><br>No significant differences in renal outcome measures by smoking status. No correlation between exposure indices and renal outcome measures.<br><br>Limitations: small sample size, data analysis – no adjustment. |

## Table AX6-4.2. Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Smith et al. (1995)<br>U.S.<br>Study date not provided | 691 construction workers.<br>96 participants with the ALAD2 allele. | Mean blood Pb<br>7.8 µg/dL (ALAD11)<br>7.7 µg/dL (ALAD12 or 22) | Higher mean BUN ($p = 0.03$) in participants with the ALAD2 allele compared to those with the ALAD11 genotype. However, after adjustment for age, alcohol ingestion, and blood Pb, the association was no longer significant. Effect modification was not evaluated. |
| **Europe** | | | |
| Bergdahl et al. (1997)<br>Sweden<br>Study date not provided | 89 Pb workers; 7 had the ALAD2 allele.<br>34 controls; 10 had the ALAD2 allele. | Median blood Pb<br>31.1 µg/dL in Pb workers with ALAD11<br>28.8 µg/dL in Pb workers with ALAD12 or 22<br>3.7 µg/dL in control workers with ALAD11<br>3.7 µg/dL in control workers with ALAD12 or 22 | Higher crude mean serum creatinine ($p = 0.11$) in participants with the ALAD2 allele compared to those with the ALAD11 genotype. Adjusted data not presented. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| C<rdenas et al. (1993)<br>Belgium<br>Study date not provided | N = 41 Pb smelter workers, 41 controls (all males).<br><br>Study started with 50 Pb smelter workers and 50 controls. Blood Pb level >35 µg/dL and exposure >1 yr were required in exposed workers. Participants with renal disease, renal risk factors, such as diabetes or regular analgesic medication use, or urinary cadmium >2 µg/g creatinine, were excluded.<br><br>Multiple linear regression; adjusted for urinary creatinine and, in some cases, BMI.<br><br><u>Serum creatinine</u><br>1.02 mg/dL (workers)<br>1.03 mg/dL (controls)<br><br>Battery of more than 20 renal biomarkers obtained including:<br><br><u>RBP</u><br>68 µg/L (workers)<br>64 µg/L (controls)<br><br><u>NAG</u><br>1.56 U/L (workers)<br>1.21 U/L (controls) | <u>Mean blood Pb</u><br>48.0 µg/dL (workers)<br>16.7 µg/dL (controls)<br><br>Mean duration of Pb exposure = 14 yrs<br><br>Urinary cadmium also measured as potential confounder. | Serum creatinine was not increased in Pb workers compared to controls; associations between Pb dose and serum creatinine, if assessed, were not specifically reported.<br><br>In all 82, blood Pb:<br>-associated with thromboxane $B_2$ (∃ = 0.36, $p < 0.01$).<br>-negatively associated with 6-keto-prostaglandin $F_{1\ alpha}$ (∃ = !0.179, $p < 0.01$).<br><br>Zinc protoporphyrin positively associated with sialic acid excretion.<br><br>NAG increased in Pb workers but associated with urinary cadmium.<br><br>Limitations = sample size, potential for healthy worker bias, limited statistical analysis. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Coratelli et al. (1988)<br>Study location and date not provided; authors from Italy | 20 Pb battery factory workers.<br><br>20 controls.<br><br>12 mo longitudinal study.<br><br>Renal outcomes = urinary alanine aminopeptidase, NAG and lysozyme. | Initial mean blood Pb<br>47.9 µg/dL (workers)<br>23.6 µg/dL (controls) | NAG and lysozyme higher in exposed compared to controls throughout study. A statistically significant decline in urinary NAG was noted in association with a one mo period of decreased occupational exposure in the Pb workers. NAG correlated with time of exposure (nonlinear) but not blood Pb. Clinical renal function measures were not studied. |
| Fels et al. (1994)<br>Study location and date not provided | 81 male Pb workers; 45 age matched controls.<br><br>Extensive exclusionary criteria.<br><br>Renal outcomes<br>Serum creatinine<br>Glomerular markers = 6-keto-prostaglandin $F_{1\ alpha}$, thromboxane $B_2$, and fibronectin.<br>Proximal tubular markers = brush border antigens (BBA, BB50, HF5) and intestinal alkaline phosphatase.<br>Distal nephron markers = prostaglandin $E_2$, prostaglandin $F_{2\ alpha}$. | Median blood Pb<br>42.1 µg/dL (workers)<br>7.0 µg/dL (controls) | Serum creatinine similar in exposed compared to controls. Medians of several markers statistically greater in workers compared to controls. After adjustment for age and erythrocyte protoporphyrin, several renal marker outcomes showed "some relation" to blood Pb. The table of these data shows r and $r^2$ but not beta coefficients making the actual statistical method used unclear.<br><br>Study limitations include lack of adjustment in statistical analysis, potential for healthy worker bias. |
| Garçon et al. (2004)<br>France<br>Study date not provided | 35 male nonferrous metal smelter workers.<br>Renal outcomes = $\alpha_1$-microprotein, $\exists_2$-microglobulin, retinol binding protein, α and π glutathione S transferases (GST).<br>Oxidative stress markers also measured.<br>All variables log transformed. | Mean blood Pb<br>39.6 µg/dL<br>Mean blood cadmium<br>5.8 µg/L<br>Mean urine cadmium<br>4.7 µg/g creatinine | Correlations between urine Pb and cadmium and the renal outcomes assessed (not blood Pb or cadmium).<br><br>Significant positive correlations included:<br>urine Pb and α GST ($p < 0.01$)<br>urine cadmium and RBP ($p < 0.05$)<br><br>Also, urine cadmium and 8-OHdG negatively correlated.<br><br>Limitations = use of urine Pb, lack of adjustment for other covariates, sample size.<br><br>Significant correlations between blood Pb and two markers of oxidative stress were observed along with a correlation between blood cadmium and one marker of oxidative stress. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Gennart et al. (1992) Study location and dates not provided; authors from Belgium | 98 Pb workers and 85 controls from initial group of 221.<br><br>Renal outcomes = urinary retinol-binding protein, ∃-2 microglobulin, albumin, NAG, and serum creatinine and ∃-2 microglobulin and estimated creatinine clearance.<br><br>Exclusionary criteria included lack of exposure to other metals or solvents, urinary cadmium <2 µg/g creatinine, neurologic or renal disease, certain medications, blood Pb level >40 µg/dL (workers) and <40 µg/dL for controls. | Mean blood Pb<br>51 µg/dL (workers)<br>20.9 µg/dL (controls)<br><br>Mean duration of employment<br>10.6 yrs | Mean renal outcomes were not different in workers compared to controls. Prevalence of abnormal values was not greater in workers compared to controls. An analysis of variance, in all participants, by categorical blood Pb, duration of employment, ZPP, and delta-aminolevulinic acid showed no relations with any of the outcomes (data were not shown).<br><br>Limitations include high Pb levels in controls, adjustment only for age in statistical analysis, potential healthy worker bias. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Gerhardsson et al. (1992)<br>Sweden<br>Study date not provided | 70 current Pb smelter workers.<br>30 retired Pb smelter workers.<br>31 active and 10 retired truck assembly workers (controls).<br>Renal outcomes = serum creatinine, urinary ∃-2 microglobulin, NAG, and albumin, clearances of creatinine, albumin, relative albumin, ∃-2 microglobulin and relative ∃-2 microglobulin.<br><br>Blood Pb measured annually since 1950; time integrated blood Pb index = summation of annual blood Pb measurements. | <u>Median blood Pb</u><br>31.9 µg/dL (current Pb workers)<br>9.9 µg/dL (retired Pb workers)<br>4.1 µg/dL (current control workers)<br>3.5 µg/dL (retired control workers)<br><br><u>Median time integrated blood Pb index</u><br>369.9 µg/dL (current Pb workers)<br>1496.1 µg/dL (retired Pb workers)<br><br><u>Median calcaneus Pb</u><br>48.6 µg/g bone mineral (current Pb workers)<br>100.2 µg/g bone mineral (retired Pb workers)<br><br><u>Median tibia Pb</u><br>13.0 µg/g bone mineral (current Pb workers)<br>39.3 µg/g bone mineral (retired Pb workers)<br>3.4 µg/g bone mineral (current control workers)<br>12.0 µg/g bone mineral (retired control workers) | Creatinine clearance was higher in Pb workers; p-values not reported for this or other median values between Pb workers and controls.<br><br>In current Pb workers, blood Pb was positively correlated with urinary ∃-2 microglobulin and time integrated blood Pb index was correlated with NAG (data not shown).<br><br>Strengths include assessment of cumulative Pb, inclusion of former workers.<br><br>Limitations = statistical analysis, lack of power by stratifying. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Pergande et al. (1994)<br>Study location and date not provided; research team is German | 82 male Pb workers.<br><br>44 age-matched healthy male volunteers without known exposure to Pb and living "in areas distant from the exposed people."<br><br>Renal outcomes = serum creatinine and $\exists_2$ microglobulin, urinary albumin and 14 other early biological effect markers.<br><br>Exclusion criteria included prescription medication use and many diseases; 11 workers and 3 controls excluded. | Mean blood Pb<br>42.1 µg/dL (workers)<br>7.0 µg/dL (controls)<br><br>Erythrocyte protoporphyrin also measured. | Serum creatinine and $\exists_2$ microglobulin not increased in exposed compared to control participants; correlations with these outcomes not reported. Blood Pb and/or erythrocyte protoporphyrin correlated with 9 of the urinary renal outcomes.<br><br>Study limitations include lack of adjustment in statistical analysis, potential for healthy worker bias, potential for differences between exposed and control groups. |
| Restek-Samaržija et al. (1996)<br>Croatia<br>Study date not provided | 74 patients treated between 1951 and 1989 for at least one episode of Pb poisoning (53 occupational, 23 environmental).<br><br>Renal outcomes = measured creatinine clearance (collection time not specified), GFR assessed with $^{99m}$Tc-diethylenetriaminepenta-acetic acid (DTPA) clearance. | | Number of past Pb poisonings negatively correlated with creatinine and DTPA clearances. |
| Restek-Samaržija et al. (1997)<br>Croatia<br>Study date not provided | 38 patients with occupational Pb poisoning, 23 occupationally exposed workers.<br><br>Renal outcomes = serum creatinine, measured creatinine clearance (collection time not specified), hippuran renal flow. | Mean blood Pb<br>1.5 µmol/L (poisoned workers)<br>1.6 µmol/L (workers) | Creatinine clearance significantly lower in poisoned group. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Roels et al. (1994)<br>Belgium<br>Study date not provided | 76 Pb smelter workers (including 21 participants from Cardenas et al. [1993] [Dr. Roels, email communication])<br>68 controls.<br>All males.<br><br>Matched for age, sex, socioeconomic status, residence, and workshift characteristics.<br><br>Extensive exclusionary criteria included renal disease, analgesic abuse, chronic medication for gout, diabetes, occupational exposure to other nephrotoxicants, and prior EDTA chelation.<br><br>Renal outcomes included serum creatinine and urea nitrogen, measured creatinine clearance, NAG, RBP, serum and urinary $\exists_2$-microglobulin, as well as other renal early biological effect markers.<br><br><u>Measured creatinine clearance</u><br>121.3 mL/min/1.73 $m^2$ (workers)<br>115.5 mL/min/1.73 $m^2$ (controls)<br><br>Multiple linear regression, adjusted for age, urinary cadmium, hypertension, serum gamma-glutamyl transpeptidase, smoking, exposure status (exposed vs. control), and interaction between exposure variables and hypertension. | <u>Mean blood Pb</u><br>43.0 µg/dL (workers)<br>14.1 µg/dL (controls)<br><br><u>Mean tibia Pb</u><br>66 µg/g bone mineral (workers)<br>21 µg/g bone mineral (controls)<br><br>Urinary cadmium also measured. | Creatinine clearance measured before and after an oral protein load to determine if eicosanoid changes in Cardenas et al. (1993) had clinical implications (Acute protein ingestion causes increased renal perfusion and transient hyperfiltration thought to be mediated by changes in vasodilator prostanoids. Therefore, it was hypothesized that, if the changes noted in Cardenas et al. (1993) were clinically significant, the hyperfiltration response would be diminished in the Pb workers.).<br><br>All participants had normal baseline creatinine clearances (>80 mL/min/1.73 m²). Both control and Pb-exposed workers showed a similar increment in creatinine clearance after protein load.<br><br>However, mean creatinine clearance was statistically higher in Pb workers compared to controls. Log tibia Pb was positively correlated with log measured creatinine clearance in the combined group ($\exists$ = 0.0319, SE not provided).<br>This was unexpected as the change in eicosanoids found in the initial study would not seem to result in vasodilatation with increased GFR. Unfortunately, it was not possible to measure eicosanoid levels in the follow-up study. No other significant associations between Pb measures and renal outcomes were observed. Urinary cadmium associated with NAG. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Verschoor et al. (1987)<br>Study location and date not provided; authors from The Netherlands | 155 Pb workers (Pb battery and plastic stabilizer).<br><br>126 control industrial workers.<br><br>Workers with renal disease, HTN, prescription medications excluded.<br><br>Renal outcomes = BUN, serum creatinine, uric acid, $\exists_2$-microglobulin, and RBP, and urinary RBP, NAG, albumin, uric acid, $\exists_2$-microglobulin, IgG, and total protein. Urine protein electrophoresis performed on subset (n = 25).<br><br>Cadmium in blood and, in a subset of exposed workers, in urine was also assessed due to this exposure in one plant each from which Pb exposed and control workers were drawn. | Mean blood Pb<br>47.5 µg/dL (workers)<br>8.3 µg/dL (controls)<br><br>Zinc protoporphyrin<br>also used as Pb dose measure. | Mean renal outcomes in all participants shown by categorical Pb levels. NAG and RBP higher at blood Pb levels >21 µg/dL compared to those below this level (statistical significance not reported). Serum $\exists_2$-microglobulin and urinary total protein lower at blood Pb levels >21 µg/dL compared to those below this level (again, statistical significance not reported).<br><br>In simple linear regression models of log transformed urinary total protein, urinary RBP, NAG and serum $\exists_2$-microglobulin, higher log transformed blood Pb was significantly associated with lower serum $\exists_2$-microglobulin and higher RBP and NAG.<br><br>A matched pair analysis of 55 pairs matched for age within 5 yrs, smoking, socioeconomic status, and duration of employment found no differences in renal outcomes between exposed and controls.<br><br>Limitations = lack of adjustment, potential for healthy worker bias, occupational cadmium exposure (including in controls) not adequately adjusted. |
| **Latin and South America** | | | |
| Cardozo dos Santos et al. (1994)<br>Study location and date not provided; authors from Brazil | 166 Pb battery workers.<br>60 control workers.<br><br>Renal outcomes = serum creatinine, NAG, urine albumin, and total urinary protein, γ-glutamyl-transpeptidase, alanine-aminopeptidase. | Median blood Pb<br>36.8 µg/dL (workers)<br>11.6 µg/dL (controls) | Significant results.<br>Median NAG higher in exposed group ($p < 0.001$).<br>Blood Pb level and duration of exposure correlated with NAG in combined group (Spearman's correlation coefficients = 0.32 and 0.22, respectively, $p < 0.001$ for both).<br>No results mentioned for serum creatinine.<br>Limitations = statistical analysis (no regression for renal outcomes). |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin and South America** (cont'd) | | | |
| Pinto de Almeida et al. (1987)<br>Northeast Brazil<br>Study date not provided | 52 primary Pb smelter workers (had to have worked ≥ 5 yrs on production line).<br><br>44 control paper mill workers in same city.<br><br>All males.<br><br>Renal outcomes = BUN, serum creatinine, uric acid, proteinuria, creatinine clearance.<br><br>Only 2 participants excluded for medical reasons. | Mean blood Pb<br>64.1 µg/dL (workers)<br>25.5 µg/dL (controls)<br><br>Also measured zinc protoporphyrin and delta-aminolevulinic acid | Mean serum creatinine and uric acid higher in exposed than controls (1.23 vs. 1.1 mg/dL; $p < 0.05$ and 6.6 vs. 4.7 mg/dL; $p < 0.001$, respectively).<br><br>Serum creatinine ∃1.5 mg/dL present in 32.7% Pb workers compared to only 2.3% controls.<br><br>Serum creatinine correlated with duration of employment.<br><br>Limitations = data analysis including lack of adjustment, several outcomes not analyzed. |
| **Australia** | | | |
| Pollock and Ibels (1988)<br>Harbor Bridge workers in Sydney, Australia<br>Study date not provided | 38 bridge workers.<br>Twenty-four h urine Pb excretion following 1 g of EDTA.<br>Renal outcomes = serum creatinine, creatinine clearance, and 24 h urine protein excretion. | Mean (range) blood Pb<br>34.8 (21.8 to 56.2) µg/dL (Pb intoxication)<br><br>19.9 (9.5 to 26.1) µg/dL (nontoxic)<br><br>EDTA chelatable Pb range<br>443 to 2366 µg/24 hrs (Pb intoxication)<br><br>131 to 402 µg/24 hrs (nontoxic) | No significant differences in renal outcomes by Pb exposure group. Two workers in high exposure group had evidence of Pb nephropathy. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Chia et al. (1994b)<br>Study location not provided; authors from Singapore<br><br>1982-1992 (blood Pb measurements obtained every 6 mos over this time) | 128 Pb workers.<br>152 control workers without Pb or cadmium exposure.<br>Renal outcomes = total NAG, NAG-B isoenzyme (released with lysosomal breakdown assoc with cell membranes, thought to indicate proximal tubular cell toxicity), NAG-A (released by exocytosis).<br>Cross-sectional outcomes but longitudinal exposure data. | Median blood Pb<br>33.8 µg/dL (workers)<br>8.7 µg/dL (controls)<br><br>Median cumulative blood Pb (mean of 3.6 blood Pb levels per worker)<br>208.3 µg·yr/dL<br><br>Mean change in blood Pb (in 6 mos preceding NAG measurement)<br>5.8% | NAG not different in exposed compared to control workers.<br>After adjustment for race, recent change in blood Pb was significantly associated with all NAG outcomes (standardized partial regression coefficients ranged from 0.31 for NAG-A to 0.64 for total NAG; neither SE nor CI provided).<br><br>In contrast, current blood Pb was inversely associated with NAG-A and NAG-B separately but, oddly, not with total NAG. Authors do not comment on these inconsistencies.<br>NAG not associated with cumulative Pb dose.<br><br>Strengths = longitudinal exposure data.<br>Limitations = data analysis clarity and adjustment. |
| Chia et al. (1994c)<br>Singapore<br><br>Study location not provided; authors from Singapore<br><br>1982-1992 (blood Pb measurements obtained every 6 mos over this time) | 63 Pb workers of >6 mos work duration (median = 3 yrs).<br>91 Pb workers of <6 mos work duration were considered controls.<br>Renal outcomes = urinary BB-50 (brush border antigen in proximal tubule), total NAG, NAG-B isoenzyme, RBP, α-1-microgobulin, albumin and urine and serum $\exists_2$-microglobulin.<br>Cross-sectional outcomes but longitudinal exposure data. | Pb dose measures<br>(means or medians not stated)<br><br>Most recent blood Pb, time integrated blood Pb index, relative % change in blood Pb, absolute change in blood Pb, number of times blood Pb level >40, 50, and 60 µg/dL. | Urinary BB-50 higher in exposed compared to recent hire "control" workers. Time integrated blood Pb, number of times blood Pb >40 µg/dL, and relative change in recent blood Pb were associated with urinary BB-50.<br>Strengths = longitudinal exposure data.<br>Limitations = data analysis content (Pb dose means not reported), clarity and adjustment. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Chia et al. (1995a)<br><br>Study location not provided; authors from Singapore<br><br>1982-1993 (blood Pb measurements obtained every 6 mos over this time) | 137 Pb stabilizer workers.<br>Control group of 153 postal workers (older than Pb workers).<br>Renal outcomes = serum creatinine, four h creatinine clearance, serum ∃-2 microglobulin, serum α-1 microglobulin, urine albumin.<br>Longitudinal blood Pb data (mean of 4.5 measurements per Pb worker). | <u>Pb dose measures</u><br>(means or medians not stated)<br><br>Most recent blood Pb, time integrated blood Pb index, relative % change in recent blood Pb, absolute change in recent blood Pb, number of times blood Pb level >40, 50, and 60 µg/dL. | In analysis of covariance modeling, adjusted for age and race, mean serum α-1 microglobulin and urine albumin were significantly higher in control compared to Pb workers. Serum ∃-2 microglobulin was significantly higher in Pb workers ≥30 yrs of age.<br><br>After adjustment for age, race, and smoking, prevalence rates for abnormal values of serum creatinine and ∃-2 microglobulin were higher in the highest category of time integrated blood Pb index in workers ∃30 yrs of age (PRR = 3.8 [95% CI: 1.1, 13.3] and 10.3 [95% CI: 3.9, 26.9], respectively).<br><br>Strengths = longitudinal exposure data.<br>Limitations = data analysis content (Pb dose means not reported), clarity and adjustment. |
| Chia et al. (1995b)<br><br>Study location not provided; authors from Singapore<br><br>1982-1993 (blood Pb measurements obtained every 6 mos over this time) | 128 Pb stabilizer factory workers.<br>93 unexposed control subjects (evaluated at pre-employment examination; all quit within 1 mo of hire).<br>Blood and urinary cadmium also measured on random subset (40 controls and 31 Pb workers).<br>Renal outcomes = serum ∃-2 microglobulin and urinary α-1 microglobulin, ∃-2 microglobulin, albumin, RBP. | <u>Mean recent blood Pb</u><br>32.6 µg/dL (workers)<br>9.0 µg/dL (controls)<br><br><u>Mean time integrated blood Pb index</u><br>119.9 µg/dL H yr (workers)<br>0.05 µg/dL H yr (controls)<br><br><u>Mean relative change in recent blood Pb</u><br>28.2 % (workers)<br><br><u>Mean absolute change in recent blood Pb</u><br>6.4 µg/dL/yr (workers)<br><br>Number of times blood Pb level >40, 50 and 60 µg/dL | Only urinary α-1 microglobulin was significantly higher in Pb workers compared to controls.<br><br>In multiple linear regression analysis, adjusted only for ethnicity and smoking, at least one Pb measure was significantly associated with each of the five renal outcomes.<br><br><u>Outcome</u> — <u>Pb measure</u> — <u>∃ (95% CI)</u><br>U α-1 MG — cum. blood Pb — 0.10 (0.06, 0.14)<br>U α-1 MG — # blood Pb >50 — 0.43 (0.04, 0.82)<br>U ∃-2 MG — cum. blood Pb — 0.05 (0.01, 0.09)<br>U RBP — # blood Pb >50 — 0.35 (0.12, 0.59)<br>S ∃-2 MG — # blood Pb >60 — 0.47 (0.29, 0.65)<br>U Alb — # blood Pb >60 — 0.66 (0.13, 1.19)<br><br>Cadmium dose measures reportedly not significant in these models (although power would have been reduced as cadmium measured only in a subset).<br><br>Strengths = longitudinal exposure data.<br>Limitations = data analysis clarity and adjustment. Overlap in populations between this study and earlier ones possible. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Endo et al. (1990)<br><br>Study location not provided; authors from Japan<br>1987 | 39 male workers.<br>7 female workers (none directly exposed to Pb).<br>Secondary Pb refinery, mean job duration = 10.5 yrs<br>Renal outcomes = BUN, serum creatinine and uric acid, urinary NAG, and tubular reabsorption of phosphate. | <u>Mean blood Pb</u><br>Ranged from 24.1 to 67.6 µg/dL (males)<br>19.6 µg/dL (females)<br><br>Other Pb measures included urinary Pb, delta-aminolevulinic acid, and coproporphyrin. | Significant correlations of blood Pb and delta-amino-levulinic acid with BUN and NAG were observed. The correlation between blood Pb and NAG was dependent on a small number of workers whose blood Pb levels were above 80 µg/dL.<br><br>Limitations include absence of adjustment in statistical analysis, small sample size. |
| Endo et al. (1993)<br><br>Study location and date not provided; authors from Japan | 99 male Pb workers.<br>Renal outcomes = serum creatinine and serum and urine alpha-1-microglobulin. | <u>Median blood Pb</u><br>Ranged from 7.9 µg/dL in category I consisting of 16 office workers who did not work directly with Pb to 76.2 µg/dL in 16 workers in the highest exposure group (category V). | Median urinary alpha-1-microglobulin significantly higher in categories III–V compared to the low exposure group of office workers. This was also the only renal outcome to be significantly correlated with blood Pb (Spearman rank correlation).<br><br>After alpha-1-microglobulin adjusted for age and blood Pb (by stratifying); few significant differences noted. However, analysis approach resulted in substantial loss of power. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Hsiao et al. (2001)<br>Taiwan, PR China<br>1991-1998 | 30 Pb battery workers.<br><br>Mean serum creatinine at baseline<br>~ 1.0 mg/dL (based on figure; exact values not provided)<br>Longitudinal Analysis, 8 annual evaluations.<br><br>Generalized estimating equations used to adjust for autocorrelation in multiple datapoints from each participant.<br><br>Adjusted for age, gender, and, in models of change in serum creatinine, creatinine at beginning of interval. | Mean blood Pb at baseline<br>~35 µg/dL (based on figure; exact values not provided)<br><br>Mean duration of exposure at baseline<br>13.1 yrs | Cross-sectional<br>higher blood Pb associated with lower concurrent serum creatinine.<br><br>Longitudinal<br>Change in blood Pb negatively associated with concurrent change in serum creatinine ($p = 0.07$).<br><br>Blood Pb at the beginning of the interval not associated with change in serum creatinine in the following yr.<br><br>Associations may represent Pb-related hyperfiltration. However, as noted by the authors, cumulative Pb dose may also be a factor. Mean blood Pb declined greatly just before renal data collection started. Therefore, the inverse longitudinal associations could be due to persistently elevated cumulative dose (which was unmeasured but, as evidenced by the long half-life of bone Pb, likely did not decline as much as blood Pb). However, authors did not model cumulative blood Pb or analyze effect modification by time period, age, or exposure duration to determine if these associations changed in a pattern consistent with hyperfiltration. The small sample size also limits conclusions that may be drawn from these results since a small number of individuals may be overly influential.<br><br>Strengths = longitudinal data.<br>Limitations = data analysis content (Pb dose means not reported), clarity and adjustment. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Huang et al. (1988)<br>Beijing, China<br>Study date not provided | 40 Pb workers (4 women).<br><br>Control group not described.<br><br>Renal outcomes = serum beta-2-microglobulin and urinary beta-2-microglobulin, total protein, IgG. | Geometric mean blood Pb<br>40 µg/dL | Increased urinary $\exists_2$ microglobulin in workers compared to controls.<br><br>Multiple limitations including lack of information on control group, data analysis. |
| Jung et al. (1998)<br>Korea<br>Study date not provided | 75 randomly selected male Pb workers.<br><br>64 male office workers (controls).<br><br>Renal outcomes = BUN, serum creatinine, uric acid and urinary NAG, albumin, $\alpha_1$ microglobulin and $\exists_2$ microglobulin. | Mean blood Pb<br>Means ranged from 24.3 to 74.6 µg/dL (workers)<br>7.9 µg/dL (controls)<br><br>Other Pb measures included zinc protoporphyrin, δ-aminolevulinic acid activity and urinary Pb, coproporphyrin, and δ-aminolevulinic acid. | Blood Pb, zinc protoporphyrin, and urinary δ-aminolevulinic acid significantly correlated with BUN, NAG, and $\alpha_1$ microglobulin (appears to be combined group analysis).<br><br>Limitation = statistical analysis - lack of adjustment. |
| Konishi, et al. (1994)<br>Study location not provided; research team from Japan<br>1991 | 99 male Pb workers, including 16 office workers to serve at controls.<br><br>renal outcomes = fractional clearances of $\alpha_1$ microglobulin and $\exists_2$ microglobulin (utilizing serum and urinary levels of both biomarkers), BUN, serum creatinine, uric acid and urinary NAG. | Median blood Pb<br>Range from 7.9 µg/dL in controls to 76.2 µg/dL in Category V | Urinary NAG, $\alpha_1$ microglobulin and fractional clearance of $\alpha_1$ microglobulin increased with higher blood Pb category. Spearman rank correlation between fractional clearance of $\alpha_1$ microglobulin and blood Pb was significant. This relation also assessed by multiple linear regression with adjustment for age; both independent variables were significantly associated with the fractional clearance of $\alpha_1$ microglobulin.<br><br>Limitation = statistical analysis - lack of adjustment. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Kumar and Krishnaswamy (1995)<br>India<br>Study date not provided | 22 auto mechanics volunteers.<br><br>27 male control workers (from Institute performing study).<br><br>Renal outcomes = serum creatinine, 4 h creatinine clearance and urinary NAG and ∃-2 microglobulin.<br><br>Renal disease, diabetes, HTN and occupational exposures excluded in controls, possibly excluded in workers. | Blood Pb range<br>24.3-62.4 µg/dL (exposed)<br>19.4-30.6 µg/dL (controls) | Urinary NAG and $\exists_2$ microglobulin levels were significantly higher in exposed compared to controls. However, only NAG was significantly correlated with blood Pb ($r = 0.58$, $p < 0.01$).<br><br>Limitations = study size and lack of adjustment in analysis, values for 4 h creatinine clearance in abnormal low range in both exposed and controls. |
| Lim et al. (2001)<br>Singapore<br>1999<br><br>Blood Pb levels every 6 mos from 1982 to 1999 | 55 male Pb workers.<br>Workers followed since 1982, many of same workers as in Chia et al. (1995b).<br>Renal outcomes = 4 h creatinine clearance and urinary albumin, RBP, $\alpha_1$ microglobulin, $\exists_2$ microglobulin, NAG, NAG-A, and NAG-B.<br><br>Exclusionary criteria included diabetes, HTN, recent ingestion of analgesics, antipyretics, or antibiotics, and thalassemia; 24 participants of the original 80 were excluded as a result. One female also excluded. | Mean current blood Pb<br>24.1 µg/dL<br><br>Cumulative blood index<br>880.6 µg H yrs/dL (geometric mean)<br><br>Number of times blood Pb exceeded 40 µg/dL<br>1.9 (geometric mean) | In separate models, after adjustment for age and smoking, higher categorical cumulative blood index and number of times blood Pb exceeded 40 µg/dL were associated with lower creatinine clearance ($P < 0.001$).<br><br>After adjustment, higher number of times blood Pb exceeded 40 µg/dL was associated with higher urinary albumin, $\alpha_1$ microglobulin, RBP, NAG, and NAG-B. Similarly, cumulative blood index was associated with higher urinary albumin, $\alpha_1$ microglobulin, RBP, and $\exists_2$ microglobulin.<br><br>No associations between recent blood Pb and any of the renal outcomes was observed.<br><br>Analysis of covariance was used to adjust for smoking and age.<br><br>Limitation = statistical analysis - lack of adjustment, small sample size, potential for healthy worker bias. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Ong et al. (1987)<br>Singapore and Japan<br>Study date not provided | 209 Pb workers (51 females).<br>30 control workers from research staff.<br>Renal outcomes = BUN, serum creatinine, calculated creatinine clearance, and urinary NAG. | Mean blood Pb<br>42.1 µg/dL (males)<br>31.9 µg/dL (females)<br><br>Urine Pb also measured. | Blood Pb correlated with BUN($r = 0.16$; $p < 0.01$), serum creatinine ($r = 0.26$; $p < 0.001$) and creatinine clearance ($r = -0.16$; $p < 0.01$). Blood Pb associated with NAG after adjustment for age (method not specified).<br><br>Higher NAG in exposed compared to controls when stratified by categorical age.<br><br>Strengths = sample size.<br>Limitations = statistical analysis - lack of adjustment, urinary NAG not adjusted for urine dilution. |
| Wang et al. (2002b)<br>Taiwan<br>Study date not provided | 229 Pb battery workers, including 109 females.<br>Renal outcomes = BUN, serum creatinine, serum uric acid.<br>Multiple linear & logistic regression.<br>Adjustment for age, gender, smoking, alcohol ingestion, milk ingestion. | Mean blood Pb<br>67.7 µg/dL (males)<br>48.6 µg/dL (females) | ∃ (95% CI) for blood Pb in model of BUN, after adjustment for Pb job duration/age = 0.062 (0.042, 0.082).<br><br>∃ (95% CI) for blood Pb in model of uric acid, after adjustment for gender and weight = 0.009 (0.001, 0.016).<br><br>Blood Pb not associated serum creatinine. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Weaver et al. (2003a)<br>South Korea<br>1997-1999 | 803 Pb workers including 164 females and 94 former Pb workers.<br>Serum creatinine<br>0.90 mg/dL<br><br>Calculated creatinine clearance<br>94.7 mL/min<br><br>4-hr measured creatinine clearance<br>114.7 mL/min<br><br>RBP<br>63.6 µg/g creatinine<br><br>NAG<br>215.3 µmol/h/g creatinine<br><br>Multiple linear regression, adjusting for age, gender, BMI, work status (current vs. former worker), HTN or blood pressure (depending on model), and, for the EBE markers, alcohol ingestion and diabetes.<br><br>42 associations modeled (7 Pb measures with 6 renal outcomes).<br>Interaction models that assessed effect modification by age in tertiles in 24 associations (4 Pb exposure/dose measures with 6 renal outcomes). | Mean blood Pb<br>32.0 µg/dL<br><br>Mean tibia Pb<br>37.2 µg/g bone mineral<br><br>Mean DMSA-chelatable Pb<br>767.8 µg/g creatinine<br><br>Pb exposure also assessed with job duration and three hematologic measures as surrogates for Pb dose (aminolevulinic acid in plasma, zinc protoporphyrin, and hemoglobin).<br><br>Mean urinary cadmium measured in subset (n = 191)<br>1.1 µg/g creatinine | After adjustment, higher Pb measures associated with worse renal function in 9 of 42 models.<br><br>Associations in the opposite direction (higher Pb measures associated with lower serum creatinine and higher creatinine clearances) in five models.<br><br>Opposite direction (inverse) associations observed only in models of the clinical outcomes whereas the associations between higher Pb dose and worse renal function were predominantly among the biomarker models.<br><br>In three of 16 clinical renal interaction models, positive associations between higher Pb measures and worse renal function in participants in the oldest age tertile were significantly different from associations in those in the youngest age tertile which were in the opposite direction.<br><br>- This pattern was observed at borderline significance ($p < 0.1$) in 3 other models.<br>- Pattern was not observed in the EBE marker models.<br><br>Urinary cadmium associated with NAG.<br><br>Authors concluded that occupational Pb exposure in the moderate dose range has an adverse effect on renal function. Inverse associations may represent hyperfiltration. Environmental cadmium may have an adverse impact, at least on NAG. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Weaver et al. (2003b)<br>Korea Pb workers<br>1997-1999 | 798 Pb workers with genotype information in same population as in Weaver et al. (2003a).<br><br>79 (9.9%) participants were heterozygous for the ALAD2 allele (none was homozygous).<br><br>89 (11.2%) had VDR genotype Bb or BB. | <u>Mean blood Pb</u><br>31.7 µg/dL (ALAD11)<br>34.2 µg/dL (ALAD12)<br><br>31.6 µg/dL (VDR bb)<br>34.8 µg/dL (VDR Bb or BB)<br><br><u>Mean tibia Pb</u><br>37.5 µg/g (ALAD11)<br>31.4 µg/g (ALAD12)<br><br>37.1 µg/g (VDR bb)<br>38.1 µg/g (VDR Bb or BB) | Data were analyzed to determine whether polymorphisms in the genes encoding δ-aminolevulinic acid dehydratase (ALAD), endothelial nitric oxide synthase (eNOS), and the vitamin D receptor (VDR) were associated with renal outcomes or modified relations of Pb exposure and dose measures with renal outcomes.<br><br>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 ALAD12 genotype, higher Pb measures were associated with lower BUN and serum creatinine and higher calculated creatinine clearance.<br><br>No significant differences were seen in renal outcomes by VDR genotype nor was consistent effect modification observed. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Weaver et al. (2005a)<br>Korea<br>1997-1999 | 803 current and former Pb workers; 164 females.<br><br>Serum Uric acid<br>4.8 mg/dL<br><br>Other renal outcomes as listed in Weaver et al., 2003a.<br><br>Multiple linear regression.<br><br>Interaction models that assessed effect modification by age in tertiles. | Mean blood Pb<br>32.0 µg/dL<br><br>Mean tibia Pb<br>37.2 (40.4) µg/g bone mineral<br><br>Mean DMSA-chelatable Pb<br>767.8 µg/g creatinine | Work to address whether one mechanism for Pb-related nephrotoxicity, even at current lower levels of Pb exposure, is via increasing serum uric acid. Assessed 1) whether Pb dose was associated with uric acid and 2) whether previously reported associations between Pb dose and renal outcomes (Weaver et al., 2003) were altered after adjustment for uric acid.<br><br>After adjustment for age, gender, body mass index, and alcohol use, Pb biomarkers not associated with uric acid in all participants. However, in interaction models, both blood and tibia Pb were significantly associated in participants in the oldest age tertile ($\exists$ = 0.0111 [95% CI: 0.003, 0.019] and 0.0036 [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 over-control. On the other hand, since nonPb 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 ($\exists$ = 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 ($\exists$ = 0.0156).<br><br>Next, in models of renal function in all workers, uric acid was significantly ($p < 0.05$) associated with all renal outcomes except NAG.<br><br>In models in the oldest tertile of workers (266 workers, median age 51.1 yrs, range 46.0 to 64.8 yrs), after adjustment for uric acid, associations between Pb dose and NAG were unchanged, but fewer of the previously significant (p # 0.05) associations noted between Pb dose and the clinical renal outcomes in Weaver et al. (2003a) remained significant. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Weaver et al. (2005b)<br>South Korea<br>1999-2001 | 652 Pb workers including 149 females and 200 former workers.<br>Patella Pb measured in the third evaluation of the same study reported in Weaver et al. (2003a). Data collection performed a mean of 2.2 yrs after collection of the data presented in Weaver et al. (2003a).<br>Same renal outcomes as Weaver et al. (2003a).<br><br>Serum creatinine<br>0.87 mg/dL<br><br>Calculated creatinine clearance<br>97.0 mL/min<br><br>Multiple linear regression, adjusting for age, gender, BMI, work status (current vs. former worker), HTN or blood pressure (depending on model), diabetes, smoking status, and, for the clinical measures, use of analgesics<br>Interaction models assessed effect modification by age, dichotomized at the 67th percentile. | Mean blood Pb<br>30.9 µg/dL<br><br>Mean tibia Pb<br>33.6 µg/g bone mineral<br><br>Mean patella Pb<br>75.1 µg/g bone mineral<br><br>Mean DMSA-chelatable Pb<br>0.63 µg Pb/mg creatinine | All 4 Pb measures were correlated (Spearman's r = 0.51 – 0.76).<br><br>Patella, blood and DMSA-chelatable Pb levels positively associated with NAG.<br><br>Higher DMSA-chelatable Pb associated with lower serum creatinine and higher calculated creatinine clearance.<br><br>Interaction models<br>All four Pb measures associated with higher NAG among participants in oldest age tertile.<br><br>Higher blood, tibia, and patella Pb associated with higher serum creatinine among older participants.<br>-Beta coefficients less in the Pb workers whose ages were in the younger two-thirds of the age range; difference between slopes in the two age groups was statistically significant only for association of blood Pb and serum creatinine.<br><br>Inverse DMSA associations (higher DMSA-chelatable Pb associated with lower serum creatinine and higher calculated creatinine clearance) significant in younger workers.<br>Patella Pb associations were consistent with those of blood and tibia Pb; DMSA-chelatable Pb associations unique.<br><br>Authors hypothesized that similarities between patella, blood, and tibia Pb associations could be due, in part, to high correlations among the Pb biomarkers in this population. Despite similar high correlations, DMSA-chelatable Pb associations with serum creatinine and calculated creatinine clearance were unique. This biomarker is dependent on renal function and the collection time was only 4 h. Therefore, the amount of Pb that is excreted in this relatively short time period after chelation may be influenced not only by bioavailable Pb burden, but also by high-normal as well as actual supranormal glomerular filtration which are more common in the younger workers. |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Weaver et al. (2005c)<br>Korea<br>1997-1999 | 798 current and former Pb workers.<br><br>Same population as in Weaver et al. (2003a,b). | | Data were analyzed to determine whether polymorphisms in the genes encoding δ-aminolevulinic acid dehydratase (ALAD), endothelial nitric oxide synthase (eNOS), and the vitamin D receptor (VDR) were associated with uric acid or modified relations of Pb exposure and dose measures with uric acid.<br><br>Uric acid not different by ALAD or VDR genotype. Among older workers (age ≥ median of 40.6 yrs), 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 ALAD11 genotype; associations were in the opposite direction in participants with the variant ALAD12 genotype. |
| Ye et al. (2003)<br>Chinese Pb workers<br>Study date not provided | 216 Pb workers.<br><br>Renal outcomes = urinary NAG and albumin. | Geometric mean blood Pb<br>37.8 µg/dL (n = 14 workers with the ALAD12 genotype)<br>32.4 µg/dL (n = 212 workers with the ALAD11 genotype)<br><br>31.9 µg/dL (VDR bb)<br>41.7 µg/dL (in 20 participants with VDR Bb or BB) | After adjustment for age, NAG was borderline higher in those with the ALAD variant allele whose blood Pb levels were ≥40 µg/dL ($p = 0.06$). 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 ALAD12 genotype but not in Pb workers with the ALAD11 genotype (the groups were analyzed separately rather than in an interaction model).<br><br>No effect modification by VDR genotype on associations between blood Pb and urinary albumin and NAG observed (separate analysis reduced power). |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Middle East** | | | |
| Al-Neamy et al. (2001)<br>United Arab Emirates<br>Feb-June, 1999 | 100 "industrial" workers exposed in a range of industries 100 working controls.<br><br>Matched for age, sex, and nationality.<br><br>Renal outcomes = BUN, serum creatinine. | Mean blood Pb<br>77.5 µg/dL (workers)<br>19.8 µg/dL (controls) | Mean BUN and serum creatinine not statistically different between exposed workers and controls.<br><br>Limitations = data analysis. |
| Ehrlich et al. (1998)<br>South Africa<br>Study date not provided | 382 Pb battery factory workers.<br><br>Mean age = 41.2 yrs.<br><br>All males.<br><br>Multiple linear regression adjusted for age, weight, and height (Covariates assessed for inclusion also included smoking, alcohol ingestion, and diabetes).<br><br>Clinical renal outcomes included serum creatinine, uric acid, and BUN.<br><br>Mean serum creatinine<br>1.13 mg/dL<br><br>Renal early biological effect markers (NAG, RBP, intestinal alkaline phosphatase, tissue nonspecific alkaline phosphatase, Tamm-Horsfall glycoprotein, epidermal growth factor, and microalbuminuria) were measured in 199 participants randomly selected by tertiles of current blood Pb. | Mean blood Pb<br>53.5 µg/dL<br><br>Mean exposure duration<br>11.6 yrs<br><br>Mean cumulative blood Pb<br>(defined as sum of the avg blood Pb in each yr over all yrs of employment; done in subset of 246 with past blood Pb data)<br>579.0 (µg H yr)/dL<br><br>Mean historical blood Pb<br>(defined as cumulative blood Pb divided by yrs of exposure)<br>57.3 µg/dL<br><br>Mean tibia Pb<br>69.7 µg/g bone mineral<br>(measured 2 yrs after initial study on random sample of 40) | After adjustment for age, weight, and height, categorical current and historical blood Pb and zinc protoporphyrin were associated with serum creatinine and uric acid, in separate models. Associations between cumulative blood Pb or exposure duration and the renal outcomes were not observed.<br><br>Among the EBE markers, only current blood Pb was borderline associated with NAG ($p = 0.09$).<br><br>Associations with renal dysfunction were observed at blood Pb levels <40 µg/dL. Not explained by an effect on blood pressure since Pb measures not associated with blood pressure. Blood cadmium measured in 56 participants 2 yrs after the initial study. All low (#1.2 µg/L) suggesting that occupational level cadmium exposure was not a contributing factor. The authors did implicate Pb body burden, which was substantial based on mean tibia Pb. However, cumulative blood Pb was not associated in this study and mean tibia Pb in Roels et al. (1994) was similar (in that study a positive association with creatinine clearance was observed). |

## Table AX6-4.2 (cont'd). Renal Effects of Lead in the Occupational Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Middle East** (cont'd) | | | |
| El-Safty et al. (2004)<br>Egypt<br>Study date not provided | 45 Pb workers with Pb job duration <20 yrs.<br><br>36 Pb workers with Pb job duration ≥20 yrs.<br><br>75 control workers.<br><br>Renal outcomes = urinary $\alpha_1$-microglobulin, NAG, and glutathione S-transferase. | <u>Median urine Pb</u><br>Ranged from 15.4 µg/g creatinine in nonsmoking control workers to 250.4 µg/g creatinine in smoking Pb workers with ∃20 yrs Pb job duration. | Medians of all 3 renal outcomes significantly higher in Pb workers regardless of smoking status (analysis stratified by smoking status).<br><br>Urine Pb significantly correlated with urinary $\alpha_1$-microglobulin and glutathione S-transferase in nonsmoking Pb workers and with NAG as well in smoking Pb workers.<br><br>Limitations include using urine Pb as sole Pb dose measure and data analysis. |
| Mortada et al. (2001)<br>Egypt<br>Study date not provided | 43 traffic policemen.<br><br>52 matched control office workers (similar in terms of age, gender, smoking, and "social life").<br><br>Renal outcomes = serum creatinine, beta-2 microglobulin, BUN and urinary ∃-2- microglobulin, NAG, alkaline phosphatase, γ-glutamyl transferase, and albumin.<br><br>Exclusionary criteria included diabetes, HTN, hepatic, renal or urologic diseases. | <u>Mean blood Pb</u><br>32.1 µg/dL (exposed)<br>12.4 µg/dL (controls)<br><br>Pb also measured in hair, urine and nails. | NAG and albumin significantly higher in policemen compared to controls. NAG positively correlated (Pearson's) with job duration and blood and nail Pb. Urinary albumin positively correlated with job duration and blood and hair Pb.<br><br>Limitations: data analysis – no adjustment, use of parametric correlation techniques with data likely to be nonparametric; study size. |

## Table AX6-4.3. Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Osterloh et al. (1989)<br>Northern CA<br>Study date not provided | 40 male subjects with hypertensive nephropathy (hypertension preceded renal insufficiency; serum creatinine 1.8-4 mg/dL).<br><br>24 controls with renal dysfunction from other causes.<br><br>Patients recruited from the Kaiser Permanente Regional Laboratory database (large health maintenance organization) in northern California. | Mean blood Pb<br>7.3 µg/dL (in both hypertensive nephropathy and controls CRI from other causes)<br><br>Mean EDTA chelatable Pb levels<br>153.3 µg/72 hrs (hypertensive nephropathy)<br>126.4 µg/72 hrs (control CRI) | No significant difference in EDTA chelatable Pb levels; highest chelatable Pb level was 609.2 µg/72 hrs.<br><br>Pb dose and serum creatinine were not correlated.<br><br>Blood and chelatable Pb levels much lower than those reported by Wedeen et al. (1983) and Sanchez-Fructuoso et al. (1996).<br><br>Only 17% of their study participants had a history of possible Pb exposure based on questionnaire, again much lower than the two other studies. |
| Steenland et al. (1990)<br>Michigan<br>Diagnosis from 1976-1984 | 325 men with ESRD (diabetes, congenital and obstructive nephropathies excluded).<br>Controls by random digit dialing, matched by age, race, and place of residence. | | Risk of ESRD significantly related to moonshine alcohol consumption (OR = 2.43), as well as analgesic consumption, family history of renal disease, and occupational exposure to silica or solvents. |
| **Europe** | | | |
| Behringer et al. (1986)<br>Germany<br>Study date not provided | 16 patients with CRI (median serum creatinine = 2.2 mg/dL) and gout.<br>19 patients with CRI (median serum creatinine = 5.1 mg/dL) without gout.<br>21 healthy controls.<br>Pb excretion in the 96 hrs after administration of 1 g EDTA iv. | Median blood Pb<br>7.2 µg/dL (controls)<br>11.5 µg/dL (CRI, no gout)<br>15.3 µg/dL (CRI & gout)<br><br>Median EDTA chelatable Pb (µg/4 days/1.73 $m^2$)<br>63.4 (controls)<br>175.9 (CRI, no gout)<br>261.3 (CRI & gout) | EDTA chelatable Pb higher in gout patients who developed gout after CRI than those in which gout preceded CRI (statistical test results not mentioned or shown). Authors conclude a role for Pb in patients with gout occurring in setting of CRI and that Pb may contributes to renal function decline in established renal disease from other causes.<br><br>Limitations = small groups, limited data analysis. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Colleoni and D'Amico (1986)<br>Italy<br>(~1982-1985) | 12 consecutive patients with CRI (mean serum creatinine = 3.3 mg/dL) and gout, renal diagnosis consistent with chronic interstitial nephritis in all; 7 had history of occupational Pb exposure.<br>12 controls with chronic glomerulonephritis and no history of Pb exposure or gout.<br>Pb excretion in the 48 hrs after administration of 1.5 g EDTA im. | Mean EDTA chelatable Pb (µg/48 hrs)<br>180 (CRI, no gout)<br>505 (CRI & gout) | Significantly higher EDTA chelatable Pb in the group with CRI and gout compared to CRI alone. EDTA chelatable Pb significantly correlated with serum creatinine in patients with CRI and gout but not CRI alone. Authors conclude that Pb is cause of CRI with gout but renal insufficiency alone not responsible for increased Pb body burden (absence of evidence for reverse causation).<br><br>Limitations = small sample size, limited data analysis. |
| Colleoni et al. (1993)<br>Italy<br>Study date not provided | All 115 patients on hemodialysis at the time of the study; 41 women.<br>Blood Pb data from prior study of 383 healthy controls in same geographical area served as comparison. | Mean blood Pb (corrected for hemoglobin)<br>19.9 µg/dL (patients)<br>14.7 µg/dL (controls) | Significantly higher mean blood Pb in hemodialysis patients compared to healthy controls. 13% had blood Pb levels >30 µg/dL. Blood Pb level was not associated with duration of hemodialysis. Mean Pb levels higher in smokers and in relation to alcohol ingestion. Pb not detectable in dialysis fluids.<br><br>Limited data analysis. |
| Craswell et al. (1987)<br>Germany and Australia<br>Study date not provided | See discussion below under Australia. | | |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Fontanellas et al. (2002)<br>Spain<br>Study date not provided | ALAD/restored ALAD as a possible index of Pb poisoning in chronic renal failure patients. | | Restored ALAD was measured after the addition of zinc and dithiothreitol (DTT) to the incubation media.<br><br>The ALAD/restored ALAD ratio was found to correlate with the results of the EDTA Pb mobilization test. Patients excreting I,115 to 3860 µg Pb per 72 hrs had a ratio of 0.19 while chronic renal failure patients excreting an avg of 322 µg Pb (range 195 to 393) had a ratio of 0.47. In comparison, normal controls had a ratio of 0.5. |
| Jones et al. (1990)<br>Study location and date not provided; authors from UK | 27 dialysis patients.<br>59 healthy controls. | Mean blood Pb<br>8.1 µg/dL (patients)<br>10.0 µg/dL (controls) | Tibia Pb levels not correlated with blood Pb but were correlated with Pb in bone biopsy measurements ($r = 0.42$).<br><br>Limitations = data analysis. |
| Koster et al. (1989)<br>Study location and date not provided; authors from Germany | 91 patients with CRI (median serum creatinine = 2.5 mg/dL).<br>46 age-matched normal controls.<br>Pb excretion in the 4 days after 1 g EDTA iv. | Mean blood Pb (corrected for hemoglobin)<br>11.2 µg/dL (patients)<br>7.6 µg/dL (controls)<br><br>Mean EDTA chelatable Pb<br>164.7 µg/4 days /1.73 m² (patients)<br>63.6 µg/4 days /1.73 m² (controls) | CRI patients had significantly higher blood and EDTA chelatable Pb levels than controls. In 13% of the CRI patients, EDTA chelatable Pb exceeded the highest value in controls (328.8 µg). EDTA chelatable Pb levels were correlated with serum creatinine in patients ($r = 0.37$; $p < 0.007$).<br><br>Limitations = data analysis. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Miranda-Carús et al. (1997)<br>Spain<br>1990-1994 | 27 patients with gout and CRI.<br><br>50 patients with gout only.<br><br>26 controls with normal renal function and no gout.<br><br>Multiple purine metabolism measures including serum urate, hypoxanthine, and xanthine, as well as their excretion, clearance and fractional excretion measures. | <u>Mean blood Pb</u><br>17.8 µg/dL (gout and CRI)<br>14.9 µg/dL (gout only)<br>12.4 µg/dL (controls)<br><br><u>Mean EDTA chelatable Pb</u><br>845 µg/120 hrs (gout and CRI)<br>342 µg/120 hrs (gout only)<br>215 µg/120 hrs (controls) | Pb dose measures significantly higher in patients with gout and CRI compared to the other two groups. EDTA chelatable Pb inversely correlated with creatinine clearance. Each of the 2 patient groups were dichotomized by EDTA-chelatable Pb level of 600 µg/120 hrs, resulting in 3 small groups (n ranging from 6 to 14) and one group of 44 participants with gout and EDTA chelatable Pb below the cut-off. No significant differences in mean purine metabolism measures were observed. It is not clear whether correlations between EDTA-chelatable Pb and the purine measures were assessed and if so whether the small groups were combined for this analysis. Thus lack of power may be one reason for the inconsistency with Lin's work. Different Pb body burdens may be a factor as well.<br><br>Uric acid parameters were unchanged following chelation in 6 participants with EDTA-chelatable above 600 µg/120 hrs. Again higher Pb body burdens may be a factor but the small number and limited details on the group make firm conclusions difficult. |
| Nuyts et al. (1995)<br>Belgium<br>Study date not provided | Case-control study.<br>272 cases with chronic renal failure (all types) matched to 272 controls by age, sex and residence.<br>Exposure assessed by 3 industrial hygienists blinded to case or control status. | | Significantly increased odds ratio for chronic renal failure with Pb exposure (OR = 2.11 [95% CI: 1.23, 4.36]) as well as several other metals. Increased risk with diabetic nephropathy. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Sánchez-Fructuoso et al. (1996)<br>Spain<br>Study date not provided | 296 patients:<br>Group I = 30 normal control subjects<br>Group II = 104 patients with essential HTN & normal renal function<br>Group III-A = 68 patients with HTN and CRI of uncertain etiology but presumed nephroangiosclerosis<br>Group III-B = 64 patients with HTN, CRI, and gout<br>Group IV = 30 patients with CRI of known etiology | Mean blood and EDTA-chelatable Pb levels<br><br>Group I<br>16.7 µg/dL<br>324 µg/72 hrs<br><br>Group II<br>16.8 µg/dL<br>487 µg/72 hrs<br><br>Group III-A<br>18.5 µg/dL<br>678 µg/72 hrs<br><br>Group III-B<br>21.1 µg/dL<br>1290 µg/72 hrs<br><br>Group IV<br>16.5 µg/dL<br>321 µg/72 hrs | EDTA chelatable Pb >600 µg/72 hrs in 16 patients in group II, 30 patients in group III-A, 44 patients in group III-B, but no patients in either group I and IV.<br><br>Mean blood and EDTA chelatable Pb levels in the patients with CRI of known cause were not statistically different from controls with normal renal function. However, baseline urinary Pb excretion was lower in group IV. This provides conflicting evidence regarding the "reverse causality" hypothesis of increased Pb burden due to decreased excretion in CRI.<br><br>Significant correlations noted between bone Pb levels (assessed by biopsy) and EDTA chelatable Pb level in 12 patients whose chelatable Pb levels were >600 µg/72 hrs; provides support for validity of chelatable Pb levels in CRI.<br><br>A positive correlation was observed between serum creatinine levels and EDTA-chelatable Pb levels >600 µg/72 hrs but not below this level.<br><br>In group III, mean measured creatinine clearance was significantly lower in those with EDTA chelatable Pb levels >600 µg/72 hrs compared to participants with chelatable Pb <600 µg/72 hrs. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Van de Vyver et al. (1988)<br>Belgium, France and Germany<br>Study date not provided | Transiliac bone biopsies obtained from:<br>11 cadavers without known Pb exposure and with normal renal function<br>13 patients with CRI, gout and/or HTN 22 Pb workers<br>153 dialysis patients | Mean transiliac Pb levels<br>5.5 µg/g (153 dialysis pts)<br>20.6 µg/g (in highest 5% dialysis pts)<br>3.7 µg/g (in 10 pts on dialysis due to analgesic nephropathy)<br>6.3 µg/g (11 cadavers)<br>30.1 µg/g (22 Pb workers) | In 5% of the hemodialysis patients studied, bone Pb concentrations approximated the levels found in active Pb workers, suggesting Pb as a primary cause of their renal failure. Levels in the 10 patients with analgesic nephropathy were the lowest (all <7 µg/g), evidence against reverse causality.<br><br>In the combined group of 13 patients with CRI, gout and/or HTN and 22 Pb workers, EDTA chelatable Pb correlated with Pb in bone biopsies (r = 0.87). |
| Winterberg et al. (1991)<br>Study location and date not provided; authors from Germany | Iliac crest bone Pb measured by biopsy in:<br>8 controls<br>8 patients with CRI<br>14 dialysis patients | Mean iliac crest bone Pb levels<br>1.63 µg/g (8 controls)<br>2.18 µg/g (8 patients with CRI)<br>3.59 µg/g (in 14 dialysis pts) | Noted that the bone Pb levels in patients with analgesic nephropathy and cadaver controls in Van de Vyver et al. (1988) were much higher than in control groups of other researchers. They reiterated the concern that Pb did accumulate due to decreased renal excretion. |
| **Latin and South America** | | | |
| Navarro et al. (1992)<br>Venezuela<br>Study date not provided | 18 dialysis patients.<br>14 controls.<br><br>Bone (biopsy) and blood levels of Pb and several other metals. | Mean blood Pb<br>5.2 µg/dL (patients)<br>11.5 µg/dL (controls)<br><br>Mean Pb in bone<br>9.7 µg/g (patients)<br>7.0 µg/g (controls) | Blood but not bone Pb significantly higher in patients compared to controls. Authors concluded that bone accumulation of aluminum, iron and vanadium, but not Pb, occurred in dialysis patients.<br><br>Limitations = sample size, data analysis including lack of adjustment. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Australia** | | | |
| Craswell et al. (1987)<br>Germany and Australia<br>Study date not provided | German participants from industrialized area where chronic Pb nephropathy not previously observed.<br>Gp 1 = 8 healthy controls (from hospital staff)<br>Gp 2a = 12 CRI patients, no gout or Pb exposure<br>Gp 2b = 7 CRI patients, no gout but + Pb exposure<br>Gp 3a = 7 CRI patients with gout but no Pb exposure<br>Gp 3b = 6 CRI patients with gout and Pb exposure<br><br>Australian participants from Queensland site of known chronic Pb nephropathy.<br>Gp 1 = 9 healthy controls (from hospital staff)<br>Gp 2a = 14 CRI patients, no gout or Pb exposure<br>Gp 2b = 11 CRI patients, no gout but + Pb exposure<br>Gp 3a = 25 CRI patients with gout but no Pb exposure<br>Gp 3b = 11 CRI patients with gout and Pb exposure<br>CRI defined as serum creatinine ≥ 1.5 mg/dL<br><br>"Excess" EDTA chelatable Pb defined as Pb excreted over 4 days after EDTA minus twice baseline Pb excreted pre-EDTA. | <u>Median blood Pb (hemoglobin corrected)</u><br><u>Gp 1</u><br>German = 6.8 µg/dL<br>Australian = 11.0 µg/dL<br><u>Gp 2a</u><br>German = 6.2 µg/dL<br>Australian = 9.1 µg/dL<br><u>Gp 2b</u><br>German = 8.5 µg/dL<br>Australian = 16.2 µg/dL<br><u>Gp 3a</u><br>German = 10.6 µg/dL<br>Australian = 12.8 µg/dL<br><u>Gp 3b</u><br>German = 12.0 µg/dL<br>Australian = 27.1 µg/dL<br><br><u>Median "excess" EDTA chelatable Pb</u><br><u>Gp 1</u><br>German = 68.4 µg<br>Australian =82.9 µg<br><u>Gp 2a</u><br>German = 126.4 µg<br>Australian = 393.7 µg<br><u>Gp 2b</u><br>German = 489.0 µg<br>Australian = 1181.1 µg<br><u>Gp 3a</u><br>German = 227.9 µg<br>Australian = 808.1 µg<br><u>Gp 3b</u><br>German = 422.7 µg<br>Australian = 1077.5 µg | Using nonparametric statistical techniques due to skewed data, German participants excreted statistically less Pb than their Australian counterparts. Mean EDTA chelatable Pb levels were significantly higher in German patients with gout than in those without gout; the observed increase in the Australian patients was of borderline significance ($p < 0.1$).<br><br>Limitations = small groups, limited data analysis. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Australia** (cont'd) | | | |
| Price et al. (1992)<br>Queensland, Australia<br>1981-1986 | 8 renal patients compared with age-matched controls.<br><br>X-ray fluorescence of finger bone Pb conducted twice 5 yrs apart. | | Authors conclude that Pb in bone half-life is similar in renal patients compared to age-matched controls. Study limitations substantial, however.<br><br>Limitations = small numbers (although bone Pb measured in more patients, many were below the limit of detection, inclusion of outliers without formal statistical analysis. |
| **Asia** | | | |
| Lin and Lim (1992)<br>Chinese population (likely in Taiwan)<br>Study date not provided | 10 healthy controls.<br>10 patients with CRI but no gout.<br>8 patients with gout and subsequent CRI.<br>6 patients with CRI and subsequent gout.<br><br>Exclusionary criteria included + history of occupational or environmental Pb exposure. | Mean EDTA chelatable Pb in µg/72 hrs/1.73 $m^2$<br>90.2 (controls)<br>98 (CRI, no gout)<br>171.6 (gout, then CRI)<br>359.8 (CRI, then gout) | Pb body burden higher in patients with CRI and gout, especially when CRI precedes gout.<br><br>Limitations = small sample sizes, statistical analysis. |
| Lin and Huang (1994)<br>Taiwan<br>Study date not provided | Group 1 = 10 patients with normal renal function and no gout; Group 2 = 10 patients with CRI (serum creatinine >1.4 mg/dL) and subsequent gout; Group 3 = 20 patients with CRI but no gout.<br><br>All males.<br><br>Pb body burden assessed with 1 g EDTA iv followed by 72 hr urine collection. | Mean EDTA chelatable Pb<br>Gp 1 = 60.55 µg/ 72 hrs<br>Gp 2 = 252.24 µg/ 72 hrs<br>Gp 3 = 84.86 µg/ 72 hrs | Mean EDTA chelatable Pb and serum urate significantly higher in the patients with gout. After adjustment for creatinine clearance, log transformed EDTA chelatable Pb was significantly associated with serum urate levels (∃ = 0.757 [95% CI: 0.142, 1.372]; $p < 0.05$), daily urate excretion (∃ = !60.15 [95% CI: !118.1, !2.16]; $p < 0.05$), urate clearance (∃ = !0.811 [95% CI: !1.34, !0.282]; $p < 0.05$), and fractional urate excretion (∃ = !1.535 [95% CI: !2.723, !0.347]; $p < 0.05$). EDTA chelatable Pb not associated with creatinine clearance.<br><br>Limitations = small sample sizes, limited adjustment in regression analyses. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lin and Lim (1994)<br>Taiwan<br>Study date not provided | Gp 1 = 12 healthy controls.<br>Gp 2 = 10 patients with HTN.<br>Gp 3 = 12 patients with HTN, then CRI (hypertensive nephropathy).<br>Gp 4 = 12 patients with CRI only.<br>Gp 5 = 12 patients with CRI not due to HTN, but subsequent HTN. | Mean EDTA chelatable Pb<br>Gp 1 = 76.6 µg/72 hrs<br>Gp 2 = 67.96 µg/72 hrs<br>Gp 3 = 182.9 µg/72 hrs<br>Gp 3 = 84.46 µg/72 hrs<br>Gp 3 = 92.86 µg/72 hrs | Higher mean EDTA chelatable Pb level in Gp 3; 5 of 12 had history of gout developing after CRI.<br><br>Limitations = small sample sizes, limited analyses. |
| Lin et al. (1999)<br>Taiwan<br>Study date not provided | 32 patients selected from 102 patients with serum creatinine from 1.5–4.0 mg/dL who were followed in the Institution's outpatient clinics.<br><br>Eligibility criteria included serum creatinine from 1.5 – 4.0 mg/dL, stable renal function over 6 mos before study entry; controlled blood pressure and cholesterol; daily protein intake <1 g/kg body wt; no known history of exposure to Pb or other heavy metals and EDTA chelatable Pb >150 but <600 µg/72 h.<br><br>Exclusionary criteria included potentially reversible or unstable renal disease (i.e., due to systemic diseases such as lupus and diabetes), and nephrotoxicant medications.<br><br>Patients divided into 16 patients receiving 1 g EDTA i.v. weekly for two mos and a control group of 16 patients who received no therapy. | Mean EDTA chelatable Pb levels pre-chelation<br>254.9 µg/72 hrs in group receiving subsequent chelation<br><br>279.7 µg/72 hrs in control group<br><br>Blood Pb levels not mentioned. | Rates of progression of renal insufficiency were followed by reciprocal of serum creatinine during the 12 mos prior to therapy and for 12 mos following therapy. Rates of progression of renal insufficiency were similar in the treatment group and the control group during the baseline observation. However, improvement in renal function was observed during EDTA chelation. Following chelation, renal function stabilized in the treated group but continued to decline in the control group. At 12 mos after treatment, the mean difference in the change in the reciprocal of serum creatinine between the two groups was 0.000042 L/µmol per mo (95% CI: 0.00001, 0.00007). Results using a sensitivity analysis for patients lost to follow-up (only one in each group) gave similar results. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lin et al. (2001a)<br>Taiwan<br>Study date not provided | 24 mo prospective observational study<br>110 patients with CRI dichotomized by EDTA chelatable Pb level of 80 µg/72 hrs into two groups of 55 each.<br><br>Eligibility criteria included serum creatinine from 1.5 – 4.0 mg/dL, stable renal function (decrease in GFR <5 mL/min over 6 mos); blood pressure <140/90 mm Hg; cholesterol level <240 mg/dL; daily protein intake <1 g/kg body wt; no known history of exposure to Pb or other heavy metals and EDTA chelatable Pb <600 µg/72 h.<br><br>Exclusionary criteria included potentially reversible or unstable renal disease (i.e., due to systemic diseases such as lupus and diabetes), nephrotoxicant medications, and drug allergies.<br><br>196 patients initially screened for study; details on reasons for non-eligibility not provided.<br><br>Primary outcome = 1.5 times increase in the initial creatinine level or need for dialysis; secondary outcome = change in creatinine clearance.<br><br>Cox proportional-hazards model analysis for primary outcome. Mean differences in creatinine clearance compared at sequential time points with t or Mann-Whitney U tests.<br><br>Adjustment for age, gender, baseline BMI, smoking, proteinuria, hypertension, hyperlipidemia, daily protein intake, and underlying renal disease.<br><br>Intention-to-Treat and sensitivity analyses compared creatinine clearance a by time period in high and low Pb groups. | Mean blood Pb levels<br>6.6 µg/dL in high normal Pb body burden group (n = 55)<br>3.9 µg/dL in low normal Pb body burden group (n = 55)<br><br>Mean EDTA chelatable Pb levels pre-chelation<br>182.9 µg/72 hrs in high normal Pb body burden group (n = 55)<br><br>37.9 µg/72 hrs in low normal Pb body burden group (n = 55) | 24 mo prospective observational study<br>Pb dose measures were only significant differences between high and low normal Pb body burden groups. Of the 96 participants who completed the observation study, 14 patients in the high normal body Pb burden group reached the primary endpoint compared to 1 patient in the low body Pb burden group ($p < 0.001$ by log-rank test).<br><br>From mo 12 to mo 24, creatinine clearance in high normal body Pb burden patients was at least borderline statistically lower than in low body Pb burden patients; from 18-24 mos, 95% CI excluded 0. 95% CI for the difference at 24 mos was (–15.0, !3.8); difference in creatinine clearance between groups was 0.15 mL/s at that point.<br><br>In a Cox multivariate regression analysis, chelatable Pb was significantly associated with overall risk for the primary endpoint (RR = 41.5 [95% CI: 3.9, 440.8]; $p = 0.002$). In this model, age, basal BMI, and basal daily proteinuria were also associated with increased risk. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lin et al. (2001a) (cont'd) | 3 mo clinical trial of chelation with 1 yr follow-up<br>At 24 mos, 36 patients whose EDTA chelatable Pb levels were 80 - 600 µg/72 hrs and serum creatinine levels of <4.2 mg/dL were randomized; 24 to a 3-mo treatment period consisting of weekly chelation with 1 g EDTA iv until their excreted Pb levels fell below 80 µg/72 hrs and 12 to placebo infusion.<br><br>Intention-to-Treat and sensitivity analyses compared creatinine clearance by time period in treated and control groups. | | 3 mo clinical trial of chelation with 1 yr follow-up<br>The two groups were similar in baseline renal risk factors (although numbers small so beta error possible).<br><br>Mean EDTA dose during the 3 mo period was 5 µg. After three mos of Pb chelation therapy, the body Pb burden of the patients in the chelation group decreased from 198 to 39.2 µg. After 3 mos of chelation and 3 mos of follow-up, creatinine clearance increased by 0.08 mL/s in the treated group but declined by 0.04 mL/s in the controls.<br><br>At the end of the study period, mean creatinine clearance was 0.68 mL/s in the chelated group compared to 0.48 mL/s in the control group ($p < 0.05$; 95% CI for the difference between groups = –25.0 to –0.2). |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lin et al. (2001b)<br>Study location and date not provided; authors from Taiwan | 101 patients with CRI (defined as serum creatinine between 1.5 and 3.0 mg/dL).<br>67 with CRI and gout.<br>34 with CRI only.<br><br>Eligibility criteria included no known history of Pb exposure, certain diagnoses, and medications. CRI must have preceded gout diagnosis.<br><br><u>Randomized chelation trial</u><br>30 participants with CRI, gout, and EDTA-chelatable Pb levels between 80.2 and 361 µg/72 hrs randomized to either a treatment group receiving 1 gram EDTA iv per wk for 4 wks (N = 20) or to a control group who received glucose in normal saline iv. | <u>Mean blood Pb</u><br>5.4 µg/dL (CRI and gout)<br>4.4 µg/dL (CRI only)<br><br><u>Mean EDTA-chelatable Pb</u><br>138.1 µg/72 hrs (CRI and gout)<br>64.2 µg/72 hrs (CRI only)<br>($p < 0.01$) | In 101, EDTA-chelatable Pb higher in patients with CRI and gout compared to those with CRI only.<br><br>EDTA-chelatable Pb, but not blood Pb, was associated positively with serum urate and negatively with daily urate excretion, urate clearance, and fractional urate excretion.<br><br><u>Randomized chelation trial</u><br>The two groups had similar uric acid, renal function, and Pb measures pre-chelation. In the treated group, mean EDTA-chelatable Pb declined from 159.2 to 41 µg/72 hrs; mean serum urate decreased from 10.2 to 8.6 mg/dL (% change compared to the control group = !22.4 [95% CI: !46.0, !1.5]; $p = 0.02$), and mean urate clearance increased from 2.7 to 4.2 mL/min (% change compared to the control group = 67.9 [95% CI: 12.2, 121.2]; $p < 0.01$). Daily and fractional urate excretion were also significantly different between the two groups. Mean measured creatinine clearance increased from 50.8 to 54.2 mL/min (% change compared to the control group = 8.0 [95% CI: !0.4, 20.1]; $p = 0.06$). |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lin et al. (2002)<br>Study location and date not provided; authors from Taiwan | 84 healthy participants.<br><br>27 participants with gout.<br><br>All with normal renal function (defined as serum creatinine ≤1.4 mg/dL).<br><br>Participants with a history of occupational heavy metal exposure, EDTA-chelatable Pb levels >600 µg/72 hrs, or systemic diseases were excluded.<br><br><u>Randomized chelation trial</u><br>24 participants with EDTA-chelatable Pb levels between 75 and 600 µg/72 hrs randomized to either a treatment group receiving 1 gram EDTA iv per wk for 4 wks (N = 12) or to a control group who received glucose in normal saline i.v.<br><br>Multiple linear regression, adjustment for age, sex, BMI, daily protein intake, and creatinine clearance. | <u>Mean blood Pb</u><br>3.9 µg/dL (controls)<br>4.2 µg/dL (gout)<br><br><u>Mean EDTA-chelatable Pb</u><br>45 µg/72 hrs (controls)<br>84 µg/72 hrs (gout)<br>($p < 0.0001$) | Significantly higher mean EDTA-chelatable Pb and lower urate clearance were present in patients with gout compared to those without (3.7 vs. 6.0 mL/min /1.73 $m^2$; $p < 0.001$ for urate clearance).<br><br>After adjustment, EDTA-chelatable Pb associated with all four uric acid measures (serum urate, daily urate excretion, urate clearance, and fractional urate excretion). Blood Pb associated with serum urate. All associations in same direction as in Lin et al. (2001).<br><br>Randomized chelation trial.<br><br>The two groups had similar urate, renal function, and Pb measures pre-chelation. In the treated group, mean blood and EDTA-chelatable Pb levels declined (from 5.0 to 3.7 µg/dL and 110 to 46 µg/72 hrs, respectively). Statistically significant improvement observed in all four urate measures in the treated group compared to the control group. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lin et al. (2003)<br>Study location and date not provided; authors from Taiwan | 24 mo prospective observational study<br>202 patients with CRI<br><br>Eligibility criteria included serum creatinine from 1.5 - 3.9 mg/dL, stable renal function (decrease in GFR <5 mL/min over 6 mos); blood pressure <140/90 mm Hg; cholesterol level <240 mg/dL; daily protein intake <1 g/kg body wt; no known history of exposure to Pb or other heavy metals and EDTA chelatable Pb <600 µg/72 h.<br><br>Exclusionary criteria included potentially reversible or unstable renal disease (i.e., due to systemic diseases such as lupus and diabetes), nephrotoxicant medications, and drug allergies.<br><br>250 patients initially observed, loss due to noncompliance or unstable renal function, baseline data on the 48 who left or were removed from the study not provided.<br><br>Cox proportional-hazards model analysis for primary outcome. Generalized estimating equations (GEE) for associations between baseline chelatable Pb or blood Pb level and longitudinal change in GFR (estimated by an MDRD equation [Levey et al., 1999]) and by measurement of creatinine clearance.<br><br>Adjustment for age, gender, baseline BMI, smoking, baseline serum creatinine, proteinuria, hypertension, hyperlipidemia, daily protein intake, and underlying renal diseases. | Mean blood Pb levels<br>5.3 µg/dL in total group (n = 202)<br><br>6.1 µg/dL pre-chelation in chelated group (n = 32)<br><br>5.9 µg/dL pre-chelation in control group<br><br>Mean EDTA chelatable Pb levels pre-chelation<br>104.5 µg/72 hrs in total group (n = 202)<br><br>150.9 µg/72 hrs pre-chelation in chelated group<br><br>144.5 µg/72 hrs pre-chelation in control group | 24 mo prospective observational study<br><br>Primary endpoint = increase in serum creatinine to 1.5 times baseline or need for hemodialysis; occurred in 24 participants. Secondary endpoint = change in estimated glomerular filtration rate (GFR).<br><br>In a Cox multivariate regression analysis, chelatable Pb was significantly associated with overall risk for the primary endpoint (hazard ratio for each 1 µg chelatable Pb was 1.00 [95% CI: 1.00, 1.01]; p = 0.03). In this model, baseline serum creatinine was also associated (hazard ratio for each 1 mg/dL was 2.75 [95% CI: 1.46, 5.18]; p = 0.002) and, at borderline significance (p < 0.1), baseline daily protein excretion and smoking were as well.<br><br>The association between baseline chelatable Pb and change in GFR was modeled using GEE. Estimate = !0.003 (p = <0.001) (neither SE nor CI provided). In this model, gender and daily protein intake were associated with increased GFR; baseline serum creatinine level, daily urinary protein excretion, and the presence of polycystic kidney disease were significant predictors of a progressive decline in glomerular filtration rate.<br><br>Based on this model, a 10 µg higher baseline chelatable Pb level was associated with a GFR decrease of 0.03 mL per minute per 1.73 $m^2$ of body-surface area during the 2 yr observation period. Although statistically significant, this effect is clinically small. Furthermore, it is 40 fold lower than that reported in Yu et al. (2004) over a follow-up period that is only two-fold shorter. |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lin et al. (2003) (cont'd)<br>Study location and date not provided; authors from Taiwan | 27 mo clinical trial of chelation<br>At 24 mos, 64 patients whose EDTA chelatable Pb levels were 80 - 600 µg/72 hrs and serum creatinine levels of <4.2 mg/dL were randomized; half to a 3-mo treatment period consisting of weekly chelation with 1 g EDTA iv until their excreted Pb levels fell below 60 µg/72 hrs and half to five wks of placebo infusion.<br><br>Intention-to-Treat analysis compared creatinine clearance and GFR by time period in treated and control groups. | | 27 mo clinical trial of chelation<br>The two groups were similar in baseline renal risk factors (although numbers small so beta error possible).<br><br>After three mos of Pb chelation therapy, the body Pb burden of the patients in the chelation group decreased from 150.9 to 43.2 µg and their mean blood Pb levels decreased from 6.1 to 3.9 µg/dL. GFR increased by 3.4 mL/min/1.73 $m^2$ in the treated group; in contrast, it decreased by 1.1 mL/min/1.73 $m^2$ in the control group. Mean EDTA dose during the 3 mo period was 5.2 µg.<br><br>In the subsequent 24 mos, chelation in 19 (59%) participants was repeated due to increases in serum creatinine in association with rebound increases in EDTA chelatable Pb levels. Each received one additional chelation series (mean 4.1 g EDTA) a mean of 13.7 mos after the first chelation period. Control patients receiving placebo weekly for five wks every six mos.<br><br>At the end of the study period, mean estimated glomerular filtration rate increased by 2.1 mL/min/1.73 $m^2$ of body-surface area in the chelated group compared to a decline of 6.0 in the controls ($p < 0.01$; 95% CI for the difference between groups = –11.0 to –5.1). |

## Table AX6-4.3 (cont'd). Renal Effects of Lead in the Patient Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Yu et al. (2004) Study location and date not provided; authors from Taiwan | 121 patients followed over a four yr observational period.<br><br>Eligibility criteria included serum creatinine from 1.5 -3.9 mg/dL, stable renal function (decrease in GFR <5 mL/min over 6 mos); blood pressure <140/90 mm Hg; cholesterol level <240 mg/dL; daily protein intake <1 g/kg body wt; no known history of exposure to Pb or other heavy metals and EDTA chelatable Pb <600 µg/72 h.<br><br>Exclusionary criteria included potentially reversible or unstable renal disease (i.e., due to systemic diseases such as lupus and diabetes), medical noncompliance (patients were followed for 6 mos to assess compliance before enrollment in the study), nephrotoxicant medications, and drug allergies.<br><br>Cox proportional hazards model analysis for primary outcomes and generalized estimating equations (GEE) for associations between baseline chelatable Pb or blood Pb level and longitudinal change in GFR (estimated by an MDRD equation [Levey et al., 1999]).<br><br>Adjustment for age, gender, baseline BMI, smoking, baseline serum creatinine, proteinuria, hypertension, hyperlipidemia, daily protein intake, use of ACE inhibitor or angiotensin-receptor antagonists (since not all patients were on these), and chronic glomerulonephritis (other underlying renal diseases included in GEE as well). | <u>Mean (SD) blood Pb at baseline</u><br>3.4 (1.3) µg/dL in 58 patients with "low-normal" EDTA chelatable Pb levels (<80 µg Pb/72 hrs)<br><br>4.9 (2.6) µg/dL in 63 patients with "high-normal" EDTA chelatable Pb levels (∃80 but <600 µg/72 hrs) | The two groups (dichotomized by diagnostic EDTA chelatable Pb of 80 µg Pb/72 hrs ) were similar in most baseline risk factors other than Pb body burden. Borderline statistically significant ($p < 0.1$) differences included mean older age in the high chelatable Pb group and certain renal diagnoses (chronic glomerulosclerosis, chronic interstitial nephritis, hypertensive nephropathy; surprisingly both of the latter two diagnoses were less common in the lower Pb body burden group).<br><br>Fifteen patients in the "high-normal" chelatable Pb 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).<br><br>In a Cox multivariate regression analysis, chelatable Pb was significantly associated with overall risk for the primary endpoint (hazard ratio for each 1 µg chelatable Pb was 1.01 [95% CI: 1.00, 1.01]; $p = 0.002$). In this model, the only other variable reaching at least borderline significance ($p < 0.1$) was baseline serum creatinine.<br><br>The associations between baseline chelatable Pb or blood Pb level and change in GFR were modeled separately using GEE.<br>∃ = !0.1295 ($p = 0.002$) for Pb body burden<br>∃ = !4.0123 ($p = 0.02$) for blood Pb<br><br>Based on these models, a 10 µg higher baseline chelatable Pb level or 1µg/dL higher blood Pb level predicted 1.3 and 4.0 mL/min declines in GFR, respectively, during the four yr study period. Similar to the primary outcome analysis, of the many traditional renal risk factors adjusted for in these models, only diagnosis of chronic interstitial nephritis was significantly associated, in this case with an increase in GFR. Of note, chronic interstitial nephritis was also a more frequent diagnosis in the group with the low-normal chelatable Pb levels ($p = 0.09$).<br><br>The authors stated that these patients were not included in earlier publications (which are described below in Section 6.4.4.3.3 Therapeutic EDTA Chelation in Patients). |

## Table AX6-4.4. Renal Effects of Lead on Mortality

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Cooper (1988); Cooper et al. (1985)<br><br>16 U.S. plants<br><br>Employment between 1946 and 1970; mortality from 1947 to 1980 | 4519 male battery plant workers.<br><br>2300 male Pb production workers.<br><br>Employed for at least one yr between 1946 and 1970.<br><br>Cause of death per death certificate (extrapolated when missing).<br><br>Standardized mortality ratios (SMRs) compared with national age-specific rates. PMR also assessed.<br><br>Analyzed separately by battery and Pb production, by hire date before and after 1/1/1946, and by cumulative yrs of employment (1-9, 10-19, 20+). | <u>Mean blood Pb</u><br>63 µg/dL in n = 1326 battery workers<br>80 µg/dL in n = 537 production workers<br><br>Past Pb exposures poorly documented prior to 1960 | Follow-up >90% in both groups; 2339 deaths observed.<br>"Chronic or unspecified nephritis" SMR:<br>222 (95% CI: 135, 343) in battery workers<br>265 (95% CI: 114, 522) in Pb production workers<br>"Other hypertensive disease" SMR ("includes HTN and related renal disease without mention of heart disease)":<br>320 (95% CI: 197, 489) in battery workers<br>475 (95% CI: 218, 902) in Pb production workers<br><br>Race adjusted proportionate mortality ratios analyses similar.<br><br>Nephritis deaths observed primarily in workers hired before 1946.<br><br>Limitations = due to mortality analysis (inaccuracies of death certificates, exposure assessment generally limited). |
| Steenland et al. (1992)<br>Idaho<br>Employed between 1940 and 1965; mortality up to 1988 | 1990 male Pb smelter workers.<br>Employed in a Pb-exposed department for at least one yr between 1940 and 1965.<br>Vital status was determined using records from the Social Security Administration and the National Death Index. | <u>Mean blood Pb</u><br>56.3 µg/dL (n = 173, measured in 1976)<br><br>High Pb exposure defined as workers from departments with an avg >0.2 mg/m$^3$ airborne Pb or ∃50% of jobs had avg levels more than twice that level (1975 survey). In this category, n = 1,436. | Compared to the U.S. white male population, the standardized mortality ratio (SMR) for chronic kidney disease, based on only 8 deaths, was 1.26 (95% CI = 0.54, 2.49). SMR = 1.55 in high Pb exposure group, also not significant. The SMR for chronic kidney disease increased with duration of exposure from 0.79 in workers exposed 1-5 yrs to 2.79 in workers exposed >20 yrs; however SMR was not significant. |

## Table AX6-4.4 (cont'd). Renal Effects of Lead on Mortality

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Fanning (1988)<br>UK<br>Deaths from<br>1926-1985 | Deceased males identified through pension records of Pb battery and other factory workers.<br><br>867 deaths of mean with high Pb exposure compared to 1206 men with low or no Pb exposure. | <u>Range of blood Pb</u><br>40-80 µg/dL since ~1968 in high Pb exposure group; thought not to have had clinical Pb poisoning due to medical surveillance.<br><br><40 µg/dL since ~1968 in little or no exposure group. | Odds ratio for renal disease = 0.62, not significant, based on only 11 deaths. Similar for diagnosis of nephritis. Possible decreasing odds ratio over time of deaths with mention of nephritis on death certificate but not significant and numbers still quite small.<br><br>Limitations = standard mortality study issues although deaths compared with other workers and not general population which is a strength in this type of study. |

## Table AX6-4.5. Renal Effects of Lead in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Hu (1991)<br>U.S.<br>Study date not provided | 21 of 192 adults who were hospitalized at Boston Children's Hospital between 1932 to 1942 for childhood Pb poisoning were traced to a Boston area address. Matched on age, sex, race, and neighborhood to 21controls. | Mean (SD) blood Pb<br>6.0 µg/dL (Pb poisoned)<br>7.5 µg/dL (controls) | No significant differences in blood Pb level, serum creatinine, or BUN. Mean measured creatinine clearance higher in the previously Pb poisoned group compared to controls (112.8 vs. 88.8 mL/min/1.73 $m^2$ [$p < 0.01$]). 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). Suggests Pb-related hyperfiltration. As noted in section 6.4, one survivor, identified but not included in the study, had disease consistent with Pb nephropathy.<br><br>Limitations = small study size and concern for survivor bias in the study group. |
| Loghman-Adham (1998)<br>Chicago, IL<br>Study date not provided | 134 children and young adults, 8 to 13 yrs after chelation therapy for severe Pb poisoning.<br><br>Mean age at poisoning = 2.3 yrs<br>Mean age at follow-up = 13.4 yrs | Mean peak blood Pb level<br>121 µg/dL<br><br>Mean blood Pb level at time of study<br>18.6 µg/dL | Mean serum creatinine was normal (0.8 mg/dL). Calculated creatinine clearance normal in all but 3 children. No correlation between either initial or current blood Pb and serum creatinine or calculated creatinine clearance.<br><br>Urinary α-amino nitrogen concentrations were significantly increased compared with 19 healthy age matched controls and were correlated with current blood Pb levels. Thirty-two children (24%) had glycosuria. Fractional excretion of phosphate, however, was normal in all children. The author concluded that a partial Fanconi syndrome could persist for up to 13 yrs after childhood Pb poisoning. The author notes that the prognostic significance of this is unknown at present. |

## Table AX6-4.5 (cont'd). Renal Effects of Lead in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| McDonald and Potter (1996)<br>Boston, MA<br>1991 | 454 pediatric hospital patients who were diagnosed with Pb poisoning between 1923 and 1966 were traced through 1991.<br>Mortality study, comparison with U.S. population. | | Chronic nephritis was not a significant cause of death. Mortality from all cardiovascular disease was elevated (observed/expected = 2.1 [95% CI: 1.3, 3.2]) and cerebral vascular deaths were particularly common among women (observed/expected = 5.5 [95% CI: 1.1, 15.9]). |
| Moel and Sachs (1992)<br>Chicago, IL<br>1974-1989 | 62 participants with blood Pb >100 µg/dL, diagnosed and chelated between 1966 and 1972, together with 19 age-matched control siblings with initial blood Pbs less than 40 µg/dL. Mean age at follow-up = 22 yrs.<br><br>Renal outcomes = serum creatinine, uric acid, and $\exists_2$-microglobulin, fractional excretion of $\exists_2$-microglobulin, urinary protein:creatinine ratio, and tubular reabsorption of phosphate. | Mean initial blood Pb<br>150.3 µg/dL (highly poisoned as children)<br>Data for siblings not available as levels <40 µg/dL not quantified. | There were no statistical differences in either renal function or blood pressure between study subjects and control siblings. Initial blood Pb level was not associated with serum creatinine, after adjustment for age, gender, and body mass index. A modest increase in serum creatinine values was observed over a nine-yr period in four of the 62 study subjects (up to 1.6 mg/dL). |
| Bernard et al. (1995b)<br>Czech Republic<br>Study date not provided | 144 children living close to a Pb smelter (exposed groups 1 and 2).<br>51 controls living in a rural area presumed to be relatively unpolluted with Pb.<br>Mean age = 13.5 yrs.<br>Renal outcome measures included urinary albumin, RBP, NAG, Clara cell protein, and $\exists_2$-microglobulin.<br>Retinol binding protein<br>73.8 µg/g creatinine (controls)<br>109.4 µg/g creatinine (exposed group 1)<br>117.8 µg/g creatinine (exposed group 2)<br>$\exists_2$-microglobulin<br>60.3 µg/g creatinine (controls)<br>89.1 µg/g creatinine (exposed group 1)<br>66.4 µg/g creatinine (exposed group 2)<br>NAG<br>1.56 IU/g creatinine (controls)<br>2.32 IU/g creatinine (exposed group 1)<br>1.46 IU/g creatinine (exposed group 2)<br>Multiple linear adjusting for age and gender. | Blood Pb<br>8.7 µg/dL (control boys)<br>8.39 µg/dL (control girls)<br>10.9 µg/dL (exposed boys 1)<br>9.4 µg/dL (exposed girls 1)<br>14.9 µg/dL (exposed boys 2)<br>12.9 µg/dL (exposed girls 2) | Mean blood Pb levels significantly higher in both exposed groups compared to the control group. In contrast, blood cadmium levels were similar among all groups. After adjustment for age, sex, blood cadmium, and zinc protoporphyrin, log transformed blood Pb was associated with log transformed RBP ($\exists$ = 0.302, p = 0.005). |

## Table AX6-4.5 (cont'd). Renal Effects of Lead in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| De Burbure et al. (2006)<br>France, the Czech Republic, and Poland<br>Study date not provided | 804 exposed and control children.<br>Exposed children recruited from residents near historical nonferrous smelters, must have lived ∃8 yrs near smelters.<br>Mean age = 10 yrs; range = 8.5-12.3 yrs.<br>Renal outcome measures included serum creatinine, cystatin C and $ß_2$-microglobulin as well as urinary RBP, NAG, Clara cell protein. | <u>Mean blood Pb</u><br>Ranged from 2.8 to 4.2 mg/dL in various control and exposed groups.<br>Urinary cadmium, arsenic and mercury as well as blood cadmium also assessed. | Serum concentrations of creatinine, cystatin C, and $ß_2$-microglobulin negatively correlated with blood Pb levels.<br>Authors state suggestive of an early renal hyperfiltration that avgd 7% in the upper quartile of PbB levels (>5.5 µg/dL; mean 7.84 µg/dL). |
| Factor-Litvak et al. (1999)<br>Kosovo, Yugoslavia<br>1985-1993 | 577 children followed at 6 mo intervals through 7.5 yrs of age.<br><br>Divided into a high exposure and a low exposure group, based on residence in Kosovska Mitrovica with a Pb smelter, refinery, and battery plant or in Pristina, 25 miles away.<br><br>Renal outcome = Proteinuria assessed with a dipstick.<br><br>Multiple logistic regression modeling of proteinuria dichotomized as either any or none, adjusting for socioeconomic status, maternal education/ intelligence, and quality of childrearing environment. | Mead blood Pb from graph peaked at ~38 µg/dL between ages 3-5 in Kosovska Mitrovica and at ~10 µg/dL in controls.<br>Blood Pb level ranged from 1 to 70 µg/dL. | In higher exposed group, adjusted OR for proteinuria was 3.5 (95% CI: 1.7, 7.2); adjusted odds of proteinuria increased by 1.15 (95% CI: 1.1, 1.2) per unit increase in blood Pb in the higher exposed group. Proteinuria unrelated to blood Pb in lower exposed control group.<br><br>Limitations = limited renal outcomes assessed, high dropout rate in the study. |

## Table AX6-4.5 (cont'd). Renal Effects of Lead in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Fels et al. (1998)<br>Poland<br>1995 | 112 children (50 controls, 62 exposed).<br><br>Mean age = 9.9 yrs and 10.6 yrs in controls and exposed group, respectively.<br><br>Numerous (29) renal outcome measures were examined including serum creatinine and $\exists_2$-microglobulin, and urinary NAG, RBP, Clara cell protein, $\exists_2$-microglobulin, 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), prostaglandin $E_2$ ($PGE_2$) and thromboxane $B_2$ ($TXB_2$).<br><br>Urinary RBP<br>46 µg/g creatinine (exposed)<br>42 µg/g creatinine (controls)<br><br>Urinary $\exists_2$-microglobulin<br>89 µg/g creatinine (exposed)<br>37 µg/g creatinine (controls)<br><br>Serum creatinine<br>0.63 mg/dL (exposed)<br>0.63 mg/dL (controls) | Mean blood Pb<br>13.3 µg/dL (exposed)<br>3.9 µg/dL (controls) | Significantly higher mean serum $\exists_2$-microglobulin, and urinary transferrin, 6-keto-$PGF_{1\alpha}$, thromboxane $B_2$, epidermal growth factor, $\exists_2$-microglobulin, $PGE_2$, and Clara cell protein in the exposed children. In contrast, NAG-B was lower in the exposed group. Categorical blood Pb associated with prevalence of values above the upper reference limits for several biomarkers. Urinary 6-keto-$PGF_{1\alpha}$, $TXB_2$, $\exists_2$-microglobulin, Clara cell protein, epidermal growth factor and $PGE_2$ positively correlated with blood Pb (r = 0.441, 0.225, 0.203, 0.261, 0.356, and 0.23, respectively; all with significant p-values).<br><br>Limitations = data analysis, limited adjustment. |
| _ktem et al. (2004)<br>Turkey<br>Study date not provided | 79 adolescent auto repair workers (mean age 17.3 yrs).<br>71 rural adolescents as negative controls (mean age 17.0 yrs).<br><br>Renal outcomes = urinary NAG, $\exists_2$-microglobulin, uric acid, and calcium; blood urea nitrogen (BUN), serum creatinine and uric acid. | Mean blood Pb<br>7.79 µg/dL (exposed workers)<br>1.6 µg/dL (controls) | No difference in mean BUN, serum creatinine, uric acid, or GFR (apparently estimated) between workers and controls.<br><br>Urinary NAG and calcium significantly higher in workers compared to controls. Urinary NAG positively correlated blood Pb (r = 0.427).<br><br>Limitations = data analysis, lack of adjustment. |

## Table AX6-4.5 (cont'd). Renal Effects of Lead in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Price et al. (1999)<br>Belgium, Poland, Germany and Italy<br>Study date not provided | Urinary Pb measured in 481 European children (236 controls, 245 exposed) aged 6 – 14 yrs.<br><br>Several renal outcome measures assessed including urinary NAG and $\exists_2$-microglobulin; values not reported. | Mean urinary Pb<br>Range from 3.9 to 7.2 µg/g creatinine (controls)<br><br>Range from 5.2 to 24.6 µg/g creatinine (exposed) | Urinary Pb generally higher in exposed children as compared to controls. Authors unexpectedly found substantial differences in renal biomarkers by study site. Authors note several renal biomarkers differed between exposed and control groups. Also questioned the use of "control" groups in ubiquitous exposures. |
| Sch≅rer et al. (1991)<br>Germany<br>1988-1989 | 22 children, age 5-14 yrs, with CRI.<br>20 siblings or neighbors as lower exposed group.<br>16 control children without known Pb exposure. | Mean blood Pb<br>2.9 µg/dL in children with CRI, not tested in other groups<br><br>Mean dental Pb content<br>2.8 µg/g in children with CRI<br>1.7 µg/g in sibs/neighbors<br>1.4 µg/g in controls | Pb levels in teeth significantly higher in both the patient and sibling/neighbor control groups compared to the unexposed control group. |
| S ¯nmez et al. (2002)<br>Turkey<br>Study date not provided | 39 adolescent auto repair workers (mean age 16.2 yrs).<br>13 adult battery workers as positive controls (mean age 32 yrs).<br>29 rural adolescents as negative controls (mean age 14.8 yrs).<br><br>Serum creatinine<br>0.99 mg/dL (exposed group)<br>0.99 mg/dL (positive/ adult controls)<br>0.89 mg/dL (negative/ adolescent controls)<br><br>Urinary NAG<br>4.7 IU/g creatinine (exposed group)<br>7.4 IU/g creatinine (positive/ adult controls)<br>3.1 IU/g creatinine (negative/ adolescent controls) | Mean blood Pb<br>8.13 µg/dL (exposed group)<br>25.3 µg/dL (positive/adult controls)<br>3.49 µg/dL (negative/ adolescent controls) | All participants had normal blood urea, creatinine, and uric acid levels as well as normal routine urinalysis.<br><br>Blood Pb level and urinary NAG significantly higher in adolescent auto repair workers compared to the negative control group.<br><br>Limitations = data analysis, lack of adjustment. |

## Table AX6-4.5 (cont'd). Renal Effects of Lead in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Staessen et al. (2001)<br>Belgium<br>1999 | 100 exposed and 100 control children.<br><br>Mean age = 17 yrs.<br><br>Two exposed groups were recruited from industrialized suburbs while the control group was recruited from a rural area.<br><br>$\exists_2$-microglobulin<br>5.22 µg/mmol creatinine (controls)<br>5.3 µg/mmol creatinine (exposed group 1)<br>9.09 µg/mmol creatinine (exposed group 2)<br><br>Cystatin-C<br>0.65 mg/L (controls)<br>0.63 mg/L (exposed group 1)<br>0.71 mg/L (exposed group 2)<br><br>Multiple linear regression adjusting for sex and smoking status. | Mean blood Pb<br>1.5 µg/dL (controls)<br>1.8 µg/dL (exposed group 1)<br>2.7 µg/dL (exposed group 2) | Blood Pb, $\exists_2$-microglobulin, and Cystatin-C levels higher in exposed group 2 as compared to controls and exposed group 1.<br><br>After adjustment for sex and smoking status, blood Pb was associated with both $\exists_2$-microglobulin and cystatin-C. A two-fold increase in blood Pb was associated with a 3.6% (95% CI: 1.5, 5.7) increase in Cystatin-C and a 16% (95% CI: 2.7, 31) increase in $\exists_2$-microglobulin. Blood cadmium was not associated with either outcome. |
| Verberk et al. (1996)<br>Romania<br>1991-1992 | 151 children who resided at different distances from a Pb smelter.<br>Mean age = 4.6 yrs.<br>Renal outcomes = urinary RBP, NAG, $\alpha_1$-microglobulin, albumin and alanine aminopeptidase.<br><br>Geometric means<br>Urinary RBP<br>49.4 µg/g creatinine<br>Urinary NAG<br>6.9 U/g creatinine<br>Urinary $\alpha_1$-microglobulin<br>2.4 mg/g creatinine<br>Urinary alanine aminopeptidase<br>19.8 U/g creatinine<br><br>Multiple regression analysis adjusting for age and gender. | Mean (SD) blood Pb<br>34.2 (22.4) µg/dL | After adjustment for age and gender, a 10 µg/dL increase in blood Pb was associated with a 13.5% increase in NAG excretion (90% CI: 10.2, 17). No threshold was observed. No other significant associations noted. |

## Table AX6-4.5 (cont'd). Renal Effects of Lead in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Africa** | | | |
| Diouf et al. (2003)<br>Senegal<br>1998 | 38 Senegalese children (19 exposed, 19 controls).<br><br>Age range = 8 – 12 yrs old.<br><br>Renal function assessed by measuring urinary alpha-glutathione S-transferase (αGST). | Mean (SD) blood Pb<br>10.7 (1.7) µg/dL (exposed)<br>6.1 (1.8) µg/dL (controls) | Blood Pb significantly higher in exposed group (urban dwellers) as compared to controls (rural dwellers).<br><br>Unclear as to whether αGST was higher or lower in controls as compared to exposed group (stated to be higher in controls in the results section BUT stated to be higher in the exposed group in the discussion). Regardless, the difference was not statistically significant.<br><br>Limitations = small sample size, data analysis. |

# ANNEX TABLES AX6-5

## Table AX6-5.1. Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Meta-analysis** | | | |
| Nawrot et al. (2002)<br><br>31 U.S. and European studies, community and occupationally exposed, published between 1981 and 2001. | 48 different groups, 32 of which were only of men, 15 of which were only of women, and one studying both sexes. Total meta-analysis N > 58,490. Age ranged from 15 to 93 yrs, depending on the study. Two methods of meta-analysis were used, subject-weighted and non-weighted, using study-reported effect sizes and standard errors, transformed from the original study specification of blood Pb (linear, logarithmic, or blood Pb group) to a single effect size for doubling of blood Pb. Also did analyses stratified by race and sex. | Mean blood Pb concentration across studies ranged from 2.3 to 63.8 µg/dL. Total range of blood Pb across studies was 0 to 97.9 µg/dL. | Each doubling of blood Pb was associated with a significant 1.0 mm Hg (95% CI: 0.5, 1.4) increase in systolic blood pressure and a significant 0.6 mm Hg (95% CI: 0.4, 0.8) increase in diastolic blood pressure. Stated that differences in Pb effect were not statistically different between sexes, but did not describe test nor give statistics other than p-values. Presented black and white differences as a trend for blacks to be "more susceptible than whites," but presented no tests.<br><br>Statistically examined assumptions of homogeneity of effect and found no significant heterogeneity. Tested for publication bias (statistically significant results tend to be published more than non-significant results) and found no evidence. Found no significant effects of removing one study at a time in sensitivity analysis. It appears that the presented results of effect sizes and confidence intervals were calculated by the subject-weighted method, but this was not made explicit. Included some studies that presented no Pb coefficients or standard errors, assuming effect size of zero, though the reported effect sizes without these studies did not appear to be different from overall effect sizes. For studies using a linear Pb measure, effect sizes were calculated by doubling the arithmetic mean blood Pb. If the concentration-response curve for the Pb-blood pressure relationship was really better characterized by a log-linear function, the authors' use of studies with a linear blood Pb term with high avg blood Pb led to over-estimation of the slope of the relationship and those studies with low blood Pb avgs produced an under-estimation of the slope of the relationship. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Cheng et al. (2001)<br>U.S.-Boston, Normative Aging Study (VA)<br>1991-1997 | 833 males (~97% white), avg age (SD):<br><br>65.5 (7.2) Normotensive subjects, N = 337<br>68.3 (7.8) Borderline hypertensive subjects, N = 181<br>67.9 (6.8) Definite hypertensive subjects, N = 314<br><br>474 males with no history of hypertension at first measurement, returning up to 6 yrs later for hypertension study.<br><br>Linear multiple regression models of blood pressure and Cox proportional hazard models of new cases of hypertension after up to 7 yrs, with one group of covariates forced into models based on biological plausibility and another group forced based on significant univariate or bivariate results or >20% effect modification of Pb variable coefficient in multiple models. Linear blood Pb, tibia Pb, and patella Pb forced in separate models. | Arithmetic mean (SD) blood Pb:<br>5.9-6.4 µg/dL (3.7-4.2), depending on hypertension group (only data shown). | Multiple regression models of blood pressure always included age, age-squared, BMI, family history of hypertension, daily alcohol consumption, and daily calcium consumption. Increasing tibia Pb concentration was associated with increased systolic blood pressure (diastolic not addressed) in baseline measurements in subjects (n = 519) free from definite hypertension (systolic >160 mm Hg, diastolic >95 mm Hg, or taking daily antihypertensive medication). Each increase of 10 µg/g tibia Pb concentration was associated with an increase in systolic blood pressure of 1.0 mm Hg (95% CI: 0.01, 1.99). Patella and linear blood Pb were not significant.<br><br>Cox proportional hazard models always included age, age-squared, BMI, and family history of hypertension. In follow up (n = 474), only increasing patella Pb predicted increasing risk of definite hypertension in those classified as normotensive at baseline. For every 10 µg/g increase in patella Pb risk ratio increased 1.14 (95% CI: 1.02, 1.28). Combining borderline hypertension (systolic 141-160 mm Hg or diastolic 91-95 mm Hg) with definite hypertension (n = 306), the relative risk ratio of becoming a combined hypertensive associated with a 10 µg/g increase in patella Pb was 1.23 (95% CI: 1.03, 1.48). Linear blood Pb and tibia Pb were not significant.<br><br>Linear blood Pb is not indicated for blood pressure models due to strong likelihood of significant residual heteroscedasticity and non-normality. Relatively small sample size may have prevented tibia blood Pb significance in the Cox proportional hazard models. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Den Hond et al. (2002)<br>U.S.-NHANES III<br>1988-1994 | 4,685 white males, 5,138 white females, 1,761 black males, 2,197 black females, from 20 yrs up. Log-transformed blood Pb, systolic and diastolic blood pressure measured at survey time and analyzed with forward, stepwise multiple regression with covariates.<br><br>Avg age:<br>White<br>Male: 44.3 yrs<br>Female: 46.2 yrs<br>Black<br>Male: 40.5 yrs<br>Female: 41.5 yrs | Geometric mean (25th-75th percentile) blood Pb:<br>White male mean 3.6 µg/dL (2.3-5.3)<br>White female mean 2.1 µg/dL (1.3-3.4)<br>Black male mean 4.2 µg/dL (2.7-6.5)<br>Black female mean 2.3 µg/dL (1.4-3.9) | After adjusting for age, age-squared, BMI, hematocrit, smoking, alcohol, and an indicator variable for use of antihypertensive medications, each model was further modified by a unique mix of other covariates, including: coffee consumption, dietary calcium, dietary sodium/calcium ration, total serum protein, total serum calcium, diabetes, and poverty index. Log Pb was forced in last.<br><br>In stratified analyses, only blacks had significant positive blood pressure associations with log blood Pb. Each doubling of blood Pb was associated with increase of black male systolic blood pressure of 0.9 mm Hg (95% CI: 0.04, 1.8), black female systolic blood pressure of 1.2 mm Hg (95% CI: 0.4, 2.0), and female diastolic blood pressure of 0.5 mm Hg (95% CI: 0.01, 1.1). In white males only, each doubling of blood Pb was significantly associated with a decrease in diastolic blood pressure of -0.6 mm Hg (95% CI: −0.9, −0.3).<br><br>Stepwise models can rely on chance associations due to multiple testing and usually lead to a different pattern of covariate adjustment in different models. Inclusion of likely confounding variables such as serum calcium could have affected estimated Pb effects. No testing for significant Pb coefficient differences between each stratum. No model diagnostic tests reported. No explanation offered for inverse relationship between Pb and diastolic blood pressure in white males. No adjustment for survey design. |
| Gerr et al. (2002)<br>U.S.-Spokane WA and area around Silver Valley ID<br>1994 | 502 young people, age 19-29 yrs, 53% female, nearly evenly divided into the Spokane group (no unusual childhood exposure) and the Silver Valley group, where a Pb smelter operated during their childhood. Multiple regression models of systolic blood pressure and diastolic blood pressure. All covariates forced into model as block with both linear blood Pb and tibia bone Pb in each model. | Mean (SD) blood Pb only given stratified on tibia Pb category:<br>Tibia <1 µg/g: 1.9 µg/dL (1.6)<br>Tibia 1-5 µg/g: 2.3 µg/dL (2.1)<br>Tibia 6-10 µg/g: 2.4 µg/dL (2.4)<br>Tibia <10 µg/g: 3.2 µg/dL (2.3)<br>No other descriptive tibia Pb data given. | Adjusting for sex, age, height, BMI, education, income, current smoker, current alcohol use, childhood residence (the two recruitment areas), current birth control pills, hemoglobin, and serum albumin, only tibia Pb, and not linear blood Pb, was significantly related to systolic and diastolic blood pressure. Compared to the <1 µg/g tibia Pb category, subjects in the >10 µg/g category had 4.3 mm Hg (95% CI: 1.4, 6.7) higher systolic blood pressure and 2.8 mm Hg (95% CI: 0.4, 5.2) higher diastolic blood pressure.<br><br>Linear blood Pb is not indicated for blood Pb-blood pressure models. No diagnostic testing reported. Insufficient descriptive data given for tibia Pb. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Glenn et al. (2003)<br>U.S.-New Jersey<br>1994-1998 | 496 males, mean (SD, range) age 55.8 (7.4, 40-71) yrs, working or formerly working at a plant producing tetraethyl or tetramethyl Pb until 1991, were followed from 10 mos to 3.5 yrs during which blood pressure was repeatedly tested. Blood Pb was tested only at baseline. Tibia Pb was tested in 1991 (at the end of organic Pb production at the plant) and called "peak tibia Pb" and again during 1997 (yr 3). Generalized estimating equations with an exchangeable correlation structure for repeated measurements were used for systolic and diastolic blood pressure. One group of covariates was forced into the model as a block (age at baseline, race, BMI, indicator variable for technician, Pb variable (linear blood Pb, peak tibia Pb, and tibia Pb each tested separately), duration of follow up, and the interaction between the Pb variable and the duration term. Potential confounding variables were entered stepwise and retained in the model if significant. Alternate models not using linear time were constructed, using quartile of follow up time to avoid assuming a linear relationship of change in blood pressure with time. | Arithmetic mean (SD, range) blood Pb at baseline:<br>4.6 µg/dL (2.6, !1 to 20)<br><br>Tibia Pb at yr 3:<br>14.7 µg/g (9.4, !1.6 to 52)<br><br>Peak tibia Pb:<br>24.3 µg/g (18.1, !2.2 to 118.8) | Controlling for baseline age, BMI, antihypertensive medication use, smoking, education, technician and number of yrs to each blood pressure measurement, each 1 µg/dL increase in linear baseline blood Pb was associated with avg systolic blood pressure increase of 0.64 mm Hg/yr (95% CI: 0.14, 1.14), each 10 µg/g increase in yr 3 tibia Pb with an avg increase of 0.73 mm Hg/yr (95% CI: 0.23, 1.23), and each increase of 10 µg/g of peak tibia Pb with an avg increase of 0.61 mm Hg/yr (95% CI: 0.09, 1.13). Similar results were obtained using the follow up time quartile designation for systolic blood pressure with all subjects and with subjects not taking antihypertensive medications.<br><br>This was one of the few studies using a prospective design and that used a statistical technique accounting for repeated measures. No justification given for using an exchangeable correlation structure instead of an alternate one. Only examined cortical bone Pb (tibia) and not trabecular bone Pb (patella or calcaneus). Linear blood Pb may not be indicated for use in blood Pb-blood pressure models. Stepwise modeling involves multiple testing of the same data set with no control for altered probabilities. No model diagnostics presented. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Glenn et al. (2001)<br>U.S.-New Jersey<br>1996-1997 | 213 males (92% white), mean (SD) age 58.0 (7.4) yrs, working or formerly working at a plant producing tetraethyl or tetramethyl Pb until 1991, were genotyped for ATP1A2(5') and ATP1A2(3') polymorphism. ATPase is thought to play a role in regulating blood pressure and Pb inhibits its activity. Blood pressure, blood Pb, and tibia Pb were measured. Multiple linear regression models were used for systolic and diastolic blood pressure. Logistic regression model was reported for hypertension (systolic >160 mm Hg, diastolic $\geq$ 96 mm Hg, or taking antihypertensive medications). Covariate entry methods not specified, but were likely stepwise. Covariates for the blood pressure model were age, use of antihypertensive medications, alcohol, smoking, season of yr, linear blood Pb, tibia Pb (the two Pb measures apparently tested separately), ATP1A2(5') and ATP1A2(3') polymorphism (each tested separately), and an interaction term between polymorphism and Pb. Covariates for the hypertension models were age, BMI, lifetime alcoholic drinks, linear blood Pb and tibia Pb, and polymorphism, each Pb measure and polymorphism tested separately. | Arithmetic mean (SD, range) blood Pb:<br>5.2 µg/dL (3.1, 1-20)<br><br>Mean (SD) tibia Pb:<br>16.3 µg/g (9.3) | None of the relationships between the ATP1A2(5') polymorphism and either blood or bone Pb or blood pressure were significant.<br><br>The ATP1A2(3') polymorphism was homogenous for the 10.5 kilobase allele (10.5/10.5) in 11 subjects, heterogeneous for the 10.5 and 4.3 kilobase allele (10.5/4.3) in 82 subjects, and heterogeneous (10.5/4.3) in 116 subjects. Prevalence of the 10.5 allele was significantly higher in blacks than in whites.<br><br>Regression coefficients of 4.3/4.3 and 10.5/4.3 genotypes were not significantly different and all subsequent analyses compared the 10.5/10.5 genotype with the combined 4.3/4.3-10.5/4.3) genotype. The significant interaction between linear blood Pb and the 10.5/10.5 genotype showed that for every 1 µg/dL of blood Pb systolic blood pressure increased 5.6 mm Hg (95% CI: 1.2, 9.9) more than the blood pressure of the combined genotype group. Blood Pb range of the combined genotype group was twice that of the 10.5/10.5 group. When data were truncated to make blood Pb of both groups cover the same range, coefficients of the genotype-linear blood Pb interaction term did not change appreciably. Authors state that tibia Pb interacted with genotype on blood pressure but showed no data to estimate either type or size of effect. Diastolic blood pressure was not related to genotype, to Pb or to the interaction between Pb and genotype.<br><br>Prevalence of hypertension (30% in total sample) was significantly higher among the 10.5/10.5 group (63.4 %) than among the combined group (28.3 %). Adjusting for age, BMI, and lifetime alcohol, the odds of hypertension in the 10.5/10.5 group were OR = 7.7 (95% CI: 1.9, 31.4) compared to the 4.3/4.3 group. The heterogeneous group was not significantly different from the 4.3/4.3 group.<br><br>Linear blood Pb specification not indicated for blood Pb-blood pressure modeling. Examination of partial residual plot for systolic blood pressure and linear blood Pb shows typical heterogeneity of residuals as a function of predicted values. Thus, presented coefficients may be inefficient and biased. Only 9 subjects were homogenous for 10.5/10.5 in the multiple regression model. Only cortical bone Pb was tested, not trabecular bone Pb. Cortical bone Pb models not shown or quantitatively described. Blood Pb rounded to nearest unit µg/dL. Mixed organic-inorganic Pb exposure. Relatively small sample size may have prevented detection of other significant effects. No model diagnostics described. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Hu et al. (1996)<br>U.S.-Boston-Normative Aging Study-VA<br>1991-1994 | 590 males (over 98% white), mean age around 67 yrs, divided into 146 hypertensives (systolic >160 mm Hg, diastolic >95 mm Hg, or daily antihypertensive medication) and 444 non-hypertensives. Linear blood Pb, tibia and patella bone Pb added separately to logistic regression model containing forced covariates of age, race, BMI, family history of hypertension, pack-yrs smoking, alcohol ingestion dietary sodium and calcium. Then, a backward elimination procedure starting with all covariates, including all Pb variables, resulted in a model in which only significant covariates were retained. | Hypertensives:<br><br>Arithmetic mean (SD) blood Pb:<br>6.9 µg/dL (4.3)<br>Mean tibia Pb:<br>23.7 µg/g (14.0)<br>Mean patella Pb:<br>35.1 µg/g (19.5)<br><br>Non-hypertensives:<br><br>Arithmetic mean (SD) blood Pb:<br>6.1 µg/dL (4.0)<br>Mean tibia Pb:<br>20.9 µg/g (11.4)<br>Mean patella Pb:<br>31.1 µg/g (18.3) | Logistic regression model with all forced covariates revealed no significant Pb effects when the three Pb variables were forced into the model separately. After backward elimination, the only significant covariates left were BMI and family history of hypertension. Of all the Pb variables, only tibia Pb remained in the model. With each increase of 10 µg/g of tibia Pb, odds of being classified hypertensive rose (OR = 1.21; 95% CI: 1.04, 1.43).<br><br>Stepwise regression, backward or forward, involves multiple testing with the same data set, capitalizes on chance occurrence in the data set, and gives over-optimistic probability values. No model diagnostic testing reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Korrick et al. (1999) U.S.-Boston-Nurse Health Study 1993-1995 | 284 women, from 47-74 yrs, mean age (SD) 58.7 (7.2), were divided into 97 cases (systolic ∃140 mm Hg, diastolic ∃90 mm Hg, or physician-diagnosed hypertension) and 195 controls. Controls were further classified as low normal (<121/75 mm Hg) and high normal >121/75 mm Hg). Three ordinal regression models were constructed, each containing either blood Pb, tibia Pb or patella Pb with forced entry of all other covariates. A final backwards elimination ordinal regression model started with all covariates, including all Pb variables, excluding each until only significant variables were left. Interactions were tested in the final model between patella Pb and alcohol use, age, and menopausal status. | Mean blood Pb (SD, range): 3.1 µg/dL (2.3, <1 to 14) Mean tibia Pb (SD, range): 13.3 µg/g (9.0, !5 to 69) Mean patella Pb (SD, range): 17.3 µg/g (11.1, !5 to 87) | Only patella Pb was significantly related to increased odds of hypertension in the preliminary models, adjusted for age, BMI, alcohol, dietary calcium and sodium, ever smoke, and family hypertension. Each 10 µg/g increase in patella Pb was associated with increased odds of hypertension OR = 1.28 (95% CI: 1.03, 1.60). In the backward elimination model adjusted for age, BMI dietary sodium and family hypertension, only natural log transformed patella Pb remained in the model. Identical odds ratios from patella Pb were obtained in both models. None of the interaction tests were significant.<br><br>Small study size may have limited power to detect significant interactions. The proportional odds assumption of the ordinal regression model was verified. Note that the odds ratios above are for movement from one of the two lower categories, low normal and high normal, to the next higher category as patella Pb increased. No other model diagnostic tests reported. |
| Morris et al. (1990) U.S.-sampled from general population around Portland, OR responding to ads to participate in clinical trials of non-pharmacological management of blood pressure. 1984-1989? | 145 males and 106 females, 73% with arterial pressures >105 mm Hg, provided blood pressure measurements once a wk over four consecutive wks. Blood for Pb analysis was collected during this period. Stepwise multiple regression was used to construct separate models of systolic and diastolic blood pressure stratified by sex. Covariates available to be entered were age, BMI, dietary calcium and "other nutrient intakes," ionized serum calcium, erythrocyte protoporphyrin and natural log transformed blood Pb. | Arithmetic mean (SD) blood Pb:<br>Males: 8.0 µg/dL (4.4)<br>Females: 6.9 µg/dL (3.6) | Natural log blood Pb was only a significant predictor of blood pressure in males. Adjusting for age and ionized serum calcium, every one natural unit increase in blood Pb was significantly associated with a 4.58 mm Hg (neither SE nor CI stated) in systolic blood pressure and, adjusting for hemoglobin, age, and current smoking, a 1.90 mm Hg (neither SE nor CI stated) in diastolic blood pressure.<br><br>The usual precautions regarding multiple testing and different covariate patterns in stratified models constructed with stepwise regression apply. Reporting of effects not complete. Small sample size limits conclusions about non-significant effects. High prevalence of hypertensives in sample due to study recruitment design. Blood Pb technique, as represented by presented graph, had a detection limit of 5 µg/dL. No model diagnostics. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Nash et al. (2003)<br>U.S.-NHANES III<br>1988-1994 | 1084 premenopausal and 633 postmenopausal women, from 40 to 59 yrs. Multiple linear regression models with covariates, including linear blood Pb, entered as a block for systolic and diastolic blood pressure. Logistic regression models with same covariates and Pb quartile added last for hypertension. | Mean (range) blood Pb by Pb quartile:<br><br>1st quartile 1.0 µg/dL (0.5-1.6)<br><br>2nd quartile 2.1 µg/dL (1.7-2.5)<br><br>3rd quartile 3.2 µg/dL (2.6-3.9)<br><br>4th quartile 6.4 µg/dL (4.0-31.1) | Linear blood Pb was entered last after forcing in age, race/ethnicity, alcohol use, cigarette smoking, BMI, and kidney function (serum creatinine) in multiple regression models for all women and women stratified by menopause status for systolic and diastolic blood pressure. Pb quartile was added to logistic regression models of hypertension (systolic ∃140 mm Hg, diastolic ∃90 mm Hg or taking antihypertensive medication with the same covariates as the blood pressure models, in all women and stratified by menopausal status. Tested additional models in which women treated for hypertension were excluded from models. All models were adjusted for sample design and weighting.<br><br>Each increase of 1 µg/dL of blood Pb was significantly associated with a 0.32 mm Hg (95% CI: 0.01, 0.63) increase of systolic blood pressure and a 0.25 mm Hg (95% CI: 0.07, 0.43) increase of diastolic blood pressure in all women without respect to menopausal status. In analyses stratified by menopausal status, only postmenopausal women showed a significant blood Pb effect. For each 1 µg/dL increase of blood Pb was associated with significantly increased diastolic blood pressure of 0.14 (95% CI: −0.11, 0.39 *sic.*) only in postmenopausal women.<br><br>Referenced to the 1st blood Pb quartile, no other quartile showed significantly increased odds for hypertension in all subjects or in subjects stratified by menopausal status. With further analyses stratified by systolic and diastolic hypertension without women taking antihypertensive medications, in the combined group of pre and postmenopausal women the odds of diastolic hypertension were significant when the 4th Pb quartile was compared to the 1st quartile (OR = 3.4 [95% CI: 1.3, 8.7]). In a model of only postmenopausal women untreated for hypertension, odds of diastolic hypertension were significantly increased in the higher three quartiles of blood Pb (OR = 4.6 [95% CI: 1.1, 19.2], OR = 5.9 [95% CI: 1.5, 23.1], OR = 8.1 [95% CI: 2.6, 24.7], respectively) and odds of systolic hypertension were significant only for the two middle Pb quartiles (OR = 3.0 [95% CI: 1.3, 6.9], OR = 2.7 [95% CI: 1.2, 6.2], respectively).<br><br>Linear blood Pb is suspect in linear regression models of blood pressure as it is usually associated with biased and inefficient estimation of Pb coefficients due to probable heteroscedasticity and non-normal distribution of residuals. No model diagnostics were reported. No statistical testing for differences in Pb coefficients according to strata. Nine stratified models overall. Not all stated significance levels and standard errors in the blood pressure model table corresponded for certain variables. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Proctor et al. (1996) U.S.-Boston-Normative Aging Study (VA) 1992-1993 | 798 men from 17 to 44 yrs. Multiple linear regression models of natural log blood Pb on systolic and diastolic blood pressure. All covariates forced into model. | Arithmetic mean (SD, range) blood Pb: 6.5 µg/dL (4.0, 0.5-35) | Natural log blood Pb, age, age-squared, BMI, adjusted dietary calcium, exercise, indicator variables for current and former smoker, daily alcohol consumption, sitting heart rate, and hematocrit were entered into multiple regression models without regard for significance.<br><br>Increased diastolic, but not systolic, blood pressure was significantly associated with increased blood Pb. Each natural log increase in blood Pb was associated with a 1.2 mm Hg (95% CI: 0.1, 2.2) increase in diastolic blood pressure.<br><br>Interactions between dietary calcium and blood Pb on blood pressure were not significant. Further analyses stratified on use of antihypertensive medication and those older than or equal to 74 yrs still revealed significant blood Pb-diastolic blood pressure relationships.<br><br>Blood Pb in over half the study group (n = 410) was determined by analyzing previously frozen erythrocytes collected several yrs prior to the blood pressure measurements used in the study and corrected by using hematocrit values also measured when blood was originally collected. Combining both groups means that nearly half the group was tested for the effects of blood Pb on blood pressure measured at the same time, the other half measured several yrs apart. There was no correction in models for this potential effect. The effect of taking antihypertensive medication could have been assessed in a single model by using an indicator variable. No statistical testing for the effects of stratification on the blood Pb-blood pressure relationship. No model diagnostics. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Rothenberg et al. (1999)<br>U.S.-Los Angeles<br>1995-1998 | 1188 immigrants and 439 nonimmigrants, from 15 to 43 yrs, all women in 3rd trimester of pregnancy. Multiple regression models of natural log blood Pb on systolic and diastolic blood pressure with all covariates forced into models. Covariates selected from larger set based on significant univariate or bivariate tests. | Geometric mean (SD) blood Pb:<br><br>Immigrants: 2.3 µg/dL (1.4)<br>Non-immigrants: 1.9 µg/dL (1.3) | Natural log blood Pb, age, BMI, coffee drinking, iron supplementation, and job stress were entered as a block without regard to significance in linear multiple regression models of systolic and diastolic blood pressure stratified by immigration status.<br><br>Increased blood Pb was significantly associated with increased blood pressure only in immigrants. Each natural log unit increase in blood Pb was associated with a 1.7 mm Hg (95% CI: 0.7, 2.8) increase in systolic blood pressure and a 1.5 mm Hg (95% CI: 0.5, 1.9) increase in diastolic blood pressure in immigrants.<br><br>Used and reported model diagnostic tests, as evidenced by the use of standard error calculations robust to residual heteroscedasticity. Stated reasons for stratification on immigrant status were significant differences between the two groups in blood Pb, blood pressure, age, BMI, and education. Did not statistically test difference in Pb coefficients between the immigration strata. Did not correct for potential non-linearity in age effects on blood pressure. |
| Rothenberg et al. (2002a)<br>U.S.-Los Angeles<br>1995-2001 | 668 women, 15 to 44 yrs, studied in 3rd trimester pregnancy and again a mean of 10 wks postpartum. Exclusion criteria were diabetes, renal or cardiovascular disease, extreme postnatal obesity (BMI >40), and subjects using stimulant drugs. Multiple linear regression models of natural log blood Pb, tibia and calcaneus Pb on systolic and diastolic blood pressure with all covariates and all Pb variables forced into model. Separate models for 3rd trimester and postpartum, excluding all women with hypertension (see below) during each specific period. Logistic regression for hypertension (systolic ∃140 mm Hg or diastolic ∃90), specific to 3rd trimester and postpartum periods with the same covariates and Pb variables. | Geometric mean blood Pb (SD):<br><br>3rd trimester: 1.9 µg/dL (1.7)<br><br>Postpartum: 2.3 µg/dL (2.0)<br><br>Tibia mean Pb (SD): 8.0 µg/g (11.4)<br><br>Calcaneus mean Pb (SD): 10.7 µg/g (11.9) | Multiple linear regression models for normotensives adjusted for postnatal hypertension (3rd trimester model only), BMI, age, parity, smoking, alcohol, immigrant status, and educational level plus all three Pb indices. Only calcaneus Pb was associated with blood pressure in 3rd trimester models. Every 10 µg/g increase in calcaneus Pb was associated with 0.70 mm Hg (95% CI: 0.04, 1.36) increase in systolic blood pressure and a 0.54 mm Hg (95% CI: 0.01, 1.08) increase in diastolic blood pressure. In postpartum models, natural log blood Pb was the only variable statistically associated with blood pressure. Every natural log unit increase in blood Pb was associated with !1.52 mm Hg (95% CI: !2.83, !0.20) decrease in systolic blood pressure and a −1.67 mm Hg (95% CI: !2.85, !0.50) decrease in diastolic blood pressure.<br><br>In logistic models, only calcaneus Pb was significantly associated with increased odds for hypertension. Each 10 µg/g increase in calcaneus Pb was associated with an OR = 1.86 (95% CI: 1.04, 3.32) of 3rd trimester hypertension. None of the Pb variables was associated with postpartum hypertension.<br><br>Models did not use age-squared covariate. Models did not use repeated measures statistics. No statistical comparisons between 3rd trimester and postpartum models. Model diagnostic tests reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Schwartz et al. (2000c)<br>U.S.-Eastern<br>1996-1997 | 543 mostly former organolead workers, predominantly white (92.8%), at a tetraethyl/tetramethyl plant, mean (SD) [range] age 7.6 (7.6) [41.7-73.7] yrs had blood Pb, DMSA-chelatable Pb (4-hr. urinary Pb excretion after a single 10 mg/kg dose of DMSA) measured for modeling systolic and diastolic blood pressure and hypertension (systolic >160 mm Hg or diastolic ∃96 mm Hg or taking antihypertensive medications. Tibia Pb ~2 yrs later was also used as a Pb index. For blood pressure, linear multiple regression with backward elimination of non-significant covariates or covariates that "had important influence on the coefficients for the Pb-dose terms." Each Pb variable was tested in a separate model. Potential covariates for these models were age, BMI, current tobacco use, and current use of antihypertensive medications. Other models were constructed taking out those subjects using antihypertensive medications. Both linear and linear + quadratic blood and tibia Pb terms were tested. Logistic regression analyses were used to test the effect of the Pb variables on hypertension, controlling for age, diabetes, lifetime alcohol consumption, and BMI. Logistic models also tested each Pb measure in interaction with age. | Blood Pb arithmetic mean (SD, range): 4.6 µg/dL (2.6, 1 to 20)<br><br>DMSA-chelatable Pb mean (SD, range): 19.0 µg (16.6, 1.2 to 136)<br><br>Tibia Pb mean (SD, range): 14.4 µg/g (9.3, !1.6 to 52) | Adjusting for age, BMI, current smoking, and current use of antihypertensive medications, each 1 µg/dL increase in blood Pb-squared was significantly associated with 0.189 mm Hg (95% CI: 0.087, 0.330) increase in systolic blood pressure with three outliers removed. With the same covariates, each 1 µg/dL increase in linear blood Pb was significantly associated with 0.310 mm Hg (95% CI: 0.028, 0.592) in diastolic blood pressure taken over a 2-yr period (n = 525). No other Pb variables were significant.<br><br>For the hypertension models, only the interaction of linear blood Pb by age was significant, with subjects showing significant decrease in odds ratio of hypertension with every joint increase of 1 µg/dL blood Pb and 1 yr increase in age (linear blood Pb X age OR = 0.98; [95% CI: 0.97, 0.99]). The interaction suggested a concentration-response relationship between linear blood Pb and hypertension only up to ~58 yrs of age.<br><br>Authors note that blood pressure findings "were not affected by exclusion or inclusion of subjects using antihypertensive medications," but do not present either the data or the statistical tests to evaluate that conclusion. No other model diagnostics were reported. Although blood Pb was also modeled as a quadratic Pb term for systolic blood pressure, no analysis was shown for non-linear blood Pb terms for diastolic blood pressure.<br><br>Trabecular bone Pb was not tested, though other studies indicate that it is a better Pb index than cortical Pb for cross-sectional blood pressure and hypertension study.<br><br>Although the backward procedures described could have resulted in less than the full set of considered covariates entering the models, all model presentations were limited to showing the Pb coefficients and all models indicated in a footnote that the Pb coefficients were adjusted for each possible covariate for that model. While this is possible with the short list of covariates, given the 14 models presented one might expect to see at least one model where one of the covariates did not remain. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Schwartz (1995)<br>15 prior U.S. and European studies published between 1985 and 1993 | Total subjects not specified, men and women ages 18 to 74 yrs. Random effects meta-analysis with inverse variance weighting of Pb-blood pressure coefficients from each study. Sensitivity analysis performed by dropping study with largest or smallest effect. | Blood Pb levels not stated. | Each doubling of natural log blood Pb level was associated with an increase of 1.25 mm Hg (95% CI: 0.87, 1.63) systolic blood pressure. Sensitivity analysis showed negligible change in meta-analysis coefficient. Concluded that adding newer studies would not change calculated coefficient. Noted Pb-blood pressure slope was larger at lower Pb levels than at higher Pb levels.<br><br>The study only analyzed systolic, not diastolic, blood pressure. Superseded by Nawrot et al. (2002). |
| Schwartz (1991)<br>NHANES II<br>U.S.<br>1976-1980 | Under 10,000 subjects (exact number not reported), males and females, aged 25 to 74 yrs for left ventricular hypertrophy results with logistic regression. Linear blood Pb used for LVH. For blood pressure results, multiple linear regressions stratified by sex, with one block of variables forced, another block of variables entered with stepwise regression, aged 6 mos to 74 yrs, exact number not given. Natural log blood Pb used for linear regression. Both logistic and linear regressions adjusted for survey design. | No blood Pb descriptive data given. | Used logistic regression to study Pb effect on left ventricular hypertrophy (LVH) determined by a combination of electrocardiogram parameters and body habitus, controlling for age, race, and sex. Every 10 µg/dL blood Pb increase was associated with increased odds of LVH of 1.33 (95% CI: 1.20, 1.47). Interaction terms for race by blood Pb and sex by blood Pb were not significant.<br><br>Blood pressure models stratified by sex always included BMI, age and age-squared, race, and natural log blood Pb. Male blood pressure model also included family history of hypertension, cholesterol, height, cigarette use, serum zinc, and tricep skin fold. Female model also included serum zinc, family history of hypertension, tricep skin fold, and cholesterol. Every 1 natural log unit of blood Pb increase was associated with an increase in diastolic blood pressure of 2.93 mm Hg (95% CI: 0.93, 4.98) in males and 1.64 mm Hg (95% CI: 0.27, 3.01). Used interaction terms for race-blood Pb and sex-blood Pb in a non-stratified model and found no significant effect of race or sex on the blood Pb-blood pressure coefficient.<br><br>Incomplete reporting of subject size for models and for descriptive statistics for all variables in models. Tested both linear and log transformed Pb in preliminary testing. Found log Pb had lower probability values than linear Pb for blood pressure, and linear Pb had lower probability values than log Pb for LVH. No testing of significant difference between the two blood Pb specifications. No model diagnostics reported. Only reported diastolic blood pressure results. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Sokas et al. (1997)<br>U.S.-Maryland<br>1989-1990 | 264 active or retired construction workers, over 99% men, who were not involved in Pb work at time of testing, mean age (range) 43 yrs (18-79). Multiple regression modeling of systolic and diastolic blood pressure adjusted for covariates of BMI, age, hematocrit, erythrocyte protoporphyrin, race, linear blood Pb and a race-linear blood Pb interaction. Method of covariate entry not made explicit, though it appeared to be forced. | Mean blood Pb (range): 8.0 µg/dL (1-30) | Linear blood Pb was not significantly related to either systolic or diastolic blood pressure, though the race by linear blood Pb interaction was marginally significant ($p = 0.09$). Each 1 µg/dL increase in blood Pb increased black systolic blood pressure 0.86 mm Hg (no SE or 95% CI reported) more than white systolic blood pressure.<br><br>Linear blood Pb term may not be appropriate. Small sample compromises interpretation of non-significant results. By using erythrocyte protoporphyrin and blood Pb in the same model, these two measures of Pb exposure may have been confounded. Incomplete reporting of procedures and results. No model diagnostic tests reported. |
| Sorel et al. (1991)<br>U.S.-NHANES II<br>1976-1980 | 2056 females, 2044 males, 473 blacks and 3627 whites, from 18-74 yrs, were used in survey design and weight adjusted multiple linear regressions stratified by sex, with separate models for systolic and diastolic blood pressure. Covariates included age, BMI, race, and poverty income ratio and linear blood Pb. Method of covariate entry not specified but may have been forced. Different covariate groups were used for different models. Primary test for the effect of race on the Pb-blood pressure relationship was to note the change in the race coefficient in models with and without the linear blood Pb variable. | Age-adjusted arithmetic mean blood Pb:<br><br>Black female: 13.2 µg/dL (no variance information for any blood Pb)<br><br>White female: 12.1 µg/dL<br><br>Black male: 20.1 µg/dL<br><br>White male: 16.8 µg/dL | Linear blood Pb was significantly related only to diastolic blood pressure in males, adjusting for age and BMI. For every 1 µg/dL blood Pb increase diastolic blood pressure increased 0.13 mm Hg (95% CI: 0.04, 0.21). Adding race to the model with and without linear blood Pb terms did not appear to change the race coefficient. Adding poverty index to the models with and without blood Pb produced the same small change in poverty index coefficient.<br><br>Linear blood Pb may not be appropriate. Only confidence intervals were used to assess the significance of changes in race and poverty index coefficients across models with and without Pb, instead of using interaction terms of these two variables with Pb. Incomplete reporting of procedures and results. No model diagnostic tests reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Sharp et al. (1990) U.S.-San Francisco, CA 1986 | After exclusion of subjects under treatment for hypertension, 249 male bus drivers, 132 of whom were black, age from 31 to 65 yrs, were used in race stratified multiple regression models of systolic and diastolic blood pressure with covariate forced entry of age, age-squared, BMI, caffeine use, tobacco use, and natural log blood Pb. Alcohol use was added in other models. Other models stratified by caffeine use. | Geometric mean (range) blood Pb:<br><br>Black males: 6.5 µg/dL (3-21)<br>Non-black males:<br>6.2 µg/dL (2-15) | Significant log blood Pb effects were noted in blacks. In models excluding alcohol use, for every one natural log unit increase of blood Pb, systolic blood pressure rose 7.53 mm Hg (95% CI: 0.86, 14.2) and diastolic blood pressure rose 4.72 mm Hg (95% CI: 0.15, 9.29). Stratified by infrequent/frequent caffeine users, only black infrequent caffeine users showed a significant response to blood Pb. For every one natural log unit increase of blood Pb, systolic blood pressure rose 16.69 mm Hg (95% CI: 3.83, 29.5) and diastolic blood pressure rose 10.43 mm Hg (95% CI: 1.26, 19.6). Non-black blood pressure was decreased with increasing natural log Pb but was marginally significant. In all non-black subjects, for every unit increase in natural log blood Pb, systolic blood pressure decreased −5.71 mm Hg (95% CI: −12.0, 0.6). Addition of alcohol to the models decreased all coefficients a small amount. Progressive addition of age, BMI, caffeine, and tobacco, in that order, progressively increased the coefficient of natural log blood Pb in models of systolic and diastolic blood pressure in blacks. Removal of two black outliers did not materially change the results for blacks.<br><br>No statistical tests for comparing stratified models, models with and without caffeine use, effect of progressive addition of covariates, or addition of alcohol. Influence diagnostics reported for detecting the two outlying subjects. No other diagnostic tests reported. Small differences in text and table reports of the same coefficients. Small sample size limits interpretation of non-significant results. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Tepper et al. (2001)<br>U.S.-Cincinnati, OH<br>After 1991 to before 2001 | 43 females and 57 males, current or former workers at a Pb-acid battery factory, between 36 and 73 yrs of age, with at least 10 yrs working in battery production, participated. Multivariate regression models and logistic regression models were constructed to assess Pb exposure effect on outcome (hypertension: >140/90 mm Hg and >160/95 mm Hg or taking antihypertensive meds; diastolic and systolic blood pressure, and left ventricular mass/body surface area ($g/m^2$). Echocardiograms were used to determine left ventricular mass. Variables used to adjust all models were age, BMI, sex, and family history of hypertension. | Plant blood Pb records were used to calculate cumulative blood Pb index (CBLI) used as a tertile measure, a linear continuous measure, and a log transformed measure.<br>CBLI µg/dL-yr<br>1st tertile: 138-504<br>2nd tertile: 505-746<br>3rd tertile: 747-1447<br><br>Time-avgd blood Pb TABL) was treated the same way:<br>TABL µg/dL<br>1st tertile: 12-25<br>2nd tertile: 26-33<br>3rd tertile: 34-50 | No odds ratios were given for hypertension and any Pb variable for hypertension defined as >140/90 mm Hg but ORs were claimed not significant. Odds ratios were 2.71 and 1.44 for the 3rd tertile CBLI and TABL Pb measures compared to 1st tertile, apparently significant, but no probabilities, SEs or CIs given.<br><br>With the 81 subjects not taking anti-hypertensive meds, neither CBLI tertile nor TABL tertile were significantly associated with either diastolic or systolic blood pressure (coefficients, SEs or 95% CIs not given). Using log transformed CBLI probability of a positive association with diastolic blood pressure was 0.06. Using log transformed TABL, probability of a positive association with diastolic blood pressure was 0.10. No coefficients, SEs, or CIs given.<br><br>Left ventricular mass adjusted for body surface area was not significantly related to any Pb measure. No coefficients, SEs or CIs given.<br><br>Despite the certainty of the authors that "we found no convincing evidence of an association…", the very low power of this study gives certainty to none of the findings. Very poor reporting of results further reduces the possibility of evaluation. No model diagnostic testing was reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Vupputuri et al. (2003)<br>U.S.-NHANES III<br>1988-1994 | 5188 white women, 2300 black women, 5360 white men, and 2104 black men, aged 18 yrs and older. Survey adjusted multiple linear and logistic regression were used to assess linear blood Pb effect on systolic and diastolic blood pressure and hypertension in race and sex stratified models. | Arithmetic mean (SD) blood Pb:<br><br>White women 3.0 µg/dL (7.2)<br>Black women 3.4 µg/dL (4.8)<br>White men 4.4 µg/dL (7.3)<br>Black men 5.4 µg/dL (9.3) | Multiple linear regression models were all adjusted for age, education, BMI, alcohol consumption, leisure time physical activity, dietary sodium and potassium, and total calories. Only black women and men showed significant linear Pb effects. Every 1 µg/dL increase in blood Pb was associated with an increase of 0.47 mm Hg (95% CI: 0.14, 0.80) in systolic and 0.32 mm Hg (95% CI: 0.11, 0.54) diastolic blood pressure in black women, and 0.25 mm Hg (95% CI: 0.06, 0.44) systolic and 0.19 mm Hg (95% CI: 0.02, 0.36) diastolic blood pressure in black men.<br><br>Odds of hypertension (systolic ∃140 mm Hg, diastolic ∃90 mm Hg, or taking antihypertensive medication) significantly increased for every SD (3.3 µg/dL) of blood Pb level in black women (OR = 1.39 [95% CI: 1.21, 1.61]), in white women (OR = 1.32 [95% CI: 1.14, 1.52]), in black men (OR = 1.26 [95% CI: 0.99, 1.19]), but not in white men.<br><br>Linear blood Pb terms are usually not appropriate in multiple linear regression models of blood pressure. Furthermore, they reported their results in terms of change in 1 SD unit of Pb. Linear SD of Pb is incorrect for log-normal distributions of blood Pb. No model diagnostic tests reported. Discrepancy between Methods report of race-Pb and sex-Pb interactions in simple, not multiple, analyses, but Results reports significant interactions for race-Pb and sex-Pb in multiple regression models for both linear regression and logistic regression models, without showing the results of the interaction analyses. The probability of the stated interactions ($p < 0.001$) appears extremely low, given the degree of 95% CI overlap in Pb coefficients among the stratified models. No model diagnostics reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Bost et al. (1999) Europe-England-Health Survey for England 1995 | 2763 women and 2563 men from a multi-stage stratified probability survey representative of the English population living in private residences, mean (SE) age for men 47.5 yrs (0.34) and for women 47.7 yrs (0.33) (all subjects 16 yrs and older) were used in an analysis of blood Pb association with systolic and diastolic blood pressure. Stepwise multiple regression analysis were used testing natural log blood Pb against common log systolic blood pressure and non-transformed diastolic blood pressure, with the following potential covariates: age, BMI, smoking status, region of residence, social class, and alcohol consumption. Models were stratified by sex, with and without adjustment for alcohol, including or excluding those taking antihypertensive medications. | Geometric mean blood Pb:<br><br>Men: 3.7 µg/dL (no stated measure of variance)<br><br>Women: 2.6 µg/dL (no stated measure of variance | Model tables presented only standardized variable coefficients. The most consistent results were reported on common log Pb association with men's diastolic blood pressure. Every doubling of blood Pb was significantly associated with an increase of 0.78 mm Hg (95% CI: 0.01, 1.55) diastolic blood pressure, adjusted for age, log BMI, and alcohol, but excluding men on antihypertensive medication. Every doubling of blood Pb was significantly associated with an increase of 0.88 mm Hg (95% CI: 0.13, 1.63) in the same model with men on antihypertensive medication. Every doubling of blood Pb was significantly associated with an increase of 0.96 mm Hg (95% CI: 0.23, 1.70) in the same model excluding men on antihypertensive medication and not adjusting for alcohol. Every doubling of blood Pb was significantly associated with an increase of 1.07 mm Hg (95% CI: 0.37, 1.78) including men taking antihypertensive medication and not accounting for alcohol. None of the multiple regression models had significant Pb terms for women.<br><br>This report was not sufficiently detailed. Stepwise regression modeling is prone to the usual pitfalls. Survey design adjusted analysis not used. Pb was not entered in models in which criterion probability was exceeded ($p > 0.05$). No rationale given for stratifying. No testing of differences among Pb coefficients for the different models was made, which would have been especially valuable to compare models adjusted and not adjusted for alcohol use. No explanation for using log systolic blood pressure as dependent variable. No model diagnostics reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Fewtrell et al. (2004)<br>Global<br>1988-2002 | Using available global figures on categorized blood Pb ranges by age group, authors calculated relative risk ratios relating increased blood pressure to ischemic heart disease, cerebrovascular disease, hypertensive disease, and other cardiac diseases. They used a calculation of "impact fraction," based on the proportion of the population within the particular Pb exposure category and the relative risk at that exposure category compared to the risk at the reference level. They used the meta-analysis of Schwartz (1995) to derive an accumulating 1.25 mm Hg increase in blood pressure in men for 5-10, 10-15, and 15-20 µg/dL, and an increase of 3.75 mm Hg for blood Pb levels above 20 µg/dL. Comparable blood pressure increases in women for each Pb category was 0.8 mm Hg for each of the first three categories and 2.4 mm Hg for blood Pb >20 µg/dL. | See left for blood Pb categories used. | The largest risk ratios were for hypertensive disease populations at ages 15-44, calculated at 1.12, 1.41, 1.78, and 2.00 for each of the four Pb categories for men, and 1.08, 1.25, 1.45, and 1.56 for women. Risk ratios for all disease categories increased with increasing Pb category and decreased for populations older than 44 yrs.<br><br>The authors assumed a linear relationship between blood pressure and blood Pb, whereas available evidence suggests it may be non-linear. If blood Pb-blood pressure concentration-response function is log-linear, as implicitly accepted by over half the reviewed studies, the calculated global risk ratios for all cardiovascular disease will be overestimated at higher blood Pb levels and underestimated at lower blood Pb levels. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Maheswaran, et al. (1993)<br>Europe-England-Birmingham<br>1981 | 809 out of 870 workers, mean (SD) age 43.3 (10.4) yrs, at an Pb acid battery plant were used in the study. Women and workers taking antihypertensive medications were excluded. Used multiple linear regression analyses of systolic and diastolic blood pressure, forcing age, BMI, alcohol use, linear blood Pb, zinc protoporphyrin, yrs of work exposure, cigarette smoking as covariates. | Geometric mean (SD) blood Pb: 31.6 µg/dL (5.5) | Linear blood Pb was not significant for either systolic or diastolic blood pressure.<br><br>Authors used two indices of Pb exposure in the same models. Over much of the studied blood Pb range, zinc protoporphyrin was likely collinear with blood Pb. Linear blood Pb may not be the appropriate metric to use in blood pressure models. Did not use age-squared to adjust for non-linear relationship of blood pressure with age. Did not report model diagnostics. |
| Menditto et al. (1994)<br>Europe-Rome-New Risk Factors Survey<br>1989-1990 | 1319 males, mean (range) age 63 (55-75) yrs, not treated for hypertension, were used in forward stepwise multiple linear regression models of systolic and diastolic blood pressure with available covariates of age, BMI, heart rate, serum high density lipoprotein, non-high density lipoprotein, triglycerides, glucose, cigarette use, alcohol use, sum of five skinfold thicknesses (triceps, biceps, subscapular, suprascapular, and suprailiac), and natural log transformed blood Pb. | Median (2.5th-97.5th percentiles, range) blood Pb: 11.3 µg/dL (6.2-24.7, 4-44.2) | Only BMI, heart rate, and serum glucose were not simultaneously and significantly correlated with both natural log blood Pb and blood pressure. In a systolic blood pressure model adjusted for BMI, age, heart rate, high and non-high density lipoprotein, triglycerides, glucose, and cigarettes, each unit increase in natural log blood Pb was significantly associated with a 5.6 mm Hg (95% CI: neither SE nor CI stated) increase in blood pressure. In a diastolic blood pressure model adjusted for BMI, heart rate, age, cigarettes, triglycerides, and high density lipoprotein, each unit increase in natural log blood Pb was significantly associated with a 1.7 mm Hg (95% CI: neither SE nor CI stated) increase in blood pressure. In stratified models for alcohol drinkers (n = 1068) and non-drinkers (n = 251) only alcohol drinkers showed significant natural log blood Pb associated blood pressure increase, with Pb coefficients similar to those of the entire group.<br><br>Authors observed change in natural log blood Pb coefficient produced by successive addition of covariates to models. In no case did the coefficients change by more than 30% after addition of a covariate. Authors noted that wine was the predominant drink in alcohol users and that the correlation between alcohol consumption and natural log blood Pb level was the highest among all correlations reported ($p < 0.001$; correlation coefficient not stated).<br><br>No statistical tests were made to determine if the change in Pb coefficients with addition of covariates was significant, nor were statistical tests made to determine if the Pb coefficients in the alcohol use stratified models were significantly different. Small size of the non-alcohol drinking group in stratified analysis precludes interpretation of non-significant effects. Incomplete reporting of results. Paper published in a supplement issue reporting meeting papers may indicate that it received less that the normal peer-review scrutiny for published research articles. No model diagnostic tests were reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Møller and Kristensen (1992) Europe-Denmark-Copenhagen County-Glostrup Population Studies 1976-1990 | A cohort born in 1936 was followed at age 40 (women n = 546, men n = 504), age 45 (women n = 430, men n = 463) and again at age 51 (men only n = 439). Reported no difference in results if subjects taking antihypertensive medications were excluded. Reported results included these subjects. Linear multiple regression models of systolic and diastolic blood pressure of follow up, stratified by sex and by yr, used a sequence of forced entry of covariates: natural log blood Pb was tested alone (unadjusted), then adjusted for tobacco, cholesterol, physical activity, and sex (Model 1), then adjusted for the above covariates plus systolic blood pressure (Model 2), and then adjusted for the above covariates plus alcohol (Model 3). Another group of linear multiple regression models of change of systolic and diastolic blood pressure from age 40 to 51 yrs in men only, following the same covariate entry scheme as above, but used change in covariates instead of the original covariates. All subjects were followed until 54 yrs of age (from 1976 to 1990) to assess Pb association with total mortality and with coronary heart disease (CHD; ICD-8 410-414) and cardiovascular disease (CVD; ICD-8 430-435) combined morbidity and mortality using Cox proportional hazards models (n = 1050). Cox models were adjusted as above. | Arithmetic mean (SD, range) blood Pb by age and sex:<br><br>Women 40 yrs: 9.6 µg/dL (3.8, 4-39)<br><br>Women 45 yrs: 6.8 µg/dL (3.5, 2-41)<br><br>Men 40 yrs: 13.6 µg/dL (5.7, 5-60)<br><br>Men 45 yrs: 9.6 µg/dL (4.3, 3-39)<br><br>Men 51 yrs: 8.3 µg/dL (4.1, 2-62) | In women, each one unit increase in natural log blood Pb was associated with a significant increase in systolic blood pressure of 4.93 mm Hg (p = 0.002; neither SE nor CI stated) at age 40 and an increase of 2.64 mm Hg (p = 0.06; neither SE nor CI stated) at age 45, in models adjusted for tobacco, BMI, and physical activity (Model 1). When alcohol (Model 2) or alcohol plus hemoglobin (Model 3) were added to the models Pb-blood pressure relationships were not significant at either age. With each one unit change in natural log blood Pb, diastolic pressure increased 4.26 mm Hg (p = 0.002; neither SE nor CI stated) at 40 yrs and 3.26 mm Hg (p = 0.002; neither SE nor CI stated) at 45 yrs in Model 1. In Model 2, the increase in diastolic blood pressure was 3.21 mm Hg (p = 0.02; neither SE nor CI stated) at 40 yrs and 2.86 mm Hg (p = 0.01; neither SE nor CI stated) at 45 yrs. In Model 3, the increase in diastolic blood pressure was 2.65 mm Hg (p = 0.07; neither SE nor CI stated) at 40 yrs and 2.78 mm Hg (p = 0.01; neither SE nor CI stated) at 45 yrs.<br><br>In men, the only significant association between natural log blood Pb and blood pressure was at 45 yrs. For every increase of one unit of natural log blood Pb the increase in systolic blood pressure was 2.73 mm Hg (p = 0.05; neither SE nor CI stated).<br><br>The change in blood Pb between 40 and 51 yrs was not significantly associated with change in systolic or diastolic blood over the same period in any of the models.<br><br>None of the relative hazard ratios for CHD and DVD combined morbidity and mortality between 40 and 54 yrs were significantly related to blood Pb concentration. Total mortality, however, was significantly increased with increased blood Pb. In Model 1, every increase of one natural log unit of blood Pb was associated with an increased relative hazard of mortality of 1.96 (p = 0.009; neither SE nor CI stated). For Model 2, every increase of one natural log unit of blood Pb was associated with an increased relative hazard of mortality of 1.82 (p = 0.03; neither SE nor CI stated). There were 40 cases of CHD recorded, of which 13 were fatal. There were 54 cases of CVD recorded, of which 19 were fatal. Of the total of 46 subjects who died during the period, 32 (70%) died of cardiovascular problems. It was not clear if blood Pb at a particular age or a mean blood Pb across ages was used in the Cox proportional hazards models. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Møller and Kristensen (1992) (cont'd) | | | Though this study was one of the few to use a longitudinal design, it did not take advantage of that design feature in blood pressure modeling. Cross-sectional multiple regression modeling at each age loses valuable information available in repeated measures modeling. Power to detect significant effects is much higher in repeated measurement modeling than in cross-sectional modeling. Analyzing only change in blood pressure loses information regarding starting and ending blood pressure. Including change in blood Pb is problematical due to the unknown history of Pb exposure prior to the start of the study, the resultant bone Pb load as a result of past exposure, the unknown Pb contribution of bone to blood, and the unknown relative contributions of past exposure and present exposure to alteration in blood pressure. Modeling other covariates as change is also questionable. BMI, to pick a covariate with known and strong effects on blood pressure, may be high and relatively constant over the study period or low and relatively constant over the study. In both cases, the change in BMI will be small, but the high BMI will be associated with higher blood pressure than will the low BMI. Thus, both cases modeled as change in BMI should have the same effect on blood pressure when the high BMI subject has expected higher blood pressure than the low BMI subject. Using difference scores for the dependent and the exposure variables also risks confounding secular trends in either or both of these variables, for whatever reasons, with independent difference variable effect on dependent difference variable effect.<br><br>The Cox proportional hazards model, however, is longitudinal in nature. Failure to detect significant associations between Pb and cardiovascular morbidity/mortality could have been due to the small sample size used for this type of analysis. The blood pressure part of the study did not take mortality into account during the study, which could have produced a progressively increasing "healthy subject" effect. Since subjects taking antihypertensive medications were included in analyses, an indicator variable should have been used to account for them, whether or not their exclusion in preliminary testing produced no apparent change in results. This paper contained a good discussion of confounding variables. Incomplete reporting of results and procedures. No model diagnostic tests were reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Staessen et al. (1996a) Europe-Belgium-PheeCad study. 1985-1995 | 359 men and 369 women participated at baseline (between 1985 and 1989) and again about 5 yrs later (median 5.2 yrs) at follow up (between 1991 and 1995), mean age (range) at baseline 46 yrs (20-82), about half of whom were recruited from towns surrounding a non-ferrous smelter (targeted to produce high cadmium exposure) and half from towns without heavy metal production. Over half the men had occupational exposure (59.0% from the near smelter towns, 17.4% from the other towns).<br><br>Four different outcomes were explored: time-integrated conventional blood pressure (avg of 10 baseline and 5 follow up blood pressure measurements), 24-h ambulatory blood pressure only during the follow up period (avg of readings every 20 minutes from 8 AM to 10 PM and every 45 minutes from 10 PM to 8 AM, weighted by interval between measurements), difference in conventional blood pressure over the five yr follow up period, and incidence of developing hypertension during follow up. | Geometric mean (5th-95th percentile) by sex and time period:<br><br>Baseline women: 6.6 µg/dL (3.3-14.5)<br><br>Follow up women: 4.8 µg/dL (1.7-11.8)<br><br>Baseline men: 11.4 µg/dL (5.6-28.8)<br><br>Follow up men: 7.7 µg/dL (3.7-20.1) | The study was one of the few prospective longitudinal studies reported and was innovative in its use of 24-h ambulatory blood pressure as one of its outcome variables.<br>Time-integrated conventional blood pressure models:<br><br>In 187 peri- and post-menopausal women, after adjusting for age, BMI, gamma-glutamyltransferase activity, and hematocrit, each increase of one unit of natural log blood Pb was associated with an increase in diastolic blood pressure of 7.49 mm Hg (95% CI: 1.48, 13.50). No other time-integrated conventional blood pressure measurements were significantly associated with time-integrated natural log blood Pb in either men or women, nor in stratified groups within sex.<br><br>Ambulatory 24-h blood pressure models:<br><br>In all 345 women, after adjusting for age, hematocrit, gamma-glutamyltransferase activity, and oral contraceptive use, each one unit increase in natural log blood Pb was associated with an increase of diastolic blood pressure of 3.49 mm Hg (95% CI: 0.02, 6.96). When the group was limited to the 174 premenopausal women each unit increase in natural log blood Pb was associated with an increase of diastolic blood pressure of 5.48 mm Hg (95% CI: 0.56, 10.40).<br><br>Difference in blood pressure between baseline and follow up:<br><br>After adjustment for change in BMI, beginning use of antihypertensive medication and contraceptive medication during the follow up period, and starting smoking there was no significant relationship between difference in either systolic or diastolic blood pressure and blood Pb in women. After adjustment for change in BMI, change in exposure at work, change in smoking, beginning use of antihypertensive medication in men there was no significant relationship between difference in either systolic or diastolic blood pressure and blood Pb in men.<br><br>Incidence of hypertension:<br><br>At baseline 107 (14.7%) and 120 (16.5%) subjects had borderline and definite hypertension, respectively. At follow up 98 (13.5%) and 186 (25.5%) had borderline and definite hypertension, respectively. 51 of 501 initially normotensive subjects became borderline hypertensive and 47 of the 501 became border line hypertensive during the follow up period. After adjusting for sex, age, and BMI, natural log baseline blood Pb was not related to significant risk ratios of becoming hypertensive (not stated, but presumably combined definite and borderline hypertension) or becoming a definite hypertensive. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Staessen et al. (1996a) (cont'd) | Multiple regression models were used to test the association between natural log transformed blood Pb (mean of baseline and follow up Pb) and blood pressure (systolic and diastolic), stratified by sex, then further stratified by use of antihypertensive medications in men and menopausal status in women. Age and age-squared (calculated in quintiles) were forced into the models, then remaining covariates were stepwise added to the model. Though not explicitly stated, natural log blood Pb (mean of baseline and follow up) was likely forced in last. Other candidate covariates were BMI, hemoglobin or hematocrit, serum gamma-glutamyltransferase activity (an index of alcohol use) and serum calcium, 24 h urinary sodium and potassium excretion, energy expenditure, exposure to heavy metals (at the workplace), social class, smoking and drinking habits, menstrual status in women, and use of antihypertensive medications, oral contraceptives, and hormone replacement therapy. In ambulatory blood pressure models, differences between baseline and follow up blood pressure models were constructed in the same way. For the difference models "concurrent variations in blood Pb concentrations" were used, presumably difference in baseline and blood Pb. | | The study does not use the full power of repeated measurements in the analyses. For problems encountered when collapsing repeated measurements to difference measures, see Møller (1992) above. Stepwise regressions are prone to capitalizing on chance results due to multiple testing of the same data and almost always produce a different mix of covariates when they are stratified. Thus, it was puzzling to find that where information on the effects of stepwise covariate addition to models was available in this article, that the same covariates were listed for both models based on the stratification variable. There is excessive reliance on fractionation of the data set due to multiple stratification, sometimes reducing the number of subjects in a model to as few as 171. Even the models using the most subjects had only 359 subjects. Low power to detect significant effects cautions against any interpretation of non-significant results. The time-integrated model used 10 baseline blood pressure measurements and 5 follow up blood pressure measurements, thus weighting the avg toward baseline blood pressure. The entry of the biochemical correlate of alcohol use in most of the models suggests that Pb effects and Pb-containing alcohol effects on blood pressure were confused, especially given the European setting and the time period during which the study was conducted. Control for use of hypertensive medication rarely entered models and partial control for this variable was achieved only by stratified analyses, further reducing power to detect significant effects in the remaining subgroup. No justification was given for stratified analyses. Incomplete information in statistical methods and results complicates interpretation. It was uncertain if stepwise regression was used for logistic models. No comparisons were performed to assess possible bias due to subject attrition over the course of the study. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Staessen et al. (1996a) (cont'd) | For the hypertension incidence model two definitions of hypertension were used: definite hypertension (systolic >160 mm Hg, diastolic >95 mm Hg or taking antihypertensive medications) and borderline hypertension (systolic between 141 to 159 mm Hg and diastolic between 91 to 94 mm Hg). Method of covariate entry into hypertension incidence models not stated. Baseline natural log blood Pb was used as the exposure index. | | The over six decades of age represented in the sample was modeled by linear and quadratic terms based on age quintiles rather than continuous age, making it likely that adequate control for age effects on blood pressure was not achieved and that the "healthy subject" effect seen in older groups was not controlled. If stepwise addition of significant covariates was used in the blood pressure difference models, were covariates in those models that were marked in the coefficient column as non-significant not included in the models, and if that were so, it is unclear from where the probability values that substitute for the coefficients of those variables were derived. There were no model diagnostic tests reported. |
| Staessen et al. (1993) Belgium-Cadmibel Study 1985-1989 | 827 males and 821 females recruited from two areas in Belgium, one of them surrounding a non-ferrous smelter, mean age (SD) 46 (15) and 44 (15) yrs, in men and women respectively. Subjects taking antihypertensive medication were excluded from the analyses. Stepwise multiple regression models of systolic and diastolic blood pressure were stratified by sex. Covariates available for entry were age and age-squared, BMI, pulse rate, log protoporphyrin, log gamma-glutamyltranspeptidase, serum calcium, log serum ferritin, log serum creatinine, log serum zinc, urinary calcium, urinary sodium, and urinary potassium. Natural log blood Pb was the only variable forced into the models. Additional models tested the interaction of serum calcium and blood Pb on blood pressure. | Geometric mean blood Pb (range), stratified by sex:<br><br>Male blood Pb: 10.4 µg/dL (2.7, 84.9)<br><br>Female blood Pb: 6.2 µg/dL (1.3, 42.4) | In men, adjusting for age and age-squared, BMI, pulse rate, log gamma-glutamyltranspeptidase, serum calcium, and log serum creatinine, every unit natural log blood Pb increase was significantly associated with a -5.2 mm Hg (95% CI: !0.5, !9.9) decrease in systolic blood pressure. Natural log blood Pb was not significant in the model for diastolic blood pressure for men nor the systolic or diastolic blood pressure for women.<br><br>Adjusting for age and age-squared, BMI, pulse rate, and log gamma-glutamyltranspeptidase, the interaction term between natural log blood Pb and serum calcium was only significant for systolic blood pressure in women. Every doubling of blood Pb was associated with a 1.0 mm Hg decrease in systolic blood pressure at serum calcium concentration of 2.31 mmol/L (25th percentile) and an increase in systolic blood pressure of 1.5 mm Hg at serum calcium concentration of 2.42 mmol/L (75th percentile).<br><br>Stepwise multiple regression analyses run risks of accepting chance associations due to multiple analyses of the same data set. The role of alcohol use or alcohol use markers in confounding Pb effect on blood pressure in this setting has already been noted. The unexplained interaction between serum calcium and blood Pb highlights the potential confounding role of serum calcium with Pb in blood pressure studies. The study shows graphs indicating distinct differences in the age-serum calcium and age-blood Pb relationships for men and women. From 50-70 yrs of age serum calcium is higher than from ≤ 29-49 yrs in women and |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Staessen et al. (1993) (cont'd) | | | exceeds serum calcium of men at those older ages. The steepest rise in women's blood Pb with age occurs between the 40-49 and 50-59 yr decades. The timing of these changes in women suggests that menopause may be a factor, which was accounted for only in the model for diastolic blood pressure. It also suggests that serum calcium level and age were also confounded in the blood pressure models. As serum creatinine clearance and blood Pb are inversely related, and serum creatinine is a significant covariate in the systolic blood pressure model for men with a significant negative blood Pb coefficient, it is possible that serum creatinine and blood Pb are confounded with blood pressure in the men's systolic blood pressure model. There were no assessments of subject selection bias due to exclusions. The authors note examining quintile blood pressure relationships with all covariates to determine the acceptability of the linear relationship implied by the linear modeling technique. No other model diagnostic tests were reported. |
| Telišman et al. (2004) Europe-Croatia-Zagreb Date of data collection not given. | 100 workers from factories producing Pb-based products, mean (range) age 30 (20-43) yrs. Exclusion criteria were absence of psychological stress (e.g., death in family) over last 4 mos, absence of verified diabetes, coronary heart disease, cerebrovascular and peripheral vascular disease, renal disease, hyperthyroidism, androgenital syndrome, primary aldosteronism, and "other diseases that could influence blood pressure or metal metabolism." Linear or natural log blood Pb were considered for stepwise entry in models of systolic and diastolic blood pressure, forcing in all other covariates: blood cadmium, BMI, age, serum zinc, serum copper, hematocrit, smoking, and alcohol. | Arithmetic mean (range) blood Pb: 36.7 µg/dL (9.9-65.9) | Neither linear nor natural log blood Pb entered as significant in multiple regression models of systolic and diastolic blood pressure.<br><br>Very small sample size limited power to detect significant effects; non-significant effects should not be interpreted as lack of effect. Too many covariates for a small study. Almost no subjects below 10 µg/dL. Taking hypertensive medications not controlled, likely a problem with top systolic and diastolic blood pressure in the group 170 mm Hg and 110 mm Hg, respectively. No model diagnostic testing reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** | | | |
| Lee et al. (2001)<br>Korea-Chonan<br>1997-1999 | 798 workers from various Pb-using or producing factories, mean (SD, range) age 40.5 yrs (10.1) [17.8-64.8], 79.4% male, were classified as to Vitamin D receptor genotype (VDR bb or Bb/BB) and delta-aminolevulinic acid dehydratase (ALAD11 or 12) genotype, as VDR polymorphism has been implicated in modifications of Pb absorption and Pb uptake and release from bone as well as risk for elevated blood pressure and hypertension, and ALAD polymorphism affects Pb binding to it in the erythrocyte, the major storage depot of Pb in blood. The hypothesis was that polymorphism type could influence the effect of Pb on blood pressure and hypertension.<br><br>Multiple linear regression models of linear blood Pb, DMSA-chelatable Pb, and tibia Pb effect on systolic and diastolic blood pressure with potential covariates of age and age-squared, sex, creatinine clearance, hemoglobin, weight, height, BMI, job duration, tobacco and alcohol consumption, pack-yrs of tobacco, and cumulative life time alcoholic drinks. Stepwise procedure allowed retention of covariates only if they were significant or "there were substantive changes in the coefficients of predictor variables after" their inclusion. In the models shown, Appearance of multiple Pb variables and the interaction between Pb variables and genotype for each gene depended upon the specific model. Both ALAD and VDR receptor polymorphism were sometimes tested simultaneously in each model containing polymorphism terms and sometimes VDR appeared without ALAD. | Arithmetic mean (SD, range) blood Pb: 32.0 µg/dL (15.0, 4-86)<br><br>Mean (SD, range) DMSA-chelatable Pb: 186 µg (208.4, 4.8-2103)<br><br>Mean (SD, range) tibia Pb: 37.2 µg/g (40.4, !7 to 338) | With simple t-tests, subjects with VDR Bb/BB allele were significantly older, had more DMSA-chelatable Pb, and had higher systolic and diastolic blood pressure than subjects with VDR bb allele.<br><br>In multiple regression models of systolic blood pressure, controlling for age and age-squared, sex, BMI, antihypertensive medication use, and cumulative life-time alcoholic drinks, adding tibia Pb, VDR type, and ALAD type, each increase of 10 µg/g of tibia Pb was associated with an increase of 0.24 mm Hg (95% CI: −0.01, 0.49) and VDR BB/Bb type was associated with an increase of 3.24 mm Hg (95% CI: 0.18, 6.30) blood pressure compared to the VDR bb type. ALAD genotype was not significant. In the same model, but substituting linear blood Pb for tibia Pb, each increase in 1 µg/dL of linear blood Pb was associated with an increase of 0.07 mm Hg (95% CI: 0.00, 0.14) and VDR BB/Bb type was associated with an increase of 2.86 mm Hg (95% CI: !0.22, 5.94) blood pressure compared to the VDR bb type. ALAD genotype had no significant effects on blood pressure.<br><br>When both tibia and linear blood Pb were entered simultaneously along with VDR genotype, adjusting for the same covariates, only VDR Bb/BB was significant; compared to VDR bb, blood pressure was 3.51 mm Hg (95% CI: 2.41, 8.61) higher. ALAD genotype had no significant effects on blood pressure.<br><br>In a model without any Pb terms, VDR genotype was interacted with the age and the age-squared terms. The VDR Bb/BB genotype interaction with the linear age term was significant for systolic blood pressure. Compared with the bb genotype the VDR Bb/BB genotypes' blood pressure increased 0.36 mm Hg (95% CI: 0.06, 0.66) per yr faster with increasing age.<br><br>There were no significant effects of any Pb variable with diastolic blood pressure, though the VDR Bb/BB genotype had significantly higher blood pressure (1.9 mm Hg; not enough information given to calculate CI) than the bb genotypes.<br><br>There were no significant interactions of the Pb measures with the genotypes for either ALAD or VDR. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lee et al. (2001) (cont'd) | Logistic regression analysis was used to test the effect of the Pb indices on hypertension (systolic >160 mm Hg or diastolic >96 mm Hg or taking antihypertensive medications) using the same group of potential covariates, testing the Pb terms and the Pb-genotype interaction terms separately. The hypertension models tested both gene polymorphisms separately. | | Subjects with the Bb/BB genotypes had a significantly higher odds hypertension prevalence (OR = 2.1 [95% CI: 1.0, 4.4]) than subjects with the bb genotype, adjusting for age, sex, BMI, tibia Pb, and current alcohol use. There were no significant effects of any Pb variable nor of ALAD on hypertension status.<br><br>Linear blood Pb may not give efficient and unbiased estimates of blood Pb effect on blood pressure. The descriptive data shows highly skewed distributions for blood Pb, DMSA-chelatable Pb, and tibia Pb in this group, suggesting that coefficients of all Pb effect on blood pressure may not have been efficient and unbiased. Stepwise models usually produce different covariate patterns for different models, though the tables indicate that the covariates used for all the models discussed above were the same. No model diagnostic tests were reported. |
| Lustberg et al. (2004)<br>Korea-Chonan<br>1997-1999 (period of enrollment; no statement on dates of data collection) | 793 (number given for genotype analysis; numbers in models not given) current and former Pb workers, mean (SD) age 40 (10) yrs and 80% male, were genotyped for the three polymorphisms of endothelial nitric oxide synthase (eNOS) (GG, GT, TT), an enzyme that is a modulator of vascular resistance. The effect of genotype and the interaction of genotype with blood Pb and tibia Pb on systolic and diastolic blood pressure were evaluated by multiple linear regression analyses, forcing covariates of age (modeled as a 2 degree of freedom spline with knot at 45 yrs), sex, natural log BMI, smoking and alcohol consumption, high school education, and job duration. Both blood Pb and tibia Pb were entered as percentiles and entered together. Logistic models of hypertension (systolic ∃140 mm Hg or diastolic ∃90 mm Hg or reported use of antihypertensive medication) used the same covariates. Interaction terms between each of the Pb measures (plus a Pb-squared term) and genotype was used to determine differential effect of Pb according to genotype. | Pb according to genotype:<br><br>Arithmetic mean (SD) blood Pb, GG: 32 (15) µg/dL<br><br>Arithmetic mean (SD) blood Pb, TG/TT: 32 (15) µg/dL<br><br>Mean (SD) tibia Pb, GG: 37 (42) µg/g<br><br>Mean (SD) tibia Pb, TC/TT: 36 (34) µg/g | 85% (673/793) of the group were typed GG, 14% (114/793) were TG, and 1% (6/793) were TT. TG and TT groups were combined for analysis (TG/TT).<br><br>Mean systolic and diastolic blood pressures, adjusted for all covariates, were not significantly different between GG and TG/TT groups.<br><br>In multiple regression models for systolic and diastolic blood pressure, neither percentile blood Pb nor percentile tibia Pb, entered together, were significant predictors. Interaction terms between the Pb variables and genotype were not significant.<br><br>In the logistic regression model for hypertension, neither percentile blood Pb nor percentile tibia Pb, entered together, were significant predictors.<br><br>Reporting was incomplete: number of subjects entering the models was not stated; no comparisons between recruited subjects and subjects not used in models. Despite reporting non-significant interactions, the paper showed both loess plots and tables of analyses stratified by genotype, reporting significant associations between both tibia and blood Pb in the GG genotype, insignificant in the other. Inspection of the loess plots revealed striking non-linearity for both adjusted blood Pb-systolic blood pressure and adjusted tibia Pb-systolic blood pressure relationships. Small group size of the TG/TT genotypes and highly unbalanced terms of the interaction may have contributed to the non-significant interactions. Although the interaction Pb term was also probed as a quadratic function, the tibia Pb interaction was not, suggesting that poor concentration-response specification in the model may also have contributed to the lack of significant main effects and interactions. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Nomiyama et al. (2002)<br>China, Beijing<br>No statement on dates of data collection | 123 female Pb-exposed leaded crystal toy workers, mean age (range) 27.3 (17-44) yrs, and 70 female sewing workers (reference group), mean age (range) 24.2 (16-58) yrs were tested. Forward stepwise multiple regression models of systolic and diastolic blood pressure of the combined groups were used with linear blood Pb and a set of covariates. Variables with $p < 0.2$ were allowed to enter. The covariate set was selected from a larger set of potential covariates by factor analysis, and a representative variable from each factor was selected for possible entry in the regressions.<br><br>Alternate models were constructed using four ordered categories of blood Pb, instead of the linear continuous blood Pb variable. Logistic regressions were used to determine the odds of elevated systolic (∃125 mm Hg) and elevated diastolic (∃80 mm Hg) blood pressure as a function of blood Pb category. | Blood Pb mean (SD, range) in Pb workers: 55.4 (13.5, 22.5-99.4 µg/dL<br><br>Blood Pb mean (SD, range) in non-Pb workers: 6.4 (1.6, 3.8-11.4) µg/dL | Adjusted for age, urine protein, and plasma triglyceride, each 1 µg/dL increase in linear blood Pb significantly associated with a 0.13 mm Hg increase in systolic blood pressure (no SE or CI given; $p = 0.0003$). Adjusted for plasma triglyceride, age, urine protein, plasma low density lipoprotein, and hypertension heredity, each 1 µg/dL increase in linear blood Pb was associated with a 0.10 mm Hg increase in diastolic blood pressure (no SE or CI given; $p = 0.0001$).<br><br>Using the ordered categories of blood Pb and the same covariates for systolic and diastolic blood pressure, the 40-60 µg/dL group had 4.2 mm Hg (95% CI: 0.0, 8.5) higher systolic blood pressure and 4.1 mm Hg (95% CI: 1.3, 6.8) higher diastolic blood pressure than the reference group (blood Pb (<11.4 µg/dL). The group with ∃60 µg/dL blood Pb had 7.5 mm Hg (95% CI: 3.0, 12.0) systolic blood pressure and 6.3 mm Hg (95% CI: 3.4, 9.1) diastolic blood pressure higher than the reference group.<br><br>Logistic regression models for "elevated" blood pressure, modeled using the same covariates were similar. In the 40-60 µg/dL group odds of systolic blood pressure ∃125 mm Hg and diastolic blood pressure ∃80 mm Hg were 4.26 (95% CI: 1.07, 17.04) and 2.43 (95% CI: 0.97, 6.04), respectively, higher than the reference group. The odds of "elevated" systolic and diastolic blood pressure in the group with blood Pb ∃60 µg/dL were 7.48 (95% CI: 1.86, 30.12) and 3.31 (95% CI: 1.29, 8.50), respectively.<br><br>Incomplete reporting in paper: no model N, no SEs for linear blood Pb regressions, no description of type of factor analysis used or dates of data collection. Innovative use of factor analysis to select covariates that, depending on how the factor analysis was run, could have produced a set of orthogonal variables for model entry. However, BMI was not included in the original set of covariates or in the models. Small sample size limits conclusions based on nonsignificant results. Stepwise regression produced a different covariate pattern for each component of blood pressure. The linear blood Pb variable may be inappropriate given the marked skewness of blood Pb in descriptive analysis. The 11 µg/dL gap in blood Pb between Pb workers and non-Pb workers could have introduced problems in analyses with continuous blood Pb. Larger age spread in non-exposed group than in exposed group could have caused misspecification of age variable. No control for antihypertensive medication use. No model diagnostics reported. |

## Table AX6-5.1 (cont'd). Effects of Lead on Blood Pressure and Hypertension

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Wu et al. (1996)<br>Central Taiwan<br>No statement on dates of data collection | 222 workers in two Pb battery plants, 112 men, mean (range) age 36.2 (18-67) yrs, and 110 women, mean (range) age 36.2 (18-71) yrs were tested for blood Pb relationships with systolic and diastolic blood pressure in multiple regression models, using a fixed, forced set of covariates: age, sex, BMI, working history, yrs of work, noise exposure, natural log ambient air Pb concentration, and ordered categorical blood Pb concentration. | Arithmetic mean (SD, range) blood Pb:<br><br>Women: 44.6 (18.4, 8.3-103.1) µg/dL<br><br>Men: 60.2 (26.8, 17.0-150.4) µg/dL | Using four ordered blood Pb categories (<25 µg/dL [n = 16/222; 6.8%], 25-40 µg/dL [58/222; 26.1%], 41-60 µg/dL [63/222; 27.9%], and >60 µg/dL [85/222; 38.3%]) adjusted systolic and diastolic blood pressure were not significantly related to the top three blood Pb categories compared to the lowest, natural log ambient Pb. Yrs in work environment was a significant predictor of both systolic and diastolic blood pressure, but age was only marginally significant for systolic blood pressure and not significant for diastolic blood pressure.<br><br>Small study size limits any conclusions drawn from non-significant results. Three measures, all related to Pb exposure, were simultaneously tested in the models. While blood Pb may only be weakly correlated with yrs of work, ambient air Pb would be expected to be much better correlated with blood Pb. There is a clear possibility of collinearity among those three variables, which would inflate standard errors and reduce coefficients. Authors selected ordered categories of Pb to "avoid unnecessary assumption of linearity." The use of natural log air Pb concentration suggests that some diagnostics were run, but no model diagnostic tests were reported. No control for antihypertensive medication use. |

## Table AX6-5.2. Effects of Lead on Cardiovascular Morbidity

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Cheng et al. (1998)<br>U.S.-Boston, Normative Aging Study (VA)<br>1991-1995 | 775 males (97% white), mean age (SD, range) 67.8 yrs (7.3, 48-93).<br><br>Multiple linear regression models of heart rate-corrected QT and QRS electrocardiogram intervals were adjusted by stepwise entry of covariates, retaining only those that remained significant at $p < 0.10$. Linear blood Pb, tibia, and patella bone Pb were apparently (not described in text) entered separately. Logistic regression models for Minnesota ECG Coding Center diagnoses of intraventricular conduction deficit (IVCD), atrioventricular conduction deficit (AVCD), and arrhythmia were adjusted by covariates the same way. Only analyses stratified by age (<65 yrs, n = 277; ∃65 yrs, n = 498) were presented | Arithmetic mean (SD) blood Pb: 5.8 µg/dL (3.4)<br><br>Mean (SD) tibia Pb: 22.2 µg/g (13.4)<br><br>Mean (SD) patella Pb: 30.8 µg/g (19.2) | Multiple regression models of QT intervals, adjusted for age, alcohol intake, BMI, and diastolic blood pressure, found that only tibia and patella Pb were significantly related to outcome in the under 65 group. Every 10 µg/g increase of tibia and patella Pb was associated with a 5.0 ms (95% CI: 0.8, 9.2) and 3.0 ms (95% CI: 0.2, 5.8) increase in QT interval, respectively. Multiple regression models of QRS intervals, adjusted for age, fasting glucose level, and diastolic blood pressure, also found that only tibia and patella Pb were significantly related to outcome in the under 65 group. Every 10 µg/g increase of tibia and patella Pb was associated with a 4.8 ms (95% CI: 1.8, 7.8) and 2.2 ms (95% CI: 0.1, 4.4) increase in QRS interval, respectively. There were no significant effects of Pb in the 65 and over group.<br><br>Logistic regression models of IVCD, adjusted for age and serum HDL level, found that only tibia Pb was significantly related to outcome in the under 65 group. Every 10 µg/g increase of tibia Pb was associated with increased odds of IVCD, OR = 2.23 (95% CI: 1.28, 3.90). There were no significant Pb effects in the 65 and over group for IVCD. Logistic regression models of AVCD, adjusted for age and serum HDL level, found that both tibia and patella Pb were significantly related to outcome in the 65 and over group. Every 10 µg/g increase of tibia Pb and patella Pb was associated with increased odds of AVCD, OR = 1.22 (95% CI: 1.02, 1.47) and OR = 1.14 (95% CI: 1.00, 1.29), respectively. Pb was not significantly related to AVCD in the under 65 group. There were no significant effects of Pb on arrhythmia in either age group.<br><br>Stepwise models may capitalize on chance associations. Linear blood Pb specification may not be appropriate in some or all of these models. Not clear if three models were constructed for each stratified analysis for each outcome, each based on a different Pb index. No statistical comparisons across strata. No model diagnostics were presented. |
| Gump et al. (2005)<br>U.S.-Oswego, NY<br>Dates of study not given | See Gump et al. (2005) entry in Blood Pressure and Hypertension section for heart rate, stroke volume, cardiac output, total peripheral resistance, and cardiac interbeat interval data. | | |

## Table AX6-5.2 (cont'd). Effects of Lead on Cardiovascular Morbidity

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Navas-Acien (2004)<br>U.S.-NHANES IV-Phase 1<br>1999-2000 | 2125 subjects (1070 males, 1055 females), age 40->70 yrs were tested for peripheral arterial disease (PAD; n = 139) by taking the ratio of the ankle mean systolic blood pressure to the arm mean systolic blood pressure. Any subject with the ratio <0.90 was classified as PAD. Logistic regression analysis was weighted and adjusted by sample design. Covariates forced into the models were age, sex, race, education, and Pb quartile (Model 1); Model 1 covariates plus BMI, alcohol intake, hypertension, diabetes, hypercholesterolemia, glomerular filtration rate, and C-reactive protein (Model 2); Model 2 covariates plus self-reported smoking status and serum cotinine (Model 3); and Model 3 covariates plus cadmium quartile (Model 4). Tested interactions between Pb and cadmium on PAD, and between Pb and sex, race, smoking status, renal function, and c-reactive protein on PAD. Tested for trend of OR as a function of Pb quartile. | Geometric mean blood Pb (25th-75th percentile): 2.1 µg/dL (1.4, 2.9)<br>Pb quartile 1: <1.4 µg/dL<br>Pb quartile 2: 1.4-2.1 µg/dL<br>Pb quartile 3: 2.1-2.9 µg/dL<br>Pb quartile 4: >2.9 µg/dL | Odds for PAD significantly increased with Pb quartile (1st quartile used as comparison) for all four models. Only models 1 and 2, however, showed a significant increase in odds of PAD for the 4th Pb quartile compared to the 1st Pb quartile, OR = 3.78 (95% CI: 1.08, 13.19) and OR = 4.07 (95% CI: 1.21, 13.73). None of the tested interactions with blood Pb quartile were significant.<br><br>Well-designed study with sound statistical analysis. Including two variables for smoking in Models 3 and 4 (smoking status and cotinine) may have over-controlled for smoking). There was a trend toward increased blood Pb level with increased smoking status and with increased cotinine levels, though no statistical tests of trend were reported. Thus the two smoking variables and Pb may have been confounded with PAD. No model diagnostic tests reported. |
| Schwartz (1991)<br>NHANES II<br>U.S.<br>1976-1980 | See Schwartz (1991) entry in Blood Pressure and Hypertension for left ventricular hypertrophy results. | | |

## Table AX6-5.2 (cont'd). Effects of Lead on Cardiovascular Morbidity

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Tepper et al. (2001)<br>U.S.-Cincinnati, OH<br>After 1991 to before 2001 | See Tepper et al. (2001) entry in Blood Pressure and Hypertension for left ventricular mass results. | | |
| **Europe** | | | |
| Gustavsson et al. (2001)<br>Europe-Stockholm, Sweden<br>1992-1994 | Study base was all Swedish citizens 45-70 yrs old from Stockholm County free of previous myocardial infarction. Cases who survived at least 28 days after infarct (1,105 males and 538 females) of which 937 men (85%) and 398 women (74%) had sufficient information on occupational exposures and "main confounders", were compared against referents (1,120 men and 538 women) matched to cases by sex, age, yr, and hospital catchment area. Risk ratios for the case group compared to referent group were adjusted on the basis of the matching variables and smoking, alcohol drinking, hypertension, overweight, diabetes mellitus, leisure physical "inactivity", and were calculated for a number of exposure factors separately, including Pb. | Pb exposure was classified as none, low or high corresponding to airborne dust levels of 0, >0 to 0.03, and $\exists$0.04 mg/m$^3$, respectively, for the highest intensity of exposure during at least one yr of work. The same three classifications were used for 0, >0 to 0.04, and $\exists$0.05 mg/m$^3$ for cumulative exposure. | All risk ratios were calculated relative to the "no exposure" groups. Adjusted risk ratios for surviving a myocardial infarction were 0.88 (95% CI: 0.69, 1.12) and 1.03 (95% CI: 0.64, 1.65) for low and high exposure groups for peak Pb exposure, and were 0.81 (95% CI: 0.60, 1.11) and 1.00 (0.74, 1.34) for the low and high cumulative exposure groups.<br><br>This study of myocardial morbidity was compromised by poor Pb exposure characterization (occupational air dust Pb concentration) and by including a covariate collinear with Pb exposure and confounded with the outcome, hypertension, in the adjusted models.<br><br>No model diagnostics were reported. |

## Table AX6-5.3. Effects of Lead on Cardiovascular Mortality

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Lustberg and Silbergeld (2002)<br>U.S.-NHANES II<br>1976-1980,<br>follow up to 1992 | 4190 persons, 30 to 74 yrs, 929 of whom died during follow up, had baseline blood Pb measurements during the NHANES II period. Proportional hazard models for circulatory disease-related death (ICD-9 codes 390-459) were based on the complex survey design, but not weighted. Presented models were unadjusted, adjusted for age and sex, and adjusted for age, sex, location, education, race, income, smoking, BMI, and exercise. Blood Pb was entered as an ordinal three-category variable. | Blood Pb <10 µg/dL, n = 818<br>Blood Pb 10-19 µg/dL, n = 2735<br>Blood Pb 20-29 µg/dL, n = 637<br>Blood Pb ∃30 µg/dL, n = 102, excluded from analysis | Crude, sex and age adjusted, and multivariate adjusted circulatory disease mortality were all significantly increased in the 20-29 µg/dL group compared to the <10 µg/dL reference group. Risk ratio for the highest Pb group for crude circulatory mortality was 1.74 (95% CI: 1.25, 2.40), for age and sex adjusted circulatory mortality was 1.48 (95% CI: 1.10, 2.01), and for multivariate circulatory mortality was 1.39 (95% CI: 1.01, 1.91).<br><br>Stratified analyses were performed by race, sex, age, smoking, education, etc., but only for all-cause mortality. No model diagnostics reported. |
| Schober et al. (2006)<br>U.S.-NHANES III<br>1988-1994,<br>follow up to 2000 | 9757 persons, age 40 yrs, 2515 of whom died during follow-up (median length of follow-up 8.55 yrs), had baseline blood Pb measurements during the NHANES III period. Analyses were performed using proportional hazard models for all cause deaths, major cardiovascular disease-related deaths (I00-I78), and malignant neoplasms (C00-C97). Multivariate models were adjusted for sex, race/ethnicity, education, and smoking status and stratified by age. Blood Pb was entered as an ordinal three-category variable. | Blood Pb <5 µg/dL (median 2.6 µg/dL), n = 6608<br>Blood Pb 5-9 µg/dL (median 6.3 µg/dL), n = 2532<br>Blood Pb 10 µg/dL (median 11.8 µg/dL), n = 617 | Multivariate-adjusted cardiovascular disease mortality was significantly increased in the 10 µg/dL group compared to the <5 µg/dL reference group. All cause and cancer mortalities were significantly increased in the 5-9 µg/dL and 10 µg/dL groups.<br><br>Relative risk for cardiovascular disease mortality, compared to <5 µg/dL:<br>5-9 µg/dL: 1.20 (95% CI: 0.93, 1.55)<br>10 µg/dL: 1.55 (95% CI: 1.16, 2.07)<br><br>Relative risk for all cause mortality, compared to <5 µg/dL:<br>5-9 µg/dL: 1.24 (95% CI: 1.05, 1.48)<br>10 µg/dL: 1.59 (95% CI: 1.28, 1.98)<br><br>Relative risk for cancer mortality, compared to <5 µg/dL:<br>5-9 µg/dL: 1.44 (95% CI: 1.12, 1.86)<br>10 µg/dL: 1.69 (95% CI: 1.14, 2.52)<br><br>Tests for trends were statistically significant for all three mortality groups. |

## Table AX6-5.3 (cont'd). Effects of Lead on Cardiovascular Mortality

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Michaels et al. (1991)<br>U.S.-New York City<br>1961-1984 | 1261 males, avg age (range) at the beginning of study 49.6 yrs (19-83), representing 24,473 person-yrs were followed. 498 died in the interval. Subjects belonged to the International Typographical Union and worked at two large city newspapers. Hot Pb linotyping was discontinued at the newspapers during 1974-1978, providing the primary source of occupational exposure. Last exposure for all subjects still employed was at the end of 1976.<br><br>Standardized mortality ratios (SMR) were calculated using the LTAS program developed by NIOSH, calculating the expected number of deaths of the cohort referenced to a comparison population, in this case disease-specific mortality rates from New York City. Cohort was stratified based on yrs of employment. Causes of death were based on ICD-8 codes. | Exposure was estimated based on yrs of linotype employment before the end of 1976. Authors note that, based on measurements at other print shops using hot Pb linotype, air Pb levels probably did not exceed 20 $\mu g/m^3$. | Standardized mortality ratio was significant (SMR = 1.68 [95% CI: 1.18, 2.31]) only for cerebrovascular disease in those working, and thus exposed, for 30 yrs or more. Neither arteriosclerotic heart disease (ICD-8 410-414) nor vascular lesions of the central nervous system (ICD-8 430-438) had significant SMR in the total cohort not stratified by yrs of exposure.<br><br>No direct measurement of Pb exposure. Many groupings of ICD codes were explored in stratified and unstratified analyses, with the only significantly elevated SMR found for cerebrovascular disease. No a priori hypotheses. General weakness of all studies relying on a comparison population is that the cohort belongs to the comparison population and can influence the comparison mortality rates in direct proportion to the ratio between cohort and comparison population size. |

## Table AX6-5.3 (cont'd). Effects of Lead on Cardiovascular Mortality

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Steenland et al. (1992)<br>U.S.-Idaho<br>>1941 to 1988 | The death certificates of 1028 males of the 1990 who worked at a smelter plant at least one yr between 1940 and 1965 were examined to construct standardized mortality ratios (SMR) for various ICD-9 disease classifications using the U.S. population as a referent group. | In 1976 blood Pb of 173 workers avgd (SD) 56.3 µg/dL (12.9). Air Pb was measured in 1975 at 3.1 $mg/m^3$ in 208 personal 8-h samples. High Pb departments in the plant were defined as those exceeding 0.2 $mg/m^3$ in the 1975 survey. | Non-malignant respiratory disease and accidents accounted for most of the significantly elevated SMR in the group. SMRs were not significantly elevated for ischemic heart disease (410-414), SMR = 0.94 (95% CI: 0.84, 1.05); hypertension with heart disease (402, 404), SMR = 0.97 (95% CI: 0.53, 1.63); hypertension with no heart disease (401, 403, 405), SMR = 1.73 (95% CI: 0.63, 3.77); or cerebrovascular diseases (430-436), SMR = 1.05 (95% CI: 0.82, 1.32). Similar results were found for the people working in the "high Pb departments."<br><br>Though there is no doubt that this group was highly exposed to Pb, exposure characterization over the working lifetime was not well defined, few blood Pb data were available, and poor demographic data for the exposed group only allowed a comparison with total U.S. population. As is usual with occupationally exposed groups, selection bias may influence results. No smoking data were available for the group. In industrial conditions smoking will be confounded with other Pb exposure (constant hand to mouth behavior on the plant floor will exposure smokers to more Pb via the oral route than in non-smokers). |

## Table AX6-5.3 (cont'd). Effects of Lead on Cardiovascular Mortality

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Gerhardsson et al. (1995)<br>Europe-southern Sweden<br>1969-1989 | 664 male workers at a secondary Pb smelter had blood Pb tested every 2-3 mos since 1969. The past blood Pb level of 201 workers who had been working at the plant from before 1969 was estimated from their 1969 results. Median (10th percentile, 90th percentile) yr of birth was 1943 (1918, 1960). Median (10th percentile, 90th percentile) duration of employment was 2.8 yrs (0.3, 25.7) and median (10th percentile, 90th percentile) duration of follow up was 13.8 yrs (2.8, 20.9). A total of 8706 person-yrs were represented in the study. Standardized mortality ratios based on county mortality tables by calendar yr, cause, sex and five-yr age group were calculated. Cardiovascular diseases were coded by ICD-8 from death certificates. | Arithmetic mean blood Pb levels dropped from ~62 µg/dL in 1969 to ~33 µg/dL in 1985. 95% CI were difficult to extract from the presented graph, but appeared to be no more than 5-6 µg/dL about the mean. | All cardiovascular disease mortality (ICD-8 390-458) was significantly elevated above that expected from the county mortality tables (SMR = 1.46 [95% CI: 1.05, 2.02]), with 39 of the 85 deaths observed in the cohort. For just ischemic heart disease (ICD-8 410-414), SMR = 1.72 (95% CI: 1.20, 2.42) in the plant workers with 34 of the 85 deaths observed in the cohort. There were no deaths recorded for cerebrovascular diseases (ICD-9 430-438). There was no apparent concentration-response relationship, using peak blood Pb and time-integrated blood Pb.<br>Problems inherent in using standardized mortality ratios in such mortality studies have been discussed above. The sample size was too small (85 all cause deaths among 664 workers) to interpret non-significant results. |
| Møller and Kristensen (1992)<br>Europe-Denmark-Copenhagen County-Glostrup Population Studies<br>1976-1990 | See Møller et al. (1992) entry in Blood Pressure and Hypertension for results of cardiovascular disease and coronary heart disease mortality. | | |

## Table AX6-5.4. Cardiovascular Effects of Lead on Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Chen et al. (2006) U.S.-Baltimore, MD; Cincinnati, OH; Newark, NJ; Philadelphia, PA ~1998-2004 | 780 children from 12-33 mos participated in a randomized clinical trial of oral succimer chelation in four clinical centers. Half the children had up to three 26-day treatments, the other half were given placebo. 75% got two treatment sessions and 81% of those with two treatments received a third.<br><br>Blood pressure was measured pre-treatment, at 7, 28, and 42 days after each treatment, then every 3 to 4 mos for five yrs of follow up. Cross-sectional multiple regression models adjusting for clinic location, baseline linear Pb, race, sex, parents' education, single parent, age at test, height at test, and BMI at test for each period of the study tested the difference of diastolic and systolic blood pressure between placebo and succimer groups. Cross-sectional multiple regression models for the effect of linear blood Pb at each period on blood pressure adjusted for clinic location, treatment group, race, sex, parents' education, single parent, age at test, height and BMI. Two mixed models, one from start of treatment to 9-mo follow up, the other from 12 to 60 mos follow up, adjusted for the same variables, and tested the effect of treatment group over time. | Blood Pb ranged from 20-44 µg/dL at pre-treatment and from 1-27 µg/dL at 5 yr follow up. Succimer-treated group had significantly lower blood Pb than placebo group only for 9-10 mos following the end of treatment. Blood Pb did not differ significantly beyond that period. | Adjusted systolic blood pressure was significantly higher in the succimer group than the placebo group at 36 mos (1.27 mm Hg [95% CI: 0.06, 2.48]) and at 60 mos follow up (1.69 mm Hg [95% CI: 0.34, 3.04]). Systolic blood pressure was not significantly different at any other time period; diastolic blood pressure was never significantly different between groups.<br><br>Concurrent linear blood Pb was not associated with blood pressure in cross-sectional models at any time point in the study. Adjusted coefficients for linear blood Pb and systolic blood pressure ranged from 1.36 mm Hg (95% CI: !0.58, 3.30) at pre-treatment to !0.72 mm Hg (95% CI: !1.91, 0.48) at 36 mos of follow up. Diastolic pressure coefficients were generally lower but followed the same pattern.<br><br>Mixed model analysis for start of treatment through 9 mos follow up showed succimer treatment effect of 0.24 mm Hg (95% CI: !0.79, 1.28) for systolic and 0.46 mm Hg (95% CI: !0.44, 1.36) for diastolic blood pressure. The treatment effect from 12 through 60 mos follow up was 1.09 mm Hg (95% CI: 0.27, 1.90) systolic and 0.15 mm Hg (95% CI: !0.45, 0.75) for diastolic blood pressure.<br><br>The only reliable effect of succimer treatment was an elevation of systolic blood pressure, especially notable between three and five yrs post treatment. The authors could not account for the apparent increase in blood pressure in the succimer-treated group 3-5 yrs after treatment ended. It is notable that the two groups had different mean blood Pb for less than a yr after succimer treatment ended, a period perhaps too short to observe any beneficial effect of treatment. Failure to find cross-sectional effects of blood Pb on blood pressure, especially pre-treatment, may indicate that Pb exposure for a period of less than three yrs after birth is not sufficient to affect blood pressure or that blood pressure measurements in the first three yrs of life are highly variable, as could be seen from scatter plots of blood pressure vs. blood Pb at pre-treatment compared 60 mo follow up. The use of linear Pb term may have reduced sensitivity to finding a significant blood Pb effect on blood pressure. No model diagnostics mentioned. |

## Table AX6-5.4 (cont'd). Cardiovascular Effects of Lead on Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Gump et al. (2005)<br>U.S.-Oswego, NY<br>Dates of study not given | 122 9.5-yr old children participated. Multiple regression models of percent changes in systolic and diastolic blood pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance due to acute stress were adjusted by stepwise entry of up to 50 possible control variables with quartile blood Pb forced in last. A linear contrast was used to test dose-response effects of quartile Pb. Linear Pb terms were also used. | Contemporary blood Pb quartile:<br>1st quartile: 1.5-2.8 µg/dL<br>2nd quartile: 2.9-4.1 µg/dL<br>3rd quartile: 4.2-5.4 µg/dL<br>4th quartile: 5.5-13.1 µg/dL | All ∃ represent percent change in outcome from nonstress to stress condition for each change in 1 µg/dL blood Pb.<br><br>Systolic blood pressure: ∃ = !0.009 (95% CI: !0.74, 0.055)<br>Diastolic blood pressure: ∃ = 0.069 (95% CI: !0.001, 0.138)<br>Heart rate: ∃ = 0.013 (95% CI: !0.046, 0.072)<br>Stroke volume: ∃ = !0.069 (95% CI: !0.124, !0.015)<br>Cardiac output: ∃ = !0.056 (95% CI: !0.113, 0.001)<br>Total peripheral resistance: ∃ = 0.088 (95% CI: 0.024, 0.152)<br>Mean successive difference of cardiac interbeat interval: ∃ = !0.028 (95% CI: (!0.098, 0.042)<br><br>Despite low power to detect significant effects, blood pressure, cardiac output, and total peripheral resistance change to stress were associated with contemporary blood Pb. Stepwise modeling creates unique models for each outcome. Some models had up to 12 control variables plus Pb, an excessive number for only 122 subjects. Scatter plots of regression with linear Pb and bar charts of response to quartile Pb showed obvious non-linearity, though all Pb effects were modeled as linear effects. Probability of contemporary exposure to mercury and PCB's was very high. No model diagnostic testing reported. |
| **Europe** | | | |
| Factor-Litvak et al. (1996)<br>Europe-Kosovska Mitrovica and Pristina, Kosovo<br>~1992-1993 | 281 5.5-yr old children studied since pregnancy participated. Multiple linear regression models of systolic blood pressure, adjusted for height, BMI, gender, ethnic group, and birth order, and diastolic blood pressure, adjusted for waist circumference, ethnic group, and birth order were constructed by stepwise elimination from a larger pool of potential confounding variables and retained if they modified the linear blood Pb coefficient by more the 10%. | Blood Pb arithmetic mean (range):<br>22.7 µg/dL (5-55) | For each increase of 1 µg/dL of blood Pb:<br>Systolic blood pressure: ∃ = 0.054 (95% CI: !0.024, 0.13)<br>Diastolic blood pressure: ∃ = 0.042 (95% CI: !0.01, 0.090)<br><br>Despite low power to detect significant effects, there was a marginally significant tendency for blood pressure to be positively associated with blood Pb. Stepwise multiple regression may have capitalized on chance results. The linear Pb term may have reduced the ability to detect significant effects of Pb if the modeled relationship were nonlinear. Log Pb was tested but not reported. A quadratic Pb term was reported nonsignificant. No model diagnostics reported. |

# ANNEX TABLES AX6-6

## Table AX6-6.1. Placental Transfer of Lead from Mother to Fetus

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Harville et al. (2005)<br>Pittsburgh, PA | 159 mother-infant pairs. | Maternal blood Pb at delivery:<br>Mean 1.93 µg/dL (range 0.55-4.70)<br><br>Cord blood Pb:<br>Mean 1.64 µg/dL (range 0.05-3.95) | Correlation coefficient = 0.79<br><br>On avg, cord blood Pb was lower than maternal blood Pb by 0.03 µg/dL (95% CI: 0.21, 0.38). |
| Angell and Lavery (1982)<br>Louisville, KY | 635 cord blood specimens. 154 maternal and infant blood samples collected 24 h postpartum from these deliveries. | Maternal blood Pb:<br>Mean 9.85 µg/dL (SD 4.4)<br><br>Infant blood Pb:<br>Mean 9.82 µg/dL (SD 4.8)<br><br>Cord blood Pb:<br>Mean 9.78 µg/dL (SD 4.1) | Maternal-infant blood Pb:<br>Correlation coefficient = 0.73, ∃ = 0.73<br><br>Maternal-cord blood Pb:<br>Correlation coefficient = 0.60, ∃ = 0.55<br><br>Cord-infant blood Pb:<br>Correlation coefficient = 0.77, ∃ = 0.90 |
| Bogden et al. (1978)<br>Newark, NJ | 25 deliveries of infants with birth weights between 1,500-2,500g and 50 matched controls with birth weights above 2,500g. | Low birth weight infants:<br><br>Maternal blood Pb:<br>Mean 16.2 µg/dL (SD 4.5)<br><br>Cord blood Pb:<br>Mean 13.8 µg/dL (SD 4.4)<br><br>Normal birth weight infants:<br><br>Maternal blood Pb:<br>Mean 15.3 µg/dL (SD 5.2)<br><br>Cord blood Pb:<br>Mean 13.1 µg/dL (SD 4.3) | No significant differences in maternal blood to cord blood ratios in low birth weight and normal birth weight infants.<br><br>Correlation coefficient = 0.55 |

## Table AX6-6.1 (cont'd). Placental Transfer of Lead from Mother to Fetus

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Fahim et al. (1976)<br>Missouri | 249 mother-infant pairs from Columbia. Samples also collected from 253 mothers from Rolla who delivered near Pb mining areas. | Term pregnancies:<br><br>Columbia (n = 240):<br><br>Maternal blood Pb:<br>Mean 13.1 μg/100 g (SE 0.31)<br><br>Fetal blood Pb:<br>Mean 4.3 μg/100 g (SE 0.10)<br><br>Placenta blood Pb:<br>Mean 7.0 μg/100 g (SE 0.01)<br><br>Cord blood Pb:<br>Mean 11.0 μg/100 g (SE 0.31)<br><br>Rolla (n = 177):<br><br>Maternal blood Pb:<br>Mean 14.3 μg/100 g (SE 0.16)<br><br>Fetal blood Pb:<br>Mean 4.6 μg/100 g (SE 0.08)<br><br>Placenta blood Pb:<br>Mean 8.0 μg/100 g (SE 0.06)<br><br>Cord blood Pb:<br>Mean 11.0 μg/100 g (SE 0.14) | Maternal-fetal blood Pb:<br>Correlation coefficient = 0.29 |

## Table AX6-6.1 (cont'd). Placental Transfer of Lead from Mother to Fetus

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Gershanik et al. (1974)<br>Shreveport, LA | 98 mother-infant pairs. | Maternal blood Pb during labor:<br>Mean 10.3 µg/dL<br><br>Cord blood Pb:<br>Mean 10.1 µg/dL | Correlation coefficient = 0.64 |
| **Europe** | | | |
| Graziano et al. (1990)<br>Kosovo, Yugoslavia | 902 births in Titova Mitrovica, site of a large Pb smelter, refinery, and battery factory, and Pristina, a non-Pb-exposed control town. | Maternal blood Pb at mid-pregnancy:<br>Geometric means:<br>Titova Mitrovica 17.1 µg/dL (95% CI: 16.9, 42.6)<br>Pristina 5.1 µg/dL (95% CI: 2.5, 10.6) | Maternal blood Pb at delivery and cord blood Pb:<br>Correlation coefficient = 0.920, ∃ = 0.928 |
| Huel et al. (1981)<br>France | Hair sample pairs (n = 100) from mothers and newborns at time of delivery. | Maternal hair Pb:<br>Geometric mean 8.5 µg/dL<br><br>Fetal hair Pb:<br>Geometric mean 7.3 µg/dL | Correlation coefficient = 0.24 |
| Lauwerys et al. (1978); Roels et al. (1978) Belgium | 474 mother-infant pairs from Antwerp, Brussels, Leuven, Tournai, and Vilvoorde. | Maternal blood Pb:<br>Mean 10.1 µg/dL (range 3.1-31)<br><br>Infant blood Pb:<br>Mean 8.3 µg/dL (range 2.7-27.3)<br><br>Placenta blood Pb:<br>Median 7.5 µg/100 g wet weight (range 1.1-39.5) | Maternal-infant blood Pb:<br>Correlation coefficient = 0.81, ∃ = 0.73<br><br>ln placenta-maternal blood Pb:<br>Correlation coefficient = 0.22<br><br>ln placenta-infant blood Pb:<br>Correlation coefficient = 0.28 |
| Barltrop (1969)<br>England | 29 paired maternal and fetal samples. | Maternal blood Pb:<br>Mean 13.9 µg/100 g<br><br>Cord blood Pb:<br>Mean 10.8 µg/100 g | Correlation coefficient = 0.86 |

## Table AX6-6.1 (cont'd). Placental Transfer of Lead from Mother to Fetus

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Barltrop (1969) England | 34 fetuses at gestational age 10 to 40 wks obtained from termination of pregnancy and neonatal deaths. | Blood Pb levels in femur, liver, blood, brain, heart, and kidney measured. | Pb became detectable at gestational age 12 -14 wks. For skeletal (femur) and soft tissue with high affinity (liver), Pb levels increased progressively until term. In contrast, in soft tissue with low affinity (heart), only a modest increase in Pb levels was observed between 14 wks and term. |
| **Latin America** | | | |
| Chuang et al. (2001) Mexico City, Mexico | 615 women recruited in 1994-1995. Investigators used structural equation modeling to estimate plasma Pb as the unmeasured variable and to quantify the interrelations of cord blood Pb with plasma Pb, whole blood Pb, and bone Pb (cortical and trabecular). | Maternal whole blood Pb:<br>Mean 8.45 μg/dL (SD 3.94)<br><br>Maternal patella bone Pb:<br>Mean 14.24 μg/g bone mineral (SD 14.19)<br><br>Maternal tibia bone Pb:<br>Mean 9.67 μg/g bone mineral (SD 9.21)<br><br>Cord blood Pb:<br>Mean 6.55 μg/dL (SD 3.45) | ln cord-ln maternal whole blood Pb:<br>Correlation coefficient = 0.82<br><br>ln cord-ln maternal plasma Pb:<br>Correlation coefficient = 0.89<br><br>ln cord-maternal patella Pb:<br>Correlation coefficient = 0.23<br><br>ln cord-maternal tibia Pb:<br>Correlation coefficient 0.18<br><br>The structural equation models indicated that maternal plasma Pb had a stronger association with fetal cord blood Pb compared to that of whole blood Pb. In addition, the models suggested a significant contribution of Pb from the skeletal system to plasma during pregnancy, a contribution that is independent of the influence of maternal whole blood Pb. |

## Table AX6-6.1 (cont'd). Placental Transfer of Lead from Mother to Fetus

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Other Locations** | | | |
| Clark (1977)<br>Zambia | 122 mother-infant pairs residing near the Broken Hill Pb Mine and Smelter. Control group of 31 mother-infant pairs. | Mine group:<br><br>Maternal blood Pb:<br>Mean 41.2 µg/dL (SD 14.4)<br><br>Infant cord blood Pb:<br>Mean 37.0 µg/dL (SD 15.3)<br><br>Control group:<br><br>Maternal blood Pb:<br>Mean 14.7 µg/dL (SD 7.5)<br><br>Infant cord blood Pb:<br>Mean 11.8 µg/dL (SD 5.6) | Mine group:<br>Correlation coefficient = 0.77<br><br>Control group:<br>Correlation coefficient = 0.56 |
| Casey and Robinson (1978)<br>New Zealand | 40 fetuses (23 stillborn and 17 died within 24 hrs), 22 to 43 wks gestation. | Pb detected in 73% of liver, 23% of kidneys, 40% of brain, 25% of heart, 33% skeletal muscle, and 70% of bone samples. Pb also detected in 11 of 14 lung samples (79%).<br><br>Overall Pb concentration in soft tissue:<br>0.1-2.4 µg/g dry matter<br><br>Pb concentration in bone samples:<br>0.4-4.3 µg/g dry matter | Pb concentrations in bone were higher than in the other tissues.<br><br>Levels in brain, heart, and muscle similar to values reported for children and adults. Levels in liver, kidney, lung, and bone were much less than adult values, suggesting much of the Pb that enters the body after birth accumulates in these tissues. |
| Chaube et al. (1972) | 50 embryos and fetuses 31 to 261 days gestational age that were aborted. | Among the 1st trimester specimens:<br>Pb detected in 77% of liver, 15% of brain, and 30% of kidney samples. | Placental transfer occurs as early as the 1st trimester of pregnancy. |

## Table AX6-6.2. Lead Exposure and Male Reproduction: Semen Quality

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Benoff et al. (2003a)<br>New York | 74 male partners of women undergoing their first in vitro fertilization cycle. | Seminal plasma Pb:<br>Mean 39.50 µg/dL (SD 35.97) | Significant negative correlation between seminal plasma Pb and fertilization rate (r = !0.447).<br><br>Statistically significant inverse correlations (r values of <!0.3) were found between seminal plasma Pb levels and sperm count, motility, and morphology. Stronger negative relationships were observed between seminal plasma Pb values and mannose receptor expression (r = !0.383), and mannose-stimulated acrosome loss (r = !0.423). |
| Benoff et al. (2003b)<br>New York | 15 semen donors in an artificial insemination program. None were occupationally exposed to Pb. | Seminal plasma Pb:<br>Range <10 to >150 µg/dL | Correlation coefficient for seminal plasma Pb and artificial fecundity rate is !0.641. |
| Cullen et al. (1984)<br>U.S. | Seven men with symptomatic occupational Pb intoxication. | Maximum whole blood Pb levels:<br>66-139 µg/dL | Although serum testosterone concentration was normal in six patients, five had defects in spermatogenesis, including two with oligospermia and two with azoospermia. Repeat examinations after chelation therapy showed only partial improvement.<br><br>Heavy occupational exposure to Pb may be associated with diffuse disturbances of endocrine and reproductive functions in men that are not rapidly reversible with standard treatment. |

## Table AX6-6.2 (cont'd). Lead Exposure and Male Reproduction: Semen Quality

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** | | | |
| Alexander et al. (1996a)<br>British Columbia | 119 workers employed at a Pb smelter. | Current blood Pb:<br>Mean 22.4 µg/dL (range 5-58) | Sperm concentration and total sperm count were inversely related to current blood Pb concentration, with the largest effects detected among men with blood Pb concentrations of 40 µg/dL or more.<br><br>Blood Pb (µg/dL) / Geometric mean sperm count×$10^6$:<br><15: 186.0<br>15-24: 153.0<br>25-39: 137.0<br>∃40: 89.1<br><br>Blood Pb levels were not consistently associated with abnormal morphology and poor motility of the sperm.<br><br>When classified by long term exposure to Pb, calculated from the mean blood Pb concentrations of the preceding 10 yrs, similar trends were observed. |

## Table AX6-6.2 (cont'd). Lead Exposure and Male Reproduction: Semen Quality

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Bonde et al. (2002)<br>UK, Belgium, Italy | European study of 503 men (362 exposed to Pb, 141 unexposed controls) employed in Pb industry. | Blood Pb:<br><br>Exposed workers:<br>Mean 31.0 µg/dL (range 4.6-64.5)<br><br>Unexposed workers:<br>Mean 4.4 µg/dL | Median sperm concentration reduced by 49% in men with blood Pb levels >50 µg/dL.<br><br>Odds ratio for sperm count #50 million/ml in men with blood Pb levels >50 µg/dL compared to <10 µg/dL was 4.4 (95% CI: 1.6, 11.6).<br><br>Regression analyses indicated a threshold value of 44 µg/dL below which no adverse associations were found. |
| Assennato et al. (1986)<br>Italy | 18 battery workers (exposed group) and 18 cement workers (control group). | Blood Pb:<br><br>Battery workers:<br>Mean 61 µg/dL (SD 20)<br><br>Cement workers:<br>Mean 18 µg/dL (SD 5)<br><br>Semen Pb:<br><br>Battery workers:<br>Mean 79 µg/dL (SD 36)<br><br>Cement workers:<br>Mean 22 µg/dL (SD 9) | Sperm count and blood Pb:<br>$r^2$ = !0.385<br><br>Sperm count and sperm Pb:<br>$r^2$ = !0.026<br><br>38% lower median sperm count and threefold greater prevalence of oligospermia (16.7% vs. 5.5%) in battery workers compared to cement workers. |
| Lancranjan et al. (1975)<br>Europe | 150 men occupationally exposed to Pb divided into four groups: Pb-poisoned workmen (n = 23) and those showing a moderate (n = 42), slight (n = 35), or physiologic absorption (n = 50). | Blood Pb:<br><br>Pb poisoned workers:<br>Mean 74.5 µg/dL<br><br>Moderately exposed workers:<br>Mean 52.8 µg/dL | Decreased sperm counts and increased prevalence of morphologically abnormal sperm amongst workers with heavy and moderate exposure to Pb. |

## Table AX6-6.2 (cont'd). Lead Exposure and Male Reproduction: Semen Quality

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Hernandez-Ochoa et al. (2005)<br>Region Lagunera, Mexico | 68 environmentally-exposed men residing in Torreón, Gómez Palacio, and Lerdo for at least 3 yrs. | Blood Pb:<br>Geometric mean 9.3 µg/dL (range 2-24)<br><br>Seminal fluid Pb:<br>Geometric mean 2.02 µg/L (range 1.14-12.4)<br><br>Pb in spermatozoa:<br>Geometric mean 0.047 ng/$10^6$ cells (range 0.032-0.245) | Decreased sperm concentration, motility, normal morphology and viability correlated with Pb in spermatozoa. Reduced semen volume associated with seminal fluid Pb.<br><br>Multiple linear regression indicated that percentages of progressive motility and morphology were the most sensitive parameters to Pb toxicity, which showed the highest percentages of abnormality among the semen quality parameters evaluated.<br><br>No associations were found with blood Pb. |
| Lerda (1992)<br>Argentina | 38 male workers exposed to Pb in a battery factory and 30 controls. | Blood Pb:<br><br>A (n = 12): mean 86.6 µg/dL (SD 0.6)<br><br>B (n = 11): mean 65.9 µg/dL (SD 1.6)<br><br>C (n = 15): mean 48.6 µg/dL (SD 4.2)<br><br>Controls (n = 30): mean 23.5 µg/dL (SD 1.4) | Decreased sperm count, decreased percent motility, and increased percent with abnormal morphology observed in all three exposure groups compared to control group. |
| **Asia** | | | |
| Chowdhury et al. (1986)<br>India | Ten men occupationally exposed to Pb in a printing press. | Blood Pb:<br><br>Exposed group:<br>Mean 42.5 µg/dL<br><br>Unexposed group:<br>Mean 14.8 µg/dL | Decrease in sperm count, percent motility and increase in number of sperm with abnormal morphology observed in these semen samples. |

## Table AX6-6.3. Lead Exposure and Male Reproduction: Time to Pregnancy

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Joffe et al. (2003)<br>Belgium, England, Finland, Italy | Asclepios Project, large European collaborative cross-sectional study. 1,108 men (638 occupationally exposed to Pb at the time of pregnancy) who have fathered a child. | Blood Pb:<br><br>Belgium: mean 31.7 µg/dL<br><br>England: mean 37.2 µg/dL<br><br>Finland: mean 29.3 µg/dL<br><br>Italy: mean 29.2 µg/dL | Blood Pb (µg/dL) / Fecundity density ratios (95% CI)<br>control 1.00<br><20 1.12 (0.84, 1.49)<br>20-29 0.96 (0.77, 1.19)<br>30-39 0.88 (0.70, 1.10)<br>∃40 0.93 (0.76, 1.15)<br><br>Results indicate that no association was found between blood Pb and delayed time to pregnancy. Similar results were found when duration of exposure or cumulative exposure was used as the exposure metric. |
| Apostoli et al. (2000)<br>Italy | Italian men included in the Asclepios project. 251 exposed men and 45 unexposed men with at least one completed pregnancy. | Blood Pb distribution among exposed men:<br><br>Blood Pb (µg/dL) / Percentage of population<br>0-19 14%<br>20-29 40%<br>30-39 32%<br>∃40 14% | Time to pregnancy shorter in couples in which male partner exposed compared to unexposed.<br><br>Among the exposed men, a longer time to pregnancy observed with blood Pb levels ∃40 µg/dL, though not statistically significant. |

## Table AX6-6.3 (cont'd). Lead Exposure and Male Reproduction: Time to Pregnancy

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Sallmén et al. (2000a) Finland | 502 occupationally exposed males monitored by the Finnish Institute of Occupational Health. | Blood Pb distribution (available close to time of conception in 62% of men; in 38% estimated based on blood Pb levels obtained at other times or based on job histories):<br>Blood Pb (µg/dL) — Percentage of population<br><10 — 35%<br>10-20 — 40%<br>21-30 — 16%<br>31-39 — 4%<br>∃40 — 5% | Results suggest that paternal exposure to Pb may be associated with increased time to pregnancy.<br>Blood Pb (µg/dL) — Fecundity density ratios (95% CI)<br><10 — 1.00<br>10-20 — 0.92 (0.73, 1.16)<br>21-30 — 0.89 (0.66, 1.20)<br>31-39 — 0.58 (0.33, 0.96)<br>∃40 — 0.83 (0.50, 1.32) |
| **Asia** | | | |
| Shiau, et al. (2004) Taiwan | 280 pregnancies in 133 couples in which male partner employed in battery plant. 127 conceived during exposure; remainder conceived prior to exposure. | Blood Pb:<br>Annual means from 1987 to 1999 ranged from 32 to 41 µg/dL. | Blood Pb (µg/dL) — Fecundity density ratios (95% CI)<br>unexposed — 1.00<br><20 — 0.91 (0.61, 1.35)<br>20-29 — 0.71 (0.46, 1.09)<br>30-39 — 0.50 (0.34, 0.74)<br>∃40 — 0.38 (0.26, 0.56)<br>Using blood Pb as a continuous variable and restricting the analysis to blood Pb levels between 10 and 40 µg/dL, time to pregnancy increased by 0.15 mos for each 1 µg/dL increase in blood Pb level. |

## Table AX6-6.4. Lead Exposure and Male Reproduction: Reproductive History

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Lin et al. (1996)<br>New York | 4,256 male workers reported to the New York State Heavy Metals Registry (exposed) and 5,148 male bus drivers from the New York State Department of Motor Vehicles file (control), frequency-matched for age and residence. Fertility during the period of 1981 to 1992. Records linked to birth certificates from the New York State Office of Vital Statistics. | Blood Pb in Pb-exposed men:<br>Mean 37.2 μg/dL (SD 11.1) | Standardized fertility ratio of Pb-exposed men in comparison with non-exposed men was 0.88 (95% CI: 0.81, 0.95).<br><br>Exposed group had fewer births than expected. Among those employed in Pb industry over 5 yrs, a relative risk of 0.38 (95% CI: 0.23, 0.61) was observed after adjusting for age, race, education, and residence. |
| **Europe** | | | |
| Gennart et al. (1992)<br>Belgium | 74 men occupationally exposed to Pb for more than 1 yr and 138 men in reference group with no occupational exposure. | Blood Pb in Pb-exposed men:<br>Mean 40.3 μg/dL<br><br>Duration of Pb exposure:<br>Mean 10.7 yrs | Compared to reference group, odds of at least one live birth reduced in exposed group during the period of Pb exposure (odds ratio of 0.65 [95% CI: 0.43, 0.98]).<br><br>Fertility decreased with increasing exposure (although number of men at higher exposure levels small). |
| Bonde and Kolstad (1997)<br>Denmark | 1,349 male employees ages 20-49 yrs from three battery plants and control group of 9,656 men not employed in Pb industry. Cohorts identified by records in a national pension fund. Information on births obtained from Danish Population Register. | Blood Pb in subset of battery worker cohort (4,639 blood samples from 400 workers):<br>Mean 35.9 μg/dL (SD 13.0) | No associations found between exposure measure and birth rate.<br><br>Relative risk comparing person yrs at risk from Pb exposure with yrs at risk in reference group was 0.88 (95% CI: 0.81, 0.95). |

## Table AX6-6.4 (cont'd). Lead Exposure and Male Reproduction: Reproductive History

| Reference and Study Location | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Sallmén et al. (2000b) Finland | Occupationally exposed males monitored by the Finnish Institute of Occupational Health. 2,111 individuals with probable exposure (a blood Pb level ∃10 µg/dL within a 5-yr time period including a calendar yr preceding the yr of marriage and 4 consecutive yrs) and 681 controls (with mean blood Pb levels <10 µg/dL). | Blood Pb distribution among individuals probably exposed:<br>Blood Pb (µg/dL) — Percentage of population<br>10-20 — 51%<br>21-30 — 30%<br>31-40 — 11%<br>41-50 — 5%<br>∃51 — 3% | Risk ratios among men in the probably exposed group:<br>Blood Pb (µg/dL) — Infertility ratios (95% CI)<br>controls — 1.00<br>10-20 — 1.27 (1.08, 1.51)<br>21-30 — 1.35 (1.12, 1.63)<br>31-40 — 1.37 (1.08, 1.72)<br>41-50 — 1.50 (1.08, 2.02)<br>∃51 — 1.90 (1.30, 2.59)<br>Results suggest that paternal exposure to Pb increases the risk of infertility at low occupational exposure levels. |

# ANNEX TABLES AX6-7

## Table AX6-7.1. Recent Studies of Lead Exposure and Genotoxicity

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Fracasso et al. (2002)<br>Italy | Case-control design.<br>37 workers employed at a battery plant.<br>29 student and office worker volunteers with no known occupational exposure to genotoxins.<br>Peripheral lymphocytes isolated from whole blood.<br>Reactive Oxygen Species (ROS) production, cellular GSH level, PKC isoforms, and DNA breaks (via comet) assayed.<br>ANOVA and logistic regression used to compare workers vs. healthy volunteers.<br>Adjusted for age, alcohol use, and smoking. | Battery plant workers. Blood Pb categories used for some comparisons, with <25, 25-35, and >35 µg/100mL as cutpoints.<br>Mean blood Pb 39.6 µg/100mL for workers, 4.4 µg/100mL for volunteers. | OR (95% CI)<br>*Workers vs. Volunteers:*<br>ROS: 1.43 (0.79, 2.60)<br>DNA breaks (tail moment): 1.07 (1.02, 1.12)<br>GSH: 0.64 (0.49, 0.82)<br>PKC α reduced in workers, atypical PKC unchanged vs. volunteers (no statistics provided).<br><br>*Means (SE) via blood Pb category for ROS and GSH:*<br><25 µg/100 mL 4.9 (0.4) and 12.8 (0.8)<br>25-35 µg/100 mL 5.4 (0.7) and 7.7 (1.7)<br>>35 µg/100 mL 5.4 (0.5) and 9.2 (1.2)<br><br>Major analyses controlled for age, smoking, and alcohol intake. Analyses by blood Pb category not controlled for age, smoking, or alcohol intake but these factors said not to influence endpoint and/or results "significantly." No control for potential coexposures. |

## Table AX6-7.1 (cont'd). Recent Studies of Lead Exposure and Genotoxicity

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Palus et al. (2003)<br>Poland | Cross-sectional design.<br>Battery plant workers: 34 acid battery, 22 alkaline battery, and 52 plant personnel from departments with no known exposure to Pb or cadmium.<br>Lymphocytes isolated from whole blood.<br>SCE, MN, DNA damage (via comet) assayed.<br>Means compared via ANOVA. | Workers considered Pb-exposed if from acid battery department, cadmium-exposed if from alkaline, unexposed if from other department.<br>Mean blood Pb 504 µg/L for Pb-exposed workers, 57 µg/L for cadmium-exposed, and 56 µg/L for other workers. | Mean (SD)<br>*Pb exposed workers (all combined):*<br>SCEs 7.48 (0.88)<br>MN 18.63 (5.01)<br>NDI 1.89 (no SD given)<br><br>*Cadmium exposed workers (all combined):*<br>SCEs 6.95 (0.79)<br>MN 15.86 (4.92)<br>NDI 1.96 (no SD given)<br><br>*Other workers (all combined):*<br>SCEs 6.28 (1.04)<br>MN 6.55 (3.88)<br>NDI 1.86 (no SD given)<br>Elevation of SCEs and MN vs. controls at $p < 0.05$ and $p < 0.01$, respectively.<br><br>Both SCEs and MN elevated among Pb-exposed workers as well as cadmium-exposed workers compared to controls. Differences greatest for Pb-exposed workers.<br>Higher SCE and MN also occurred among Pb-exposed workers after stratification by smoking status.<br>No direct control for potential coexposures, but mean blood cadmium no higher in Pb-exposed than in other worker group. |

## Table AX6-7.1 (cont'd). Recent Studies of Lead Exposure and Genotoxicity

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Van Larebeke et al. (2004)<br>Belgium | Cross-sectional design.<br>99 female nonsmokers, ages 50-65, drawn from rural and industrial areas.<br>Peripheral lymphocytes isolated from blood. HPRT variant frequency determined. | Pb concentration measured in blood (serum).<br>Women also classified as above vs. below median for blood Pb. | HPRT variant frequency<br>*Above median serum Pb: 9.45* H $10^{-6}$<br>*Below median serum Pb: 5.21* H $10^{-6}$<br><br>P-value for difference = 0.08 adjusted for age, education, smoking, BMI, and serum selenium. (Significant inverse association noted between variant frequency and serum selenium.) Uncontrolled for potential exposure to other genotoxins. |
| **Latin America** | | | |
| Minozzo et al. (2004)<br>Brazil | Cross-sectional design.<br>26 workers employed at a battery recyclery for 0.5 to 30 yrs.<br>29 healthy volunteers of similar age range and SES.<br>Peripheral lymphocytes isolated from whole blood.<br>Fixed blood slides stained with Giemsa visually evaluated to determine micronuclear frequency (MN) and cellualr proliferation as nuclear division index (NDI).<br>ANOVA and logistic regression used to compare workers vs. healthy volunteers. Adjusted for age, alcohol use, and smoking. | Battery recyclery workers were considered exposed.<br>Blood Pb also determined.<br>Mean blood Pb 35.4 µg/dL for workers, 2.0 µg/dL for volunteers. | *Means (SD) for workers and volunteers*<br>MN: 3.85 (2.36) and 1.45 (1.43)<br>NDI: 1.77 (0.22) and 1.89 (0.18)<br><br>Kendal correlation coefficient:<br>*All workers* {assuming recyclery workers only, not total population, but no population number given in table.}<br>Blood Pb H MN: 0.061 (p = 0.33)<br>Blood Pb H NDI: 0.385 (p = 0.003)<br><br>Not controlled for age or SES, although worker and volunteer populations said to be of similar age and SES. Uncontrolled for potential coexposures. Correlations appear uncontrolled for smoking, age, or other factors. Differences in MN and NDI minor for smokers vs. nonsmoker, however. Diet "type" "similar" for workers and controls, although no definition of similarity provided. |

## Table AX6-7.2. Key Occupational Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **United States** | | | |
| Steenland et al. (1992) (follow-up of Selevan et al. (1985) U.S. 1940-1988 | Cohort design. 1,990 male workers employed for at least 1 yr in a Pb-exposed department at a U.S. Pb smelter in Idaho during 1940-1965. Mortality traced through 1988 to determine cause of death. SMR computed for workers vs. national rates for age-comparable counterparts. | Exposure categorizations based on airborne Pb measurements from 1975 survey. High-Pb-exposure subgroup consisted of 1,436 workers from departments with an avg of least 0.2 $mg/m^3$ airborne Pb or ≥50% of jobs showing 0.40 $mg/m^3$ or greater. Mean blood Pb 56 µg/dL in 1976. | SMR (95% CI); number of deaths<br>*Total cohort:*<br>Nonsignificantly elevated RRs: kidney, bladder, stomach, and lung cancer.<br><br>*High-Pb-exposure subgroup:*<br>Kidney 2.39 (1.03, 4.71); 8<br>Bladder 1.33 (0.48, 2.90); 6<br>Stomach 1.28 (0.61, 2.34); 10<br>Lung 1.11 (0.82, 1.47); 49<br><br>No control for smoking or exposure to other metals. |
| Wong and Harris (2000) (follow-up of Cooper et al. (1985) U.S. 1947-1995 | Cohort design. Pb battery plant (4,518) and smelter (2,300) workers. Worker mortality was followed up through 1995. Cause of death was identified from death certificates. Mortality was compared with U.S. national age-, calendar-yr-, and gender-specific rates to compute the SMR. (See additional entry for nested study of stomach cancer.) | Workers were evaluated as a whole, and also as separate battery plant and smelter worker populations. Job histories were also used to stratify workers by cumulative yrs of employment (1-9, 10-19, 20+), date of hire (pre-1946 vs. 1946 on), and lag between exposure and cancer (<20, 20-34, >34 yrs). Mean blood Pb 80 µg/dL during 1947-72 among smelter workers, 63 µg/dL among battery workers. | SMR (95% CI)<br>*Battery plant workers:*<br>All cancer 1.05 (0.97, 1.13)<br>All respiratory 1.13 (0.98, 1.29)<br>Stomach 1.53 (1.12, 2.05)<br>Lung, trachea, bronchus 1.14 ( 0.99, 1.30)<br>Thyroid, Hodgkin's: nonsignificant<br>Bladder 0.49 (0.23, 0.90)<br>*Smelter workers:*<br>Digestive, respiratory, thyroid: nonsignificant<br>Lung 1.22 (1.00, 1.47)<br>*Battery plant and smelter workers combined:*<br>All cancer 1.04 (0.97, 1.11)<br>All respiratory 1.15 (1.03, 1.28)<br>Stomach 1.47 (1.13, 1.90)<br>Lung, trachea, bronchus 1.16 ( 1.04, 1.30)<br>Thyroid/endocrine 3.08 (1.33, 6.07)<br><br>Lung and stomach risks lower pre-1946 hires; higher for workers employed 10-19 yrs than <10, but lower for >19 yrs; SMRs peaked with 20- to 34-yr latency for lung, but <20 yrs for stomach. No control for smoking or exposure to other agents. No assessment of employment history after 1981. |

## Table AX6-7.2 (cont'd). Key Occupational Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Wong and Harris (2000)<br>U.S.<br>1947-1995.<br>(Nested in Wong and Harris 200 cohort.) | Case-control design.<br><br>*Cases*: the 30 stomach cancer cases occurring in a Philadelphia Pb battery plant.<br><br>*Controls*: 120 age-matched cohort members.<br><br>Mean exposure was compared for cases vs. controls. Odds of exposure were also computed for increasing quartiles of cumulative exposure. | Job titles were used to classify Pb exposure as low, intermediate, or high; total mos of any exposure, of intermediate or high exposure only, and of cumulative exposure, with mos weighted by 1, 2, or 3 if spent in low-, intermediate-, or high-exposure job. | Mean mos of employment, of intermediate or high exposure, or of weighted exposure to Pb were all nonsignificantly lower among cases.<br><br>OR for cumulative weighted exposure in the 10 yrs prior to death:<br>1st quartile 1.00<br>2nd quartile 0.62<br>3rd quartile 0.82<br>4th quartile 0.61<br><br>p for trend = 0.47; ORs showed no positive association with any index of exposure.<br>Analyses appear uncontrolled for smoking, other occupational exposures, or other risk factors. |
| **Europe** | | | |
| Fanning (1988)<br>(Cases overlap those occurring in Dingwall-Fordyce and Lane, 1963; and Malcolm and Barnett, 1982).<br>U.K.<br>1926-1985 | Proportional mortality/cohort design.<br>*Subjects:* 2,073 deceased males identified through pension records of Pb battery and other factory workers in the U.K.<br>Workers dying from a specific cancer were compared with workers dying from all other causes | Workers were classified as High or moderate Pb exposure vs. little or no exposure based on job titles. | OR (95% CI); number of deaths<br>Lung cancer: 0.93 (0.8, 1.1); 76<br>Stomach cancer: 1.34; 31<br><br>No associations for other cancer types; elevations in stomach and total digestive cancers limited to the period before 1966. |

## Table AX6-7.2 (cont'd). Key Occupational Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Anttila et al. (1995)<br>Finland<br>1973-1988 | Cohort plus case-referent design. 20,700 workers with at least one blood Pb measurement between 1973 and 1983.<br><br>Workers were linked to the Finnish Cancer Registry for follow-up through 1988. For deceased workers, cause of death was identified from death certificate.<br><br>Mortality and incidence were compared with gender-, 5-yr age, and 4-yr calendar-yr matched national rates. | Exposure was categorized according to the highest peak blood level measured:<br>Low: 0-0.9 µmol/L (0-18.6 µg/dL)<br>Moderate: 1-1.9 µmol/L (20.7-39.4 µg/dL)<br>High: 2-7.8 µmol/L (41.4-161.6 µg/dL)<br><br>Mean blood Pb 26 µg/dL. | *Total cohort:*<br>No elevation in total or site-specific cancer mortality.<br><br>*Moderately exposed:*<br>Total respiratory and lung cancer:<br>SIR = 1.4 (95% CI: 1.0, 1.9) for both<br>Total digestive, stomach, bladder, and nervous system: nonsignificant elevations.<br><br>*Highly exposed:*<br>No increase in risks.<br><br>*All cancer:*<br>RR = 1.4 (95% CI: 1.1, 1.8)<br><br>*Lung or tracheal:*<br>RR = 2.0 (95% CI: 1.2, 3.2)<br>No increase in high-exposure group.<br>No RRs reported for other cancers.<br><br>*Case-referent substudies:*<br>Lung cancer ORs increased with increasing cumulative exposure to Pb.<br>Highly exposed: squamous-cell lung cancer OR of 4.1 (95% CI: 1.1, 15) after adjustment for smoking.<br>Short follow-up period limits statistical power, offset to a large degree by the substantial sample size. No control for exposure to other potential carcinogens. |

## Table AX6-7.2 (cont'd). Key Occupational Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Anttila et al. (1996)<br>Finland<br>1973-1988<br>(Nested analysis based on Antilla et al., 1995 cohort) | Case-control design.<br>(See Anttila et al., 1995 for basic information on the source population.)<br><br>*Cases*: 26 Finnish men with CNS cancer.<br><br>*Controls:* 200 Finnish men without CNS cancer.<br>Nested case-control analysis. | Peak blood Pb levels used to categorize exposure as 0.1-0.7, 0.8-1.3, and 1.4-4.3 µg/L.<br>Cumulative exposure estimated by using mean annual blood Pb level to categorize exposure as 0, 1-6, 7-14, or 15-49 µg/L.<br>Interviews were used to obtain occupational history and other risk-factor data from patients or next of kin. | Number of cases or deaths<br>CNS cancer incidence *(26 cases):* Rose with increasing peak lifetime blood Pb measurements; not significant.<br>Glioma mortality *(16 deaths):* Rose consistently and significantly with peak and mean blood Pb level, duration of exposure, and cumulative exposure.<br><br>Mortality by cumulative exposure, controlled for cadmium, gasoline, and yr monitoring began:<br>Low (13 subjects) 2.0 (2)<br>Medium (14 subjects) 6.2 (2)<br>High (16 subjects) 12.0 (5)<br>One death among 26 subjects with no exposure: test for trend significant at p = 0.02.<br><br>Controlled for smoking as well as exposure to cadmium and gasoline.<br>Complete follow-up with minimal disease misclassification. |
| Gerhardsson et al. (1995)<br>Sweden<br>1969-1989 | Cohort design.<br>684 male Swedish secondary Pb smelter workers with Pb exposure.<br>Cancer incidence among workers was traced through 1989.<br>Incidence was compared with county rates. | Blood Pb level: any worker with a detectable blood Pb level was classified as exposed. | SIR (95% CI); number of cases<br>*All malignancies:*<br>1.27 (0.91, 1.74); 40<br>*Respiratory:*<br>1.32 (0.49, 2.88); 6<br>*All gastrointestinal:*<br>Cohort 1.84 (0.92, 3.29); 11<br>Highest quartile 2.34 (1.07, 4.45); 9<br>*Stomach:*<br>1.88 (0.39, 5.50); 3<br>*Colon:*<br>1.46 (0.30, 4.28); 3<br><br>SIRs for all other sites except brain were nonsignificantly elevated; too few cases.<br>No control for smoking. Small numbers, so meaningful dose-response analyses not possible for most cancer sites. |

## Table AX6-7.2 (cont'd). Key Occupational Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Lundström et al. (1997) (follow-up of Gerhardsson et al. (1986) (see also subcohort analyses of Englyst et al., 2001). Sweden 1928-1987 | Cohort design. 3,979 copper and Pb smelter workers. Standardized mortality and incidence ratios were computed for workers compared with age-, yr-, gender-, and county-specific rates for the general population. | For some analyses, the entire cohort was treated as exposed. For others, job histories were used to single out 1,992 workers belonging to departments thought to be exposed to "Pb only." Mean blood Pb monitoring test results across time were used to single out a "highly exposed" group of 1,026 workers with blood Pb levels ≥10 µmol/L [≥207 µg/dL]. Mean blood Pb 60 µg/dL in 1959. | SMR (95% CI); number of deaths<br>*Lung:*<br>Total cohort 2.8 (2.0, 3.8); 39<br>Highly exposed 2.8 (1.8, 4.5); 19<br><br>SIR (95% CI); number of cases<br>*Lung with 15-yr lag:*<br>Total cohort 2.9 (2.1, 4.0); 42<br>Highly exposed 3.4 (2.2, 5.2); 23<br>Pb-only 3.1 (1.7, 5.2); 14<br>Pb-only highly exposed 5.1 (2.0, 10.5); 7<br><br>*Other highly exposed (total cohort), with 15-yr lag:*<br>Brain 1.6 (0.4, 4.2); 4<br>Renal pelvis, ureter, bladder 1.8 (0.8, 3.4); 9<br>Kidney 0.9 (0.2, 2.5); 3<br>All cancer 1.1 (0.9, 1.4); 83<br>No control for smoking. |
| Englyst et al. (2001) (follow-up and sub-analysis of Lundström et al., 1997). Sweden 1928-1987 | Nested cohort analysis.<br><br>Limited to 1,093 workers in the smelter's Pb department, followed through 1997.<br><br>Incidence was compared with county rates; age-specific SIRs with 15-yr lag. | Workers were divided into Subcohorts I and II for ever and never worked in areas generally associated with exposure to arsenic or other known carcinogens (701 and 383 workers, respectively). Detailed individual assessment of arsenic exposure was made for all lung-cancer cases. | SIR (95% CI); number of cases<br>Subcohort I (coexposed):<br>Lung 2.4 (1.2, 4.5); 10<br><br>Subcohort II (not coexposed):<br>Lung 3.6 (1.2, 8.3); 5<br><br>Subjects with lung cancer found to have history of "considerable" exposure to arsenic: 9/10 among Subcohort I, 4/5 among Subcohort II.<br>No control for smoking. |

## Table AX6-7.2 (cont'd). Key Occupational Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Carta et al. (2003)<br>Sardinia<br>1972-2001 | Cohort design.<br>918 Pb smelter workers.<br><br>Mortality traced from 1972 through 2001.<br><br>Standardized mortality ratios computed. | Smelter workers considered exposed. Job histories also used to categorize degree of exposure based on environmental and blood Pb measurements for specific departments and tasks during 1985-2001. | SMR; number of cases<br>*Smelter workers as a whole*<br>All cancer 1.01; 108<br>Gastric cancer 1.22; 4<br>Lymphoma/leukemia 1.82; 6<br>Lung cancer 1.21; 18<br><br>*Highly exposed workers*<br>Lung cancer 1.96 (95% CI: 1.02, 3.68) for highest exposure group, with statistically significant upward trend.<br>Analyses for worker population as a whole supported by presence of dose-response pattern for lung cancer based on estimated exposure. Modest population size, inability to assess dose-response for cancers of interest other than lung. No control for smoking or other occupational exposures. |

## Table AX6-7.3. Key Studies of Lead Exposure and Cancer in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **United States** | | | |
| Jemal et al. (2002) (same cohort as in Lustberg and Silbergeld, 2002 except for inclusion criteria)<br>U.S.<br>1976-1992. | Cohort design.<br>3,592 white participants from the 1976-1980 NHANES II survey who had blood Pb measured at entry.<br>Mortality was followed through 1992 via NDI and SSADMF.<br>RRs were calculated for the various exposure groups compared to survey participants with the lowest exposure, adjusted for age and smoking. | Blood Pb (µg/dL) was measured by atomic absorption and used to classify subjects into exposure quartiles or groups above vs. below median exposure.<br>Median blood Pb 12 µg/dL. | RR (95% CI); number of deaths<br>Lung (above vs. below median):<br>Total cohort 1.5 (0.7, 2.9); 71<br>Male 1.2 (0.6, 2.5); 52<br>Female 2.5 (0.7, 8.4); 19<br><br>Stomach (above vs. below median):<br>Total cohort 2.4 (0.3, 19.1); 5<br>Male 3.1 (0.3, 37.4); 4<br>Female no deaths in referent group<br><br>All cancer: total cohort by quartile (age-adjusted) 1.0, 1.2, 1.3, 1.5 ($p = 0.16$ for trend).<br><br>Smoking was controlled for. Pb levels occurring in the general population were examined, not just those in workers with high occupational exposure potential. Exposure to other carcinogens were not examined. Potential for residual confounding by degree and duration of smoking exists (only controlled for never, former, current <1, current 1+ pack/day). Limited case numbers yield low statistical power for stomach or other cancers. |

## Table AX6-7.3 (cont'd). Key Studies of Lead Exposure and Cancer in the General Population

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **United States** | | | |
| Lustberg and Silbergeld (2002) (same cohort as Jemal et al., 2002 except for inclusion criteria)<br>U.S.<br>1976-1992. | Cohort design.<br>4,190 U.S. participants from the 1976-1980 NHANES II health and nutrition survey who had blood Pb measured at entry and whose levels fell below 30 µg/dL.<br>Mortality was followed through 1992 via NDI and SSADMF.<br>RRs were calculated for the various exposure groups compared to survey participants with the lowest exposure, adjusted for age, smoking and other factors. | Blood Pb (µg/dL) measured by atomic absorption was used to classify subjects into exposure groups:<br>Low: <10<br>Medium: 10-19<br>High: 20-19<br>Mean blood Pb 14 µg/dL. | RR (95% CI)<br>*All cancer, vs. low exposure:*<br>Medium 1.5 (0.9, 2.5)<br>High 1.7 (1.0, 2.8)<br><br>*Lung, vs. low exposure:*<br>Medium 1.7 (0.6, 4.8)<br>High 2.2 (0.8, 6.1)<br><br>*Non-lung, vs. low exposure:*<br>Medium 1.5 (0.8, 2.8)<br>High 1.5 (0.8, 2.8).<br><br>Significant upward trends noted for all-cause and for cardiovascular mortality with increasing Pb category.<br>Smoking was controlled for in the analysis. Pb levels occurring in the general population were examined, with individuals showing levels consistent with intense occupational exposure excluded, thus allowing exploration of potential effects outside of groups experiencing intense occupational exposure. Exposure to other carcinogens were not examined. Potential for residual confounding by degree and duration of smoking exists (only controlled for never, former, current <1, current 1+ pack/day). Limited case numbers yield low statistical power for stomach or other cancers. |

## Table AX6-7.4. Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **United States** | | | |
| Mallin et al. (1989)<br>Illinois<br>1979-1984 | Case-control design.<br>Cases: random sample of 10,013 deaths from 7 specific cancers, identified from death certificates for Illinois males between 1979 and 1984.<br>Controls: 3,198 randomly selected deaths from other causes.<br>Odds of exposure computed for glass workers vs. other occupations. | Exposure was based on occupations abstracted from death certificates.<br>No specific measure of Pb exposure; glass workers can be considered potentially exposed. | Brain cancer, white male glass workers:<br>OR = 3.0, $p < 0.05$<br>No significant associations for other cancer sites.<br>No control for smoking or other risk factors. Poor specificity for Pb exposure. |
| Cocco et al. (1998a)<br>U.S.<br>1984-1992 | Case-control design.<br>Cases: all 27,060 brain cancer deaths occurring among persons aged 35 or older during 1984-1992, from U.S. 24-state death certificate registry.<br>Controls: 4 gender-, race-, age-, and region-matched controls per case selected from deaths due to nonmalignant causes.<br>Subjects were subdivided into 4 groups by gender and race (white or African-American) for all analyses. | A job-exposure matrix was applied to death certificate-listed occupations to categorize persons as having low, medium, or high probability and intensity of exposure. | Risk of brain cancer mortality increased consistently with intensity of exposure among African-American males, but not other race-gender groups.<br><br>Probability of exposure alone was not consistently associated with risk.<br><br>In the high-probability group, risk increased with exposure intensity for all groups except African-American women (only 1 death in the high-probability group).<br><br>Exposure estimate was based solely on occupation listed on death certificate, hence there was substantial opportunity for misclassification. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Cocco et al. (1998b)<br>U.S.<br>1984-1992 | Case-control design.<br>Cases: all 28,416 CNS cancer deaths occurring among persons aged 35 or older during 1984-1992, from U.S. 4-state death certificate registry.<br>Controls: 4 gender-, race-, age-, and region-matched controls per case selected from deaths due to nonmalignant causes.<br>Subjects were subdivided into 4 groups by gender and race (white or African-American) for all analyses. | Death certificate listed industry and occupation was used to categorize decedents. No estimates of Pb exposure specifically. | OR (95% CI)<br>All occupations or industries with ORs above 1.0 and $p < 0.05$ in at least one race-gender group were reported<br>Newspaper printing and publishing industry:<br>White male 1.4 (1.1, 1.8)<br>Black male 3.1 (0.9, 10.9)<br><br>Typesetting and compositing:<br>White male 2.0 (1.1, 3.8)<br>White female 1.3 (0.4, 3.8)<br>Black female 4.2 (0.6, 30.7)<br><br>No deaths among black males.<br>Only two Pb exposure associated occupations or industries showed a statistically significant elevation of mortality. No specific measures of Pb exposure. Occupation based solely on death certificate, hence there was substantial opportunity for misclassification. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Cocco et al. (1999)<br>U.S.<br>1984-1996 | Case-control design.<br>Cases: all 41,957 stomach cancer deaths occurring among persons aged 35 or older during 1984-1996, from U.S. 24-state death certificate registry.<br>Controls: 2 gender-, race-, age-, and region-matched controls per case selected from deaths due to nonmalignant causes.<br>Subjects were subdivided into 4 groups by gender and race (white or African-American) for all analyses. | A job-exposure matrix was applied to death certificate-listed occupations to categorize persons as having low, medium, or high probability and intensity of exposure. | OR (95% CI)<br>Adjusted for age, ethnicity, marital status, urban residence, and socioeconomic status.<br><br>Elevated ORs:<br>White female, high probability of exposure 1.53 (1.10, 2.12)<br>Black male, high probability of exposure 1.15 (1.01, 1.32)<br>Black female, high probability of exposure 1.76 (0.74, 4.16)<br><br>Highly exposed group included 1,503 white and 453 black men and 65 white and 10 black women; no pattern of increase across exposure levels.<br><br>Intensity of exposure showed no association with stomach cancer except for black women:<br>Low 1.82 (1.04, 3.18)<br>Moderate 1.39<br>High 1.25<br><br>No control for other occupational exposures. Exposure estimate based on occupation listed on death certificate and hence subject to misclassification due to missing longest-held job. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Canada** | | | |
| Risch et al. (1988)<br>Canada<br>1979-1982 | Case-control design.<br>*Cases:* 826 Canadian men with histologically confirmed bladder cancer during 1979-1982.<br>*Controls:* 792 controls from Canadian population, matched on age, gender, and area.<br>Odds of exposure to Pb for cases vs. controls were computed, adjusted for smoking and other risk factors. | Subjects were interviewed regarding length of occupational exposure to Pb compounds, as well as 17 other substances. | OR (95% CI)<br>*61 men ever exposed to Pb (smoking-adjusted):*<br>2.0 (1.2, 3.5)<br>*Trend per 10 yrs duration of exposure:*<br>1.45 (1.09, 2.02)<br>No other substances showed significant associations with bladder cancer.<br>Controlled for smoking, marital status, socioeconomic status, education, ethnicity, and urban vs. rural residence.<br>No control for other occupational exposures. Low control interview rate (53%), which could result in biased control sample. |
| Siemiatycki et al. (1991)<br>Canada | Case-control design.<br>*Cases:* 3,730 various histologically confirmed cancers.<br>*Controls:* specific cancer types were compared with other cancers as a control group, excluding lung cancer.<br>Separate subgroup analysis was restricted to French Canadians. | Occupational exposure to 293 substances, including Pb, was estimated from interviews. Exposure was classified as "any"; a subgroup with "substantial" exposure also was identified. | OR (90% CI); number of cases<br>*Any exposure to Pb:*<br>Lung 1.1 (0.9, 1.4); 326<br>(French Canadians only)<br>Stomach 1.2 (1.0, 1.6); 126<br>Bladder 1.3 (1.0, 1.6); 155<br>(French Canadians only)<br>Kidney 1.2 (1.0, 1.6); 88<br>ORs rose in the "substantial" exposure subgroup for stomach and lung, but not for bladder or kidney cancer.<br>Controlled for smoking but not for other occupational exposures. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Sankila et al. (1990)<br>Finland<br>1941-1977 | Cohort design.<br>1,803 male and 1,946 female glass workers employed for at least 3 mos at one of 2 Finnish glass factories in 1953-1971 or 1941-1977.<br>Cancer incidence was compared with age-, gender-, and calendar-yr-specific national rates.<br>Stomach, lung, and skin cancer rates also were compared separately for 201 male and 34 female glassblowers and non-glassblowers. | No specific Pb exposure indices were computed. Analyses did examine glass workers as a whole and then glassblowers specifically, which comprised the group at highest risk for Pb exposure. | SIR (95% CI); number of cases<br>*Lung cancer, all glass workers:*<br>Male 1.3 (1.0, 1.7); 62<br>Female 1.1 (0.5, 2.3); 7<br>Lung cancer risk showed no specificity for glassblowers.<br><br>*Skin cancer, males and females combined:*<br>All workers 1.5 (0.8, 2.7); 11 (little difference between genders)<br>Glassblowers 6.2 (1.3, 18.3); 3<br><br>*Stomach cancer, males and females combined:*<br>Glassblowers 2.3 (0.9, 5.0); 6<br>No increase in other glass workers<br><br>No increase in cancers of other sites. No control for smoking or occupational coexposures. |
| Kauppinen et al. (1992)<br>Finland<br>1976-1981 | Case-control design.<br>*Cases:* 344 primary liver cancer deaths reported to the Finnish Cancer Registry in 1976-1978 or 1981.<br>*Controls:* registry-reported stomach cancer (476) or myocardial infarction (385) deaths in the same hospitals, frequency matched by age and gender. | Questionnaires regarding job history and personal habits were sent to the closest available relative.<br>U.K. based job-exposure matrix was used to rate potential exposure to 50 substances, including Pb compounds<br>Industrial hygienists also inspected histories to identify those with highly probable exposure and rate it as high, low, or moderate (<10 yrs high or 10+ yrs low exposure). | OR (95% CI)<br>*52 workers with potential Pb exposure*:<br>0.91 (0.65, 1.29)<br><br>*11 women with potential Pb exposure*:<br>1.84 (0.83, 4.06)<br><br>*5 men with probable moderate exposure:*<br>2.28 (0.68, 7.67)<br><br>None had high exposure and only 1 had low exposure, whereas 4 controls had high exposure.<br>Female controls appeared to underreport their job history.<br>Most controls had stomach cancer, which if caused by Pb would bias results toward the null. Few subjects were rated as having a high probability of exposure. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Wesseling et al. (2002)<br>Finland<br>1971-1995 | Cohort design, but at ecologic level.<br>413,877 Finnish women with occupation reported in 1970 linked to Finnish Cancer Registry to identify new cases of brain or nervous system cancer arising form 1971 to 1995.<br><br>Poisson regression was used to calculate SIRs for exposed vs. unexposed groups. | Reported occupation in 1970 was used to classify women into job titles. Potential exposure for each job title was estimated using a job matrix after excluding women in the highest social classes or in farming. Pb and 23 other workplace agents examined. Rates for each job title were calculated, and SIRs for low and medium/high exposure calculated (avg estimated blood Pb of 0.3 μmol/L served as cut point between low and medium/high exposure). | SIR (95% CI), unadjusted for other metals<br>Low exposure: 1.25 (0.68, 1.81)<br>Medium/high exposure: 1.33 (0.90, 1.96)<br>SIR (95% CI), adjusted for cadmium and nickel exposure<br>Low exposure: 1.18 (0.88, 1.59)<br>Medium/high exposure: 1.24 (0.77, 1.98)<br>All results were adjusted for birth cohort, period of diagnosis, and job turnover rate.<br><br>Incidence, exposure to Pb, and potential confounding factors were calculated at the level of job title rather than at the individual level. Exposure and other estimates were based on data for all workers pooled, not for women specifically. Job classification was based on a single yr, not lifetime job history. |
| Pesch et al. (2000)<br>Germany<br>1991-1995 | Case-control design.<br>*Cases:* 935 renal-cell cancer patients in five German areas.<br>*Controls:* 4,298 region, age, and gender-matched controls from the surrounding population.<br>ORs were adjusted for age, center, and smoking. | Job histories were used to categorize exposure to cadmium, Pb, and other potential as low vs. medium, high, or substantial. Separate exposure estimates were obtained from British and from German-derived job-exposure matrices. | OR (95% CI); number of cases<br>*Substantial Pb exposure based on British matrix:*<br>Male 1.5 (1.0, 2.3); 29<br>Female 2.6 (1.2, 5.5); 11<br><br>*Substantial Pb exposure based on British matrix:*<br>Male 1.3 (0.9, 2.0); 30<br>Female not reported<br>Analyses controlled for smoking. No control for exposure to other occupational agents. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Kandiloris et al. (1997)<br>Greece | Case-control design.<br>*Cases:* 26 patients with histologically confirmed laryngeal carcinoma and no history of Pb exposure or toxicity.<br>*Controls:* 53 patients with similar demographic profiles and no history of cancer from the same hospital. | Blood Pb levels and ALAD activity were measured. | Blood Pb levels were similar, but ALAD activity was significantly lower in cases than controls (Mean 50.79 U/L vs. 59.76 U/L, $p < 0.01$). No control for other risk factors. Potential distortion by effects of disease on Pb and/or ALAD parameters.) |
| Cordioli et al. (1987)<br>Italy<br>1953-1967 | Cohort design.<br>468 Italian glass workers employed for at least one yr between 1953 and 1967.<br>Mortality among workers was tracked and cause of death was determined for deceased workers. Standardized mortality ratios were computed for workers vs. national population counterparts. | Workers producing low-quality glass containers were classified as Pb-exposed. | SMR (95% CI); number of deaths<br>All cancer 1.3 (0.8, 1.8); 28<br>Lung 2.1 (1.1, 3.6); 13<br>Laryngeal 4.5 (1.2, 11.4); 4 |
| Cocco et al. (1994a)<br>(expansion of Carta et al., 1994).<br>Sardinia<br>1931-1992 | Cohort design.<br>1,741 male Sardinian Pb and zinc miners from two mines employed at least one yr between 1931 and 1971.<br>Mortality traced through 1992 to determine cause of death.<br>Mortality among miners was compared with age- and calendar-yr-specific regional rates to compute an SMR. | All miners were considered to be exposed to Pb. | SMR (95% CI); number of deaths<br>All cancer 0.94 (0.83, 1.05); 293<br>Prostate 1.21; 16<br>Bladder 1.15; 17<br>Kidney 1.28; 7<br>Nervous system 1.17; 8<br>Oral 0.61; 8<br>Lymphohemopoietic 0.91; 21<br>Digestive 0.83; 86<br>Peritoneum 3.67 (1.35, 7.98); 6<br>No other $p < 0.05$.<br>No control for smoking or exposure to silica, radon, or other exposures. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Cocco et al. (1994b)<br>Sardinia<br>1951-1988 | Cohort design.<br>526 female Sardinian Pb and zinc miners from the same mines as in Cocco et al. (1994a).<br>Mortality traced through 1992 to determine cause of death.<br>Mortality among miners was compared with age- and calendar-yr-specific regional rates to compute an SMR. | All miners were considered to be exposed to Pb. | SMR (95% CI)<br>Liver 5.02 (1.62, 11.70)<br>Lung 2.32 (0.85, 5.05)<br><br>Other cancers showed nonsignificantly reduced rates.<br>No control for smoking or exposure to silica, radon, or other exposures.<br>Low statistical power due to small population and paucity of cancers during follow-up. |
| Cocco et al. (1996)<br>Sardinia<br>1973-1992 | Cohort design.<br>1,222 male Sardinian Pb and zinc smelter workers whose G6PD phenotypes had been determined, employed any time from 1973-1990.<br>Mortality traced through 1992 to determine cause of death.<br>Mortality was compared with regional rates. | All workers were considered to be exposed to Pb.<br>Workers were subdivided into 6PD-normal and -deficient groups. | All cancer and lung cancer: mortality lower than expected<br>Stomach cancer: mortality higher than expected<br><br>G6PD deficiency had little apparent effect on mortality: cancer and all-cause mortality was slightly lower among G6PD-deficient workers than among G6PD-normal workers.<br>No control for smoking or exposure to other agents in the smelter.<br>Healthy worker bias-evident (all-cause mortality 31 observed vs. 44 expected), brief follow-up, low proportion of older ages (mean age at entry 30, avg follow-up less than 11 yrs), no cumulative exposure data. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Cocco et al. (1997)<br>Sardinia<br>1931-1992 | Cohort design.<br>1,388 male production and maintenance workers employed for at least 1 yr at a Sardinian Pb and zinc smelter between June of 1932 and July of 1971.<br>Mortality was followed up through 1992.<br>Mortality was compared with age- and calendar-yr-specific regional rates.<br>Since regional rates were only available for 1965 and later, analyses were limited to this period. | All workers were considered to be exposed to Pb. | SMRs vs. regional rates (95% CI); number of deaths<br>Lung 0.82 (0.56, 1.16); 31<br>Stomach 0.97 (0.53, 1.62); 14<br>All cancers 0.93 (0.78, 1.10); 132<br>Kidney 1.75 (0.48, 4.49); 4<br>Bladder 1.45 (0.75, 2.53); 12<br>Brain 2.17 (0.57, 5.57); 4<br><br>Kidney cancer showed a significant trend toward increasing risk with increasing duration of exposure<br>No significant trends were noted for lung or other cancers<br>Brain cancer excess was limited to workers employed for 10 yrs or less.<br>No control for smoking or exposure to arsenic or other smelter-related exposures. No data on intensity of exposure.<br>Strong association of smelter work with pneumoconiosis and other respiratory disease (SMR = 4.47, 95% CI: 3.37, 5.80); since this outcome includes silicosis, which is thought to predispose individuals to lung cancer, some lung cancer deaths may have been missed due to misclassification of cause of death based on death certificates. |
| Wingren and Axelson (1987, 1993) (update of Wingren and Axelson, 1985, same basic cohort as in Wingren and Englander (1990)<br>Sweden<br>1950-1982 | Case-control design.<br>*Source population:* 5,498 men aged 45 or older in 11 Swedish parishes, including 887 glass workers.<br>Cancer-specific nested case-control analysis:<br>*Cases:* deaths due to stomach, colon, and lung cancer from 1950-1982<br>*Controls:* deaths due to causes other than cancer or cardiovascular disease | Glass workers were considered exposed.<br>Glassblowers also singled out as workers with higher exposure potential.<br>Job history applied to job matrix to categorize occupations as low, moderate, or high Pb exposure. | OR (90% CI); number of deaths<br>*All glass workers:*<br>Lung 1.7 (1.1, 2.5); 86<br>Stomach 1.5 (1.1, 2.0); 206<br>Colon 1.6 (1.0, 2.5); 79<br><br>*Glassblowers:*<br>Lung 2.3<br>Stomach 2.6<br>Colon 3.1<br><br>Glassblowers singled out from glass workers as a whole thus showed higher estimated risk. ORs for high or moderate vs. low exposure showed no consistent increase for lung or stomach cancer, however, although they did show mild upward trend for colon cancer.<br>No control for smoking or other occupational exposures. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Wingren and Englander (1990)<br>Sweden<br>1964-1985<br>(same population as in case-control analyses of Wingren and Axelson 1985, 1987, 1993) | Cohort design.<br>625 Swedish glass workers employed for at least 1 mo between 1964 and 1985.<br>Mortality was compared with national rates. | Workers from areas with airborne Pb levels up to 0.110 $mg/m^3$ were classified as exposed. | SMR (95% CI)<br>*Pharyngeal:* 9.9 (1.2, 36.1)<br>*Lung:* 1.4 (0.5, 3.1)<br>*Colon*: nonsignificant |
| Dingwall-Fordyce and Lane (1963)<br>U.K.<br>1925-1962 | Cohort design.<br>425 male employees drawing pensions from U.K. battery plants.<br>Standardized mortality for employees vs. national population counterparts. | Battery plant workers were assumed to be exposed, and their mortality compared to that of like age and gender in the U.K. population as a whole. Urinary Pb excretion was also used to categorize workers by estimated exposure (none, light, or heavy): 80 lightly and 187 heavily (at least 100 μg/L) exposed. | SMR (95% CI); number observed deaths<br>All cancer: 1.2 (0.8, 1.7); 267<br><br>No consistent increase in SMRs across categories of increasing Pb exposure.<br><br>Limitations: No cancer site-specific analyses. No control for potential confounders including smoking and exposure to arsenic or other metals. |
| Malcolm and Barnett (1982) (follow-up of Dingwall-Fordyce and Lane, 1963)<br>U.K.<br>1925-1976 | Cohort design.<br>1,898 Pb-acid battery workers.<br>Mortality was traced for the Pb-acid battery workers to determine cause of death. The proportion of deaths due to cancer (all types and major subcategories) among the worker population was compared to that seen in corresponding members of the general population, yielding a PMR. | Job histories were reviewed to classify workers' Pb exposure as high, medium, or none. | Proportionate mortality ratio (PMR)<br>*All cancers:*<br>1.15 (136 deaths), $p > 0.05$<br><br>By exposure:<br>None 1.02<br>Medium 1.06<br>High 1.30<br><br>No significant excesses for individual cancer sites except for digestive cancer PMR of 1.67, $p < 0.01$, among nonexposed workers.<br><br>The difference in exposure for the high and medium exposure groups narrowed greatly over the follow-up, thus complicating interpretation of dose-response patterns. No control for smoking or occupational exposure to other carcinogens. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Ades and Kazantzis (1988)<br>U.K.<br>1943-1982 | Cohort design.<br>4,393 male zinc, Pb, and cadmium smelter workers.<br>(Workers born after 1939 or who had worked less than one yr at the facility were excluded.)<br>Workers followed up for mortality.<br>Nested case-control analysis also conducted to quantitatively assessed cadmium and, secondarily, arsenic, Pb, and other metal exposures among 174 cases. | Job histories were used to quantify cadmium exposure and assign ordinal ranks for exposure to Pb and other metals.<br><br>Standardized lung cancer mortality ratio computed for workers vs. national rates. | SMR (95% CI); number of deaths<br>*Cohort:*<br>Lung 1.25 (1.07, 1.44); 174<br>Increased significantly with duration of employment.<br><br>Nested case-control analyses did not implicate any department or process, nor did cadmium, zinc, sulfur dioxide, or dust exposure account for the observed increase.<br>Cumulative exposure to Pb and to arsenic both showed positive associations with lung cancer, but the relative importance of these two exposures could not be determined.<br>Cadmium exposure did not account for the elevated SMR, but analyses could not control for exposure, and were not adjusted for smoking. |
| **Asia** | | | |
| Hu et al. (1998)<br>China<br>1989-1996 | Case-control design.<br>*Cases:* 218 patients with histologically-confirmed primary gliomas occurring during 1989-1996 at 6 Chinese hospitals.<br>*Controls:* 436 patients with non-neurological, nonmalignant disease, matched by age, gender, and residence from the same hospitals (excluding one cancer-only center). | Patients were interviewed, and those with factory or farm occupations were further interviewed to identify exposure to Pb (or other potentially toxic substances). | *Occupational exposure to Pb*:<br>Not reported for any glioma patients, but was reported for 4 controls.<br>No control for exposure to other occupational or environmental agents. |

## Table AX6-7.4 (cont'd). Other Studies of Lead Exposure and Cancer

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings and Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Hu et al. (1999)<br>China<br>1989-1996 | Case-control design.<br>*Cases:* 383 patients with histologically confirmed primary meningiomas occurring during 1989-1996 at 6 Chinese hospitals.<br>*Controls:* 366 patients with non-neurological, nonmalignant disease matched by age, gender, and residence from the same hospitals (excluding one cancer-only center). | Patients were interviewed, and those with factory or farm occupations were further interviewed to identify exposure to Pb (or other potentially toxic substances). | OR (95% CI); number of cases<br>*Occupational exposure to Pb:*<br>Male: 7.20 (1.00, 51.72); 6<br>Female: 5.69 (1.39, 23.39); 10<br><br>Results were adjusted for income, education, and fruit and vegetable intake, plus cigarette pack-yrs for the women. No control for exposure to additional metals or other occupational exposures. |
| Shukla et al. (1998)<br>India<br>1995-1996 | Case-control design.<br>*Cases:* 38 patients with newly diagnosed, histologically confirmed gall bladder cancer cases assembled from a surgical unit.<br>*Controls:* 58 patients with gall stones diagnosed at the same surgical unit, matched on geographic area.<br>Mean bile Pb content was compared between cases and controls. | Heavy metal content was measured in bile drawn from the gall bladder at time of surgery. | *Bile Pb content: mean (SE)*<br>Gall bladder cancer: 58.38 mg/L (1.76)<br>Gallstones: 3.99 mg/L (0.43)<br><br>Cadmium and chromium levels also were elevated in cancer patients, but less than Pb. No control for smoking or any other risk factors. |

# ANNEX TABLES AX6-8

## Table AX6-8.1. Effects of Lead on Immune Function in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Joseph et al. (2005)<br>SE Michigan<br>(1994-1998) | Design: prospective (1 yr following 3-yr baseline recruitment)<br>Subjects: children (n = 4634), age range 0.4–3.0 yr<br>Outcome measures: asthma prevalence and incidence.<br>Analysis: multivariate proportional hazard model (Cox) | Blood Pb (µg/dL) mean (SD, median, % >10):<br>5.5 (4.0, 4.0, 8.6%) | Covariate-adjusted hazards ratio (HR, asthma incidence <5 µg/dL compared to ∃5 or ∃10 µg /dL):<br>Caucasian: ∃5 µg/dL, 1.4 (95% CI: 0.7, 2.9)<br>∃10 µg/dL, 1.1 (95% CI: 0.2, 8.4)<br>African American: ∃5 µg/dL, 1.0 (95% CI: 0.8, 1.3)<br>∃10 µg/dL, 0.9 (95% CI: 0.5, 1.4)<br><br>HR for asthma incidence in African Americans, compared to Caucasians (<5 µg/dL):<br><5 µg/dL: 1.6 (95% CI: 1.4, 2.0)<br>∃5 µg/dL: 1.4 (95% CI: 1.2, 1.6)<br>∃10 µg/dL: 2.1 (95% CI: 1.2, 3.6)<br><br>Covariates included: avg annual income, birth weight, and gender. |
| Sarasua et al. (2000)<br>ATSDR Multi-site Study: Granite City, IL, Galena, KA; Joplin, MO; Palmerton, PA<br>1991 | Design: cross-sectional<br>Subjects: children and adults (n = 2036)<br>Outcome measures: total lymphocyte count, lymphocyte phenotype abundance, serum IgA, IgG, and IgM.<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) mean (SD, 5th–95th %):<br>6–35 mo: 7.0<br>(16, 1.1–16.1)<br>36–71 mo: 6.0<br>(4.3, 1.6–14.1)<br>6–15 yr: 4.0<br>(2.8,1.1–9.2)<br>16–75 yr: 4.3<br>(2.9, 1.0–9.9) | Significant association ($p < 0.05$) between increasing blood Pb and increasing serum IgA, IgG, IgM, and B-cell abundance (%, number), and decreasing T-cell abundance (%) in 6–35 mo age category; adjusted for age, sex, and study site. Comparison of outcome means across blood Pb quartiles (1st quartile as reference, [+], higher, [−] lower): [+] lymphocyte count (4th quartile, $p = 0.02$), T-cell count (4th quartile, $p = 0.09$), B-cell count (4th quartile, $p < 0.01$), B-cell % (4th quartile, $p = 0.09$). |
| Rabinowtiz et al. (1990)<br>Boston, MA<br>1979–1987 | Design: cross-sectional<br>Subjects: infants/children (n = 1768)<br>Outcome measures: incidence of illness in children was solicited from parents by questionnaire.<br>Analysis: relative risk of illness estimated from incidence ratios, highest: combined lower blood Pb deciles, without adjustment for covariates or confounders. | Cord blood Pb (µg/dL) ~90th %: 10<br>Shed tooth Pb (µg/g) ~90th %: 5 | Relative risk (unadjusted) was elevated for the following illness categories: severe incidence of ear infection, 1.2 (95% CI: 1.0, 1.4), other respiratory illness, 1.5 (95% CI: 1.0, 2.3), school absence for illness other than cold or flu, 1.3 (95% CI: 1.0, 1.5). |

## Table AX6-8.1 (cont'd). Effects of Lead on Immune Function in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Lutz et al. (1999)<br>Springfield-Green Co, MO<br>NR | Design: cross-sectional<br>Subjects: children (n = 279; age range 9 mo–6 yr)<br>Outcome measures: differential blood cell counts; lymphocyte phenotype abundance (%); and serum IL-4, soluble CD25, CD27, IgE and IgG (Rubella).<br>Analysis: nonparametric comparison of outcome measures (adjusted for age) for blood Pb categories, correlation | Blood Pb (µg/dL) range: 1–45<br>Blood Pb categories: <10 µg/dL, 10–14 µg/dL, 15–19 µg/dL, 20–45 µg/dL | Significant association ($p < 0.05$) between increasing blood Pb (categorical) and increasing serum IgE levels, after adjusting for age. |
| **Europe** | | | |
| Annesi-Maesano et al. (2003)<br>France<br>1985, 1992 | Design: cross-sectional<br>Subjects: mother/newborn pairs (n = 374), mean age 30 yr<br>Outcome measures: maternal venous and newborn cord serum IgE levels<br>Analysis: multivariate linear regression, ANOVA | Blood Pb (µg/dL) mean (SD):<br>Infant cord: 67.3 (47.8)<br>Maternal: 96.4 (57.7)<br><br>Hair Pb (ppm) mean (SD):<br>Infant: 1.38 (1.26)<br>Maternal: 5.16 (6.08) | Significant ($p < 0.0001$) association between increasing infant hair Pb and infant cord serum IgE levels.<br>Although medical histories were taken to identify potential IgE risk factors (asthma, allergies) and "confounders" (e.g., smoking), these do not appear to have been quantitatively integrated into the regression models. Allergy status and blood levels were reportedly unrelated to load biomarkers or serum IgE (basis for conclusion not reported). |
| Karmaus et al. (2005)<br>Germany<br>1994–1997 | Design: cross-sectional<br>Subjects: children (n = 331, 57% male), age 7–8 yrs (96%), 9–10 yrs (4%)<br>Outcome measures: differential blood cell count; lymphocyte phenotype abundance; and serum IgA, IgE, IgG, IgM<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) mean (95% CI):<br>Males: 2.5 (1.1, 4.4)<br>Females (2.8 (1.5, 4.8)<br><br>Blood Pb quartile ranges:<br><2.2 (n = 82)<br>2.2–2.8 (n = 81)<br>2.8–3.4 (n = 86)<br>>3.4 (n = 82) | Significant association between blood Pb ($p < 0.05$) and serum IgE (not monotonic with quartile range). Comparison of adjusted mean outcomes (p#0.05) across blood Pb quartiles (1st quartile as reference, [+], higher, [−] lower): [−] $CD3^+$ T-cells (2nd quartile), [−] $C3^+CD8^+$ T-cells (2nd quartile), [+] $C3^+CD5^+CD19^+$ B-cells (2nd quartile).<br>Covariates retained: age, sex, environmental exposure to tobacco smoke, infections (in last 12 mo), serum cholesterol, and triglycerides. |

## Table AX6-8.1 (cont'd). Effects of Lead on Immune Function in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Reigart and Graber (1976)<br>NR<br>NR | Design: clinical<br>Subjects: children (n = 19), ages 4–6 yrs<br>Outcome measures: serum IgA, IgG, IgM, total complement and C-3, before and after immunization with tetanus toxoid<br>Analysis: none; presentation of prevalence of clinically low, normal, and high values of outcome measures | Blood Pb (µg/dL) mean (range):<br>High: >40 (n = 12): 45.3 (41–51)<br>Low: #30 (n = 7): 22.6 (14–30) | No apparent difference in prevalence of abnormal values for serum immunoglobulin or complement (no statistical analysis applied). |
| Wagnerova et al. (1986)<br>Czech<br>NR | Design: longitudinal cohort (repeated measures for 2-yrs)<br>Subjects: children (n = 92, 38 females) ages 11–13 yrs residing near a smelter; reference group (n = 67, 36 females), ages 11–13 yrs<br>Outcome measures: serum IgA, IgE, IgG, IgM<br>Analysis: comparison of outcome measures and between exposed and reference groups, stratified sex and season of sampling | Blood Pb (µg/dL) mean:<br>Pb: ~23–42<br>Reference: ~5–22 | Significant (p NR, statistic NR) lower serum IgE and IgM levels in exposed group compared to reference group. |
| **Latin America** | | | |
| Pineda-Zavaleta et al. (2004)<br>Mexico<br>NR | Design: cross-sectional<br>Subjects: children (n = 30 female, 35 male) ages 6–11 yrs, residing near smelter<br>Outcome measures: mitogen- (PHA) and cytokine- (IFN-() induced nitric oxide and superoxide production in lymphocytes<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) mean (range) for 3 schools:<br>1 (n = 21): 7.0 (3.5–25.3)<br>2 (n = 21): 20.6 (10.8–49.2)<br>3 (n = 23): 30.4 (10.3–47.5) | Significant (p = 0.036) association between increasing blood Pb concentration and covariate adjusted decreasing nitric oxide production in PHA-activated lymphocytes (∃ = −0.00089 [95% CI: −0.0017, −0.00005]).<br>Significant (p = 0.034) association between increasing blood Pb concentration and covariate adjusted increasing super oxide production in IFN-(-activated lymphocytes (∃ = −0.00389 [95% CI: 0.00031, 0.00748]). Covariates considered included age, sex, allergies, and blood arsenic (age, sex, and blood arsenic were retained).<br>Significant effect of sex on associations, significant blood Pb-arsenic interaction.<br>Covariates considered included age, sex, allergies, urinary arsenic (age, sex, and urinary arsenic were retained). |

## Table AX6-8.1 (cont'd). Effects of Lead on Immune Function in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** | | | |
| Sun et al. (2003); Zhao et al. (2004)<br>China<br>NR | Design: cross-sectional<br>Subjects: children (n = 73) age 3–6 yrs<br>Outcome measures: serum IgE, IgG, IgM; lymphocyte phenotype abundance<br>Analysis: Nonparametric comparisons of outcome measures stratified by blood Pb | Blood Pb (µg/dL) mean (SD, range) (n = 217): 9.5 (5.6, 2.6–43.7) | Females: significantly higher ($p < 0.05$) IgE levels in high blood Pb category (∃10 µg/dL, n = 16) compared to low category (<10 µg/dL, n = 17), and significantly lower IgG and IgM levels. A multivariate analysis of association between blood Pb and IgE was noted but not described in sufficient detail to evaluate.<br>All children: significantly lower ($p < 0.05$) $CD3^+CD4^+$ (%), $CD3^+CD8^+$ (%), $CD4^+CD8^+$ (%) in high blood Pb (∃10 µg/dL, n = 38) compared to low blood Pb (10 µg/dL, n = 35) group. |

## Table AX6-8.2. Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Pinkerton et al. (1998)<br>U.S.<br>NR | Design: cross-sectional cohort<br>Subjects: adult male smelter workers (n = 145, mean age 32.9∀8.6); reference group, male hardware workers (n = 84, mean age 30.1∀9.3)<br>Outcome measures: differential blood cell counts; lymphocyte phenotype abundance; serum IgA, IgG, IgM; salivary IgA; lymphocyte proliferation (tetanus toxoid)<br>Analysis: multivariate logistic regression with comparison of adjusted outcome measures between exposed and nonexposed groups | Blood Pb (µg/dL) median (range)<br>Pb: 39 (15–55)<br>Reference: <2 (<2–12) | Covariate-adjusted outcomes in Pb workers that were significantly ($p < 0.05$) different from nonexposed ([+], higher, [−] lower): [−] % monocytes, [−] % $CD4^+CD8^+$ cells, [−] % $CD8^+CD56^+$ cells.<br>Significant ($p < 0.05$) adjusted regression coefficients in exposed group for independent variable:<br>blood Pb: [+] $CD19^+$ B-cells (%, no)<br>time-integrated blood Pb: [−] serum IgG, [+] $CD4^+CD45RA^+$ cells (%, number)<br>Covariates considered in the analysis included age, race, smoking habits, alcohol consumption, marijuana use, work shift, and various factors that might stimulate or suppress the immune system (e.g., exposure to direct sunlight, sleep hrs, allergy, flu or cold symptoms).<br>Covariates retained in the final model were age, race, work shift, smoking habits. |
| Sarasua et al. (2000)<br>ATSDR Multi-site Study: Granite City, IL, Galena, KA; Joplin, MO; Palmerton, PA<br>1991 | Design: cross-sectional cohort<br>Subjects: children and adults (n = 2036)<br>Outcome measures: total lymphocyte count, lymphocyte phenotype abundance, serum IgA, IgG, and IgM<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) mean (SD, 5th–95th %):<br>6–35 mo: 7.0 (16, 1.1–16.1)<br>36–71 mo: 6.0 (4.3, 1.6–14.1)<br>6–15 yr: 4.0 (2.8,1.1–9.2)<br>16–75 yr: 4.3 (2.9, 1.0–9.9) | No significant association ($p < 0.05$) between blood Pb and outcomes in adults (age ∃16 yr).<br>Covariates retained: age, sex, cigarette smoking, and study site. |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Fischbein et al. (1993)<br>New York<br>NR | Design: cross-sectional cohort<br>Subjects: adult firearms instructors (n = 51), mean age 48 yr; age-matched reference subjects (n = 36).<br>Outcome measures: lymphocyte phenotype abundance, lymphocyte proliferation (PHA, PWM, *Staph. aureus*)<br>Analysis: comparison of outcome measures between reference and blood Pb categories; multivariate linear regression | Blood Pb (µg/dL) mean (SD)<br>Pb high (∃25): 31.4 (4.3)<br>Pb low (<25): 14.6 (4.6)<br>Reference: <10 | Outcomes in Pb workers that were significantly ($p < 0.05$) different from reference group ([+], higher, [−] lower):<br>[−] $CD^{+}_{3}$ cells (%, number), [−] $CD4^{+}$ cells (%, number), [−] $CD4^{+}CD8^{+}$ cells (number), [−] HLA-DR cells (number), [+] $CD20^{+}$ cells (%, number), [−] mitogen (PHA)-induced lymphocyte proliferation, [−] mitogen (PWM)-induced lymphocyte proliferation; [−] lymphocyte response in mixed-lymphocyte culture. No effect on antigen (*Staph. aureus*)-induced lymphocyte proliferation.<br>Significant ($p < 0.05$) association between increasing blood Pb and decreasing abundance of $CD4^{+}$ phenotypes (%), and decreasing lymphocyte proliferative response in mixed lymphocyte cultures.<br>Covariates retained: age, sex, smoking habits, and duration of exposure. |
| **Europe** | | | |
| Bergeret et al. (1990)<br>France<br>NR | Design: cross-sectional cohort<br>Subjects: adult battery smelting workers (n = 34), mean age 40 yr; reference subjects (n = 34), matched for age, sex, ethnic origin, smoking and alcohol consumption habits, intake of antibiotics, and NSAIDs<br>Outcome measures: PMN chemotaxis (FMLP); PMN phagocytosis (opsonized zymosan)<br>Analysis: comparison of outcome measures between worker and reference groups | Blood Pb (µg/dL) mean (SD):<br>Pb: 70.6 (18)<br>Reference: 9.0 (4.3) | Significantly ($p < 0.05$) lower PMN chemotactic response (index) and phagocytic response in Pb workers. |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Ewers et al. (1982)<br>Germany<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture or smelter workers (n = 72), mean age 36.4 yr (16–58); reference workers (n = 53), mean age 34.8 yr (21–54)<br>Outcome measures: serum IgA, IgG, IgM, C3; saliva IgA<br>Analysis: parametric and nonparametric comparison of outcome measures between Pb workers and reference subjects; linear regression | Blood Pb (µg/dL) mean (range):<br>Pb: 55.4.0 (18.6–85.2)<br>Reference: 12.0 (6.6–20.8) | Significantly ($p < 0.05$) lower serum IgM, lower salivary IgA in Pb workers compared to reference group. |
| Coscia et al. (1987)<br>Italy<br>NR | Design: cross-sectional cohort<br>Subjects: adult Pb workers (n = 32, 2 female), mean age 42.8 yr (SD 11.5); reference subjects (n = 25), mean age 38.6 yr (SD 13.3)<br>Outcome measures: serum IgA, IgG, IgM, C3-C4; lymphocyte phenotype abundance<br>Analysis: parametric comparison of outcome measures between worker and reference groups | Blood Pb (µg/dL) mean (SD):<br>Pb: 62.3 (21.6)<br>Reference: NR | Outcomes in Pb workers that were significantly ($p < 0.05$) different from reference group ([+], higher, [−] lower): [−] serum IgM, [+] serum C4, [+] lymphocyte abundance (%), [−] T-cell abundance (%, number, E-rosette forming cells), [+] B-cell abundance (%,number, immunoglobulin-bearing cells), [+] $CD8^+$ cell abundance (number). |
| Governa et al. (1987)<br>Italy<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 9), mean age 38.4 yr (SD 13.7); age-matched reference subjects (n = 18)<br>Outcome measures: PMN chemotaxis (zymosan-activated serum)<br>Analysis: parametric comparison of outcome measures between worker and reference groups, correlation | Blood Pb (µg/dL) mean (SD):<br>Pb: 63.2 (8.2)<br>Reference: 19.2 (6.4) | Significantly ($p < 0.05$) lower PMN chemotactic response to zymosan activated serum. Effect magnitude was not correlated with blood Pb. |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Valentino et al. (1991)<br>Italy<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb scrap refining workers (n = 10), mean age 41.1 yr (SD 7.3, range 28–54); age-matched reference subjects (n = 10)<br>Outcome measures: PMN chemotaxis (C5 or FMLP) and phagocytosis (FMLP)<br>Analysis: comparison of outcome measures between worker and reference groups, correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 33.2 (5.6, 25–42)<br>Reference: 12.6 (2.5, 8.9–18) | Significantly ($p < 0.002$) lower PMN chemotactic response to C5 or FMLP and higher stimulated production of LT (leukotriene)B4 in Pb workers compared to reference group. Effect magnitude correlated with blood Pb. No effect on phagocytic activity. |
| Kimber et al. (1986)<br>UK<br>NR | Design: cross-sectional cohort<br>Subjects: adult male TEL manufacture workers (n = 39) mean age: 45.1 yr; and age-matched reference subjects (n = 21); mean age 32.2 yr<br>Outcome measures: serum IgA, IgG, IgM; mitogen (PHA)-induced lymphoblastogenesis; and NK cell cytotoxicity<br>Analysis: comparison of outcome measures for exposed and reference groups | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 38.4 (5.6, 25–53)<br>Reference: 11.8 (2.2, 8–17) | No significant ($p < 0.05$) differences in outcomes between exposed and reference groups. |
| **Latin America** | | | |
| Queiroz et al. (1993)<br>Brazil<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 39), mean age 33.9 yr (SD 12.1, range 18–56); reference subjects (n = 39) matched by age and race<br>Outcome measures: PMN chemotaxis (endotoxin LPS); phagocytic (endotoxin LPS) respiratory burst activity (NBT reduction)<br>Analysis: nonparametric comparison of outcome measures between worker and reference groups | Blood Pb (µg/dL) range:<br>Pb: 14.8–91.4 (>30, n = 52)<br>Reference: <10 | Significantly ($p < 0.001$) lower chemotactic activity of PMNs, and lower phagocytic respiratory burst, in Pb workers relative to reference group. |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** (cont'd) | | | |
| Queiroz et al. (1994a)<br>Brazil<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 60), mean age 33.9 yr (range 18–56); reference subjects (n = 49) matched by age and race<br>Outcome measures: PMN phagocytic/lytic activity (opsonized yeast)<br>Analysis: nonparametric comparison of outcome measures between worker and reference groups | Blood Pb (µg/dL) range:<br>Pb: 14.8–91.4 (>30, n = 27)<br>Reference: <10 | Significantly ($p < 0.001$) lower lytic activity of PMNs in Pb workers relative to reference group. |
| Queiroz et al. (1994b)<br>Brazil<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 33), mean age 32.4 yr (range 18–56); reference subjects (n = 20) matched by age and race<br>Outcome measures: serum IgA, IgG, IgM; mitogen (PHA)-induced lymphocyte proliferation<br>Analysis: parametric comparison of outcome measures between worker and reference groups | Blood Pb (µg/dL) range:<br>Pb: 12.0–80.0 (>30, n = 27)<br>Reference: <10 | No significant difference in outcomes ($p <$ NR; SD of Pb worker and reference groups overlap) between Pb workers and reference group. |
| **Asia** | | | |
| Kuo et al. (2001)<br>China<br>NR | Design: cross-sectional cohort<br>Subjects: adult battery manufacture workers (n = 64, 21 female) 14 subject aged <40 yr and 14 subjects aged >50 yr; nonexposed reference subjects (n = 34, 17 female).<br>Outcome measures: differential blood cell counts, lymphocyte phenotype abundance<br>Analysis: comparison of outcome measures in exposed and reference groups, multivariate linear regression | Blood Pb (µg/dL) mean:<br>Pb: 30 | Significantly ($p < 0.05$) adjusted mean higher monocytes (%, number), lower B cells (%), lower lymphocytes (number), and lower granulocytes (number) in Pb workers compared to controls.<br>Covariates retained: age, gender, and disease status (definition not reported). |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Mishra et al. (2003)<br>India<br>NR | Design: cross-sectional cohort<br>Subjects: adult males occupationally exposed to Pb (n = 84), mean age 30 yr; reference subjects (n = 30), mean age 29 yr<br>Outcome measures: serum IFN-( level, mitogen (PHA)-induced lymphocyte proliferation, NK cell cytotoxicity<br>Analysis: comparison of outcome measures between Pb-exposed and reference groups, correlation | Blood Pb (µg/dL) mean (SD, range):<br>3-wheel drivers (n = 30): 6.5 (4.7, 0.0–17.5)<br>Battery workers (n = 34): 128.1 (13.2–400.8)<br>Jewelry makers: 17.8 (18.5, 3.1–76.8)<br>Reference: 4.5 (NR, 1.6–9.8) | Significantly ($p < 0.001$) lower lymphocyte proliferative response to PHA in Pb-exposed groups compared to reference groups, higher IFN-( production by blood monocytes. |
| Alomran and Shleamoon (1988)<br>Iraq<br>NR | Design: cross-sectional cohort<br>Subjects: adult Pb (oxide) workers (n = 39), mean age 35.6 yr (9,2, SD); age-matched reference subjects (n = 19)<br>Outcome measures: serum IgA, IgG; mitogen (PHA, Con-A)-induced lymphocyte proliferation<br>Analysis: comparison of outcome measures between Pb workers and reference group | Blood Pb (µg/dL) mean:<br>Pb: 54–64<br>Reference: NR | Significantly ($p < 0.05$) lower lymphocyte proliferative response to PHA or Con A in Pb workers, compared to reference group. |
| Cohen et al. (1989)<br>Israel<br>NR | Design: cross-sectional cohort<br>Subjects: adult male occupationally Pb exposed (n = 10), age range 22–70; age-matched reference subjects (n = 10)<br>Outcome measures: mitogen (Con A, PHA)-induced-lymphocyte proliferation and T-suppressor cell proliferation; lymphocyte phenotype abundance<br>Analysis: parametric comparison of outcome means between Pb-exposed and reference groups | Blood Pb (µg/dL) range:<br>Exposed: 40–51<br>Reference: <19 | Significantly ($p < 0.02$) higher mitogen (Con-A)-induced suppressor cell activity. No significant (p not reported) effects on abundance of T-cells (E-rosette-forming cells), $OKT^{+}_{4}$, $OKT^{+}_{8}$, or $OKT4^{+}/T8^{+}$ ratio; mitogen (Con A or PHA)-induced lymphocyte proliferation. |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Sata et al. (1998)<br>Japan<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb stearate manufacture workers (n = 71), mean age 48 yr (range 24–74); reference subjects (n = 28), mean age 55 yr (range 33–67).<br>Outcome measures: lymphocyte phenotype abundance<br>Analysis: comparison of outcome measures in exposed and reference groups (ANCOVA), multivariate linear regression | Blood Pb (µg/dL) mean (range):<br>Pb: 19 (7–50)<br>Reference: NR | Pb workers vs. reference: significantly ($p < 0.05$) covariate-adjusted lower $CD3^+CD45RO^+$ (number) and higher $CD8^+$ cells (%).<br>Significant ($p < 0.05$) association between exposure (categorical: yes/no) and lower $CD3^+CD45RO^+$cells (number).<br>Covariates retained: age and cigarette smoking habits. |
| Sata et al. (1997)<br>Japan<br>NR | Design: clinical<br>Subjects: adult male Pb smelter workers (n = 2) who underwent CaEDTA therapy<br>Outcome measures: serum IgA, IgG, IgD, IgM; lymphocyte phenotype abundance<br>Analysis: Parametric comparison of outcome measures before and after treatment, correlation of outcome means with blood Pb | Blood Pb (µg/dL):<br><br>Subject 1: 81 µg/dL at referral; mean before EDTA: 45.1 (SD 16.0); after chelation: 31.0 (9.8)<br><br>Subject 2: 68 µg/dL at referral; mean before EDTA: 43.3 (SD 14.1); after chelation: 33.7 (7.2) | Blood Pb and outcome measures were sampled prior to and 24 hrs after 3 CaEDTA treatments (on consecutive days) per wk for 10 wks. Comparison of mean outcome measures assessed before and after treatments showed significantly ($p < 0.05$) higher IgA, IgG, and IgM; and significantly higher $CD8^+$ T-cells and $CD57^+$ NK cells after treatment in subject 1. Serum IgG levels in subject 1 were significantly correlated ($r = -0.72$) with blood Pb concentration. |
| Heo et al. (2004)<br>Korea<br>NR | Design: cross-sectional cohort<br>Subjects: adults, battery manufacture workers (n = 606; 52 females); ages: <30 yr, n = 184; >40 yr, n = 123.<br>Outcome measures: serum IgE, IL-4, IFN(<br>Analysis: comparison of outcomes measures (ANOVA), stratified by age and blood Pb | Blood Pb (µg/dL) mean (SD):<br><30 yr: 22.0 (10.4)<br>30–39 yr: 23.0 (11.3)<br>∃40 yr: 24.1 (9.3) | Significantly higher ($p < 0.05$) serum IgE levels in blood Pb category (∃30 µg/dL) compared to low categories (<10 or 10–29 µg/dL). |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Ünde er et al. (1996); Ba∏aran and Ünde er (2000)<br>Turkey<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 25), mean age, 33 yr (22–55); reference subjects (n = 25) mean age 33 yr (22–56).<br>Outcome measures: differential blood cell counts; lymphocyte phenotype abundance; serum IgA, IgG, IgM, C3, and C4; neutrophil chemotaxis (zymosan-activated serum); latex particle-induced neutrophil phagocytic (latex particles) respiratory burst (NBT reduction)<br>Analysis: nonparametric and parametric comparisons of outcome measures for exposed and reference groups | Blood Pb (µg/dL) mean (SD):<br>Pb: 74.8 (17.8)<br>Reference: 16.7 (5.0) | Workers relative to reference: significantly ($p < 0.05$) lower serum IgG, IgM, C3, and C4 levels; lower $CD4^+$ ("T-helper") abundance, lower neutrophil chemotactic response; no significant difference in $CD20^+$ (B-cell) , $CD8^+$ ("T-suppressor") cell, $CD56^+$ (NK) cell abundance, or particle-induced NK cell respiratory burst. |
| Yücesoy et al. (1997a)<br>Turkey<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 20), ages 39–48 yr; age-matched reference subjects (n = 12)<br>Outcome measures: serum cytokines IL-1∃, IL-2, TNF∀, IFN-(<br>Analysis: parametric and nonparametric comparison of outcome measures in exposed and reference groups | Blood Pb (µg/dL) mean (SE, range):<br>Pb: 59.4 (3.2, 42–94)<br>Reference: 4.8 (1.0, 2–15) | Significantly ($p < 0.05$) lower serum IL-1∃ and IFN-( levels in Pb workers compared to controls. |
| Yücesoy et al. (1997b)<br>Turkey<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 50), ages 39–48 yr; age-matched reference subjects (n = 10)<br>Outcome measures: lymphocyte phenotype abundance, NK cell cytotoxicity<br>Analysis: comparison of outcome measures in exposed and reference groups | Blood Pb (µg/dL) mean (SE, range):<br>Pb 1 (n = 20): 59.4 (3.2, 42–94)<br>Pb 2 (n = 30): 58.4 (2.5, 26–81)<br>Reference: 4.0 (0.4, 2–6) | Significantly ($p < 0.05$) lower $CD20^+$ B-cell (%) abundance in Pb workers compared to controls, no difference in % $CD4^+$ T-cell abundance. |

## Table AX6-8.2 (cont'd). Effects of Lead on Immune Function in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Africa** | | | |
| Anetor and Adeniyi (1998)<br>Nigeria<br>NR | Design: cross-sectional cohort<br>Subjects: adult male "Pb workers" (n = 80), mean age, 36 yr (21–66) and reference subjects (n = 50), mean age 37 yr (22–58).<br>Outcome measures: serum IgA, IgG, and IgM; lymphocyte count<br>Analysis: comparison of outcomes measures in workers and reference group, linear regression, principal component analysis | Blood Pb (µg/dL) mean (SE):<br>Pb: 53.6 (0.95)<br>Reference: 30.4 (1.4) | Significantly lower ($p < 0.05$) serum IgA, IgG, and total blood lymphocyte levels; significant associations and interactions between blood Pb and serum total globulins (note high blood Pb levels in reference). |

# ANNEX TABLES AX6-9

## Table AX6-9.1. Effects of Lead on Biochemical Effects in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Marcus and Schwartz (1987)<br>U.S.<br>1976–1980 | Design: cross-sectional national survey (NHANES II)<br>Subjects: ages 2-6 yr (n = 1677)<br>Outcome measures: EP, red blood cell count, mean corpuscular volume, iron status variables<br>Analysis: nonlinear least squares regression | Blood Pb (µg/dL) range: 6-65 | Non-linear regression used to fit kinetic model relating blood Pb to EP, in strata having low (<14%), medium (14-31%), or high (>31%) percent transferrin saturation (PST). Parameters in model included: parameters for total red cell surface area, maximum red cell Pb concentration, equilibrium concentration ratio for plasma and whole blood. Blood Pb increase (from 10 µg/dL) predicted to double EP: 22 (PST < 14%), 24 (PST = 14-31%), 37 (PST > 31%). |
| Piomelli et al. (1982)<br>New York<br>1976 | Design: cross-sectional<br>Subjects: children (n = 2002), ages 2–12 yr<br>Outcome measures: EP<br>Analysis: linear regression | Blood Pb (µg/dL) range: 2–98 | Regression equation relating blood Pb concentration to EP (log-transformed):<br>$\forall = 1.099, \exists = 0.016, r = 0.509, p < 0.001$<br>Threshold for increase in EP estimated to be: 15.4 µg/dL (95% CI: 12.9, 18.2) |
| Soldin et al. (2003)<br>Washington DC<br>2001–2002 | Design: cross-sectional<br>Subjects: children (n = 4908, 1812 females), age range 0–17 yr<br>Outcome measures: EP<br>Analysis: locally weighted scatter plot smoother (LOWESS) | Blood Pb (µg/dL):<br>Mean (range 1–17 yr): 2.2–3.3<br>Median (1–17 yr): 3<br>Range: <1–103 | EP increases as blood Pb concentration increased above 15 mg/dL. A doubling of EP occurred with an increase in blood Pb concentration of ~20 µg/dL (a polynomial expression for EP as a function of blood Pb (PbB) is:<br>$EP = -0.0015(\text{blood Pb})^3 + 0.1854(\text{blood Pb})^2 - 2.7554(\text{blood Pb}) + 30.911$ ($r^2 = 0.9986$)<br>(derived from data in Table 2 of Soldin et al. (2003) |
| **Europe** | | | |
| Roels and Lauwerys (1987)<br>Belgium<br>1974–1980 | Design: cross-sectional<br>Subjects: children (n = 143), age range 10–13 yr<br>Outcome measures: ALAD, urinary ALA, EP<br>Analysis: linear regression, correlation | Blood Pb (µg/dL) range: 15–41 | Linear regression for EP (log-transformed) and blood Pb concentration:<br>$\forall = 1.321, \exists = 0.025, r = 0.73$ (n = 51)<br>Linear regression for ALA (log-transformed) and blood Pb concentration:<br>$\forall = 0.94, \exists = 0.11, r = 0.54$ (n = 37)<br>Linear regression for ALAD (log-transformed) and blood Pb concentration:<br>$\forall = 1.864, \exists = -0.015, r = -0.87$ (n = 143) |

## Table AX6-9.1 (cont'd). Effects of Lead on Biochemical Effects in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Perez-Bravo et al. (2004)<br>Chile<br>NR | Design: cross-sectional;<br>Subjects: children (n = 93, 43 males), aged 5-12 yrs who attended school near a powdered Pb storage facility<br>Outcome measures: blood Hgb and Hct, ALAD genotype<br>Analysis: comparison of outcome measures between ALAD genotype strata | Blood Pb (µg/dL) mean (SE):<br>ALAD1 (n = 84): 13.5 (8.7)<br>ALAD2 (n = 9): 19.2 (9.5) | Mean blood Pb, blood Hgb, and Hct not different between ALAD genotypes (p = 0.13). |

## Table AX6-9.2. Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Gennart et al. (1992)<br>Belgium<br>NR | Design: cross-sectional cohort<br>Subjects: adult battery manufacture workers (n = 98), mean age, 37.7 yr (range 22–55); reference group (n = 85), mean age 38.8 yr (24–55)<br>Outcome measures: blood Hct, blood EP, urine ALA<br>Analysis: linear regression | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 51.0 (8.0, 40–70)<br>Reference: 20.9 (11.1, 4.4–30.0) | Significant association between increasing blood Pb concentration and increasing (log) blood EP ($\forall$ = 0.06, $\exists$ = 0.019, r = 0.87, p = 0.0001) or (log) urine ALA ($\forall$ = 0.37, $\exists$ = 0.008, r = 0.64, p < 0.0001)<br>(No apparent analysis of covariables) |
| Mohammed-Brahim et al. (1985)<br>Belgium<br>NR | Design: cross-sectional cohort<br>Subjects: adult smelter and ceramics manufacture workers (n = 38, 13 females); reference subjects (n = 100) matched with worker group by age, sex, and socioeconomic status.<br>Outcome measures: blood P5N, EP, ALAD, R/ALAD (ratio of ALAD before and after reactivation).<br>Analysis: comparison of outcome measures (ANOVA) between Pb workers and reference group; correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 48.5 (9.1, 27.8–66.6)<br>Reference: 14.3 (6.7, 5.6–33.6)<br><br>Urine Pb (µg/g creatinine) mean (SD, range):<br>Pb: 84.0 (95.9, 21.8–587)<br>Reference: 10.5 (8.2, 1.7–36.9) | Significantly lower (p = NR) P5N in Pb workers (males or females, or combined) compared to corresponding reference groups.<br>Correlations with blood Pb:<br>log P5N r = −0.79 (p < 0.001)<br>log ALAD r = −0.97 (p = NR)<br>R/ALAD r = −0.94 (p < 0.001)<br>log EP r = 0.86 (p = NR)<br>Correlations with urine Pb:<br>log P5N r = −0.74 (p = NR)<br>log ALAD r = −0.79 (p = NR)<br>R/ALAD r = −0.84 (p < 0.001)<br>log EP r = 0.80 (p = NR) |
| Roels and Lauwerys (1987)<br>Belgium<br>1974–1980 | Design: cross-sectional<br>Subjects: adults (n = 75, 36 females)<br>Outcome measures: ALAD, urinary ALA, EP<br>Analysis: linear regression, correlation | Blood Pb (µg/dL) range:<br>adult males: 10–60<br>adult females: 7–53 | Linear regression for EP (log-transformed) and blood Pb concentration:<br>adult male (n = 39): $\forall$ = 1.41, $\exists$ = 0.014, r = 0.74, p < 0.001<br>adult female (n = 36): $\forall$ = 1.23, $\exists$ = 0.027, r = 0.81, p < 0.001<br>Linear regression for ALA (log-transformed) and blood Pb concentration:<br>adult male (n = 39): $\forall$ = 0.37, $\exists$ = 0.006, r = 0.41, p < 0.01<br>adult female (n = 36): $\forall$ = 0.15, $\exists$ = 0.015, r = 0.72, p < 0.001 |

## Table 6-9.2 (cont'd). Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Grandjean (1979)<br>Denmark<br>NR | Design: longitudinal<br>Subjects: male battery manufacture workers (n = 19), mean age 32 yr (range 22–49)<br>Outcome measures: EP<br>Analysis: EP and blood Pb for serial measurements displayed graphically | Blood Pb (µg/dL) median (range):<br>Group 1 (n = 5): 47.7 (22.8–53.9)<br>Group 2 (n = 5): 37.3 (35.2–53.9) | Five subjects (group 1) showed declines in EP with declining blood Pb (33–58 µg/dL) over a 10-mo period; 5 subjects (group 2) showed no change in EP with a change in blood Pb concentration (25–54 µg/dL) over the same period. |
| Alessio et al. (1976)<br>Italy<br>NR | Design: cross-sectional<br>Subjects: adult male Pb worker (n = 316), age range NR<br>Outcome measures: blood ALAD, EP, urine ALA, CP<br>Analysis: linear regression, correlation | Blood Pb (µg/dL) range: 10–150 | Regression relating outcomes to blood Pb concentration:<br>ALAD (ln-transformed) (n = 169): $\forall = 3.73$, $\exists = -0.031$, r = 0.871<br>ALAU (ln-transformed) (n = 316): $\forall = 1.25$, $\exists = 0.014$, r = 0.622<br>UCP (ln-transformed) (n = 252): $\forall = 2.18$, $\exists = 0.34$, r = 0.670<br>EP (log-transformed (males, n = 95): $\forall = 0.94$, $\exists = 0.0117$<br>EP (log-transformed (females, n = 93): $\forall = 1.60$, $\exists = 0.0143$ |
| Cocco et al. (1995)<br>Italy<br>1990 | Design: longitudinal<br>Subjects: adult male foundry workers (n = 40), mean age 25.1 yr (SD 2.1, range 21–28)<br>Outcome measures: serum total-, HDL- and LDL-cholesterol, blood Hgb, urine ALA, erythrocyte G6PD<br>Analysis: comparison of outcomes between pre-exposure (at start of employment, sample 1) and after 172 (range 138–217, sample 2) days | Blood Pb (µg/dL) mean (range):<br>Sample 1: 10.0 (7–15)<br>Sample 2: 32.7 (20–51) | G6PD levels were unrelated to starting blood Pb; however, they increased in subjects whose blood Pb concentration increased from <30 µg/dL to >30 µg/dL or decreased from >30 µg/dL to <30 µg/dL. Increasing exposure duration was significantly associated with decreasing magnitude of change in G6PD.<br>Sample 1 <30 µg/dL: $\exists = -0.3980$ (SE 0.1761), $p < 0.05$<br>Sample 1 >30 µg/dL: $\exists = -1.3148$ (SE 0.3472), $p < 0.05$<br>In the >30 µg/dL subgroup, increasing blood Pb was associated with decreasing magnitude of change of G6PD ($\exists = -2.0797$ [SE 0.7173], $p < 0.05$).<br>Serum cholesterol levels were unrelated to blood Pb concentration. |

## Table 6-9.2 (cont'd). Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Fracasso et al. (2002)<br>Italy<br>NR | Design: cross-sectional cohort<br>Subjects: adult battery manufacture workers (n = 37, 6 females), mean age 41 yr (SD 7); reference office workers (n = 29, 8 females), mean age 38 yr (SD 21)<br>Outcome measures: lymphocyte DNA strand breaks, ROS, GSH<br>Analysis: comparison of outcome measures between Pb workers and reference group (ANOVA), logistic regression | Blood Pb (µg/dL) mean (SD):<br>Pb: 39.6 (7.6)<br>Reference: 4.4 (8.6) | Covariate-adjusted DNA strand breaks were significantly higher in Pb workers compared to the reference group and significantly associated with increased blood Pb ($p = 0.011$).<br>Covariate-adjusted lymphocyte ROS was significantly higher and GSH significantly lower in the Pb workers compared to the reference group. Lower GSH levels were significantly associated with increasing blood Pb concentration ($p = 0.006$).<br>Odds ratios (OR) for DNA strand breaks and lower GSH levels were significant (Pb workers vs. reference):<br>DNA strand breaks: OR = 1.069 (95% CI: 1.020, 1.120), $p = 0.005$<br>GSH: OR = 0.634 (95% CI: 0.488, 0.824), $p = 0.001$<br>ROS: OR = 1.430 (95% CI: 0.787, 2.596), $p = 0.855$<br>Covariates retained: age, alcohol consumption and tobacco smoking. |
| Hernberg et al. (1970)<br>Poland<br>NR | Design: cross-sectional<br>Subjects: adult Pb workers (n = 166); reference group (n = 16)<br>Outcome measures: blood ALAD<br>Analysis: regression, correlation | Blood Pb (µg/dL) range: 5–95 | Linear regression for blood ALAD (log-transformed) and blood Pb concentration (n = 158):<br>$\forall = 2.274$, $\exists = -0.018$, $r = -0.90$, $p < 0.001$ |
| Bergdahl et al. (1997)<br>Sweden<br>NR | Design: cross-sectional<br>Subjects: adult smelter worker (n = 89); reference groups (n = 24)<br>Outcome measures: blood Pb, erythrocyte ALAD-bound Pb, ALAD genotype<br>Analysis: comparison of outcome measures | Blood Pb (µg/dL) range: 0.8–93<br><br>Urine Pb (mg/L) range: 1–112<br><br>Bone Pb (µg/g) range: −19–101 | No association between ALAD genotype and Pb measures. |
| Selander and Cramør (1970)<br>Sweden<br>NR | Design: cross-sectional<br>Subjects: adult battery manufacture workers (n = 177)<br>Outcome measures: urine ALA<br>Analysis: regression, correlation | Blood Pb (µg/dL) range: 6–90 | Linear regression for urine ALA (log-transformed) and blood Pb concentration (n = 150):<br>$\forall = -1.0985$, $\exists = 0.0157$, $r = 0.74$ |

## Table 6-9.2 (cont'd). Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Wildt et al. (1987)<br>Sweden<br>NR | Design: longitudinal<br>Subjects: adult battery manufacture workers (n = 234, 37 females) mean age 35 y (range 17–70); reference group (n = 951, 471 females), mean age 39 yr (range 19–67)<br>Outcome measures: EP<br>Analysis: analysis of variability over time, linear regression, correlation | Blood Pb (µg/dL) mean (range):<br>Pb: 10–80<br>Reference:<br>Male: 11.3 (8–27)<br>Female: 8.5 (5–21) | Linear regression for EP (log-transformed) and blood Pb concentration:<br>Males (n = 851): $\forall = 1.21$, $\exists = 0.0148$, r = 0.72<br>Females (n = 139): $\forall = 1.48$, $\exists = 0.0113$, r = 0.56 |
| **Asia** | | | |
| Hsieh et al. (2000)<br>China<br>NR | Design: cross-sectional<br>Subjects: Adults in general population (n = 630, 255 females)<br>Outcome measures: blood Hgb, Hct, RBC count, ALAD genotype<br>Analysis: comparison of outcome measures between ALAD genotype strata | Blood Pb (µg/dL) mean (SD):<br>ALAD1,1 (n = 630): 6.5 (5.0)<br>ALAD1,1/2,2 (n = 30): 7.8 (6.0) | Mean blood Pb not different between ALAD genotype strata (p = 0.17). RBC count, Hgb, Hct not different between ALAD genotype strata (p = 0.7) |
| Jiun and Hsien (1994)<br>China<br>1992 | Design: longitudinal<br>Subjects: adult male Pb workers (n = 62), ages NR; reference group (n = 62, 40 females), ages NR<br>Outcome measures: plasma MDA<br>Analysis: comparison of outcome measures between Pb workers and reference group, linear regression | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 37.2 (12.5, 18.2–76.0)<br>Reference: 13.4 (7.5, 4.8–43.9) | Plasma MDA levels significantly ($p < 0.0001$) higher (~2x) in Pb workers whose blood Pb concentration 35 µg/dL compared to #30 µg/dL. In subjects with blood Pb >35 µg/dL, blood Pb and plasma MDA were significantly correlated:<br>blood Pb = 9.584(MDA) + 24.412 (r = 0.85) |
| Froom et al. (1999)<br>Israel<br>1980–1993 | Design: longitudinal survey<br>Subjects: adult male battery manufacturing workers (n = 94), mean age, 38 yr (SD 9, range 26–60)<br>Outcome measures: blood Hgb, blood EP<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) range of 13-yr individual subject means:<br>20–61 µg/dL | Weak (and probably not significant) covariate-adjusted association between blood Hgb and individual sample blood Pb ($\exists = -0.0039$ [SE 0.0002]), subject avg blood Pb ($\exists = -0.0027$ [SE 0.0036]), or blood EP ($\exists = -0.001$ [SE 0.0007])<br>Covariates retained in model were age and smoking habits. |

## Table 6-9.2 (cont'd). Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Kristal-Boneh et al. (1999)<br>Israel<br>1994–1995 | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 56), mean age 43.1 yr (SD 10.6); reference group (n = 87), mean age 43.2 yr (SD 8.3)<br>Outcome measures: serum total-, HDL-, LDL-cholesterol, HDL: total ratio, triglycerides<br>Analysis: comparison of outcome measures between Pb workers and reference group (ANOVA), multivariate linear regression | Blood Pb (µg/dL) mean (SD):<br>Pb: 42.3 (14.9)<br>Reference: 2.7 (3.6) | Covariate-adjusted serum total-cholesterol ($p = 0.016$) and HDL-cholesterol ($p = 0.001$) levels were significantly higher in Pb workers compared to reference group. Covariates retained in ANOVA: age, body mass index, season of sampling, nutritional variables (dietary fat, cholesterol, calcium intakes), sport activities, alcohol consumption, cigarette smoking, education, job seniority. Increasing blood Pb concentration was significantly associated with covariate-adjusted total cholesterol ($\exists = 0.130$ [SE 0.054], $p = 0.017$) and HDL-cholesterol ($\exists = 0.543$ [SE 0.173], $p = 0.002$). Covariates retained: age, body mass index. Stepwise inclusion of other potential confounders had no effect. |
| Solliway et al. (1996)<br>Israel<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 34), mean age: 44 yr (SD 13); reference subjects (n = 56), mean age 43 yr (SD 12); cohorts constructed to have similar age, ethnic characteristics, socioeconomic status, education level, and occupation<br>Outcome measures: urinary ALA, erythrocyte GSH-peroxidase<br>Analysis: parametric comparison of outcome measures between Pb and reference groups, correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 40.7 (9.8, 23–63)<br>Reference: 6.7 (2.4, 1–13) | Significantly lower mean erythrocyte GSH-peroxidase activity ($p < 0.005$) in and higher urinary ALA ($p < 0.001$) in Pb workers compared to reference group. |
| Ito et al. (1985)<br>Japan<br>NR | Design: cross-sectional cohort<br>Subjects: adult male steel (smelting, casting) workers (n = 712), age range 18–59 yr; reference (office workers) group (n = 155, total), age range 40–59 yr<br>Outcome measures: serum LPO and SOD, total and HDL-cholesterol, phospholipid<br>Analysis: comparison of outcome measures between Pb workers and reference group, correlation | Blood Pb (µg/dL) range:<br>Pb: 5–62<br>Reference: NR | When stratified by age, significantly ($p < 0.05$) higher serum HDL-cholesterol and LPO in Pb workers, age range 40–49 yr, compared to corresponding strata of reference group. Serum lipoperoxide levels increased as blood Pb increased above 30 µg/dL (p = NR), SOD appeared to decrease with increasing blood Pb concentration (p = NR) |

## Table 6-9.2 (cont'd). Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Makino et al. (1997)<br>Japan<br>1990–1994 | Design: longitudinal survey<br>Subjects: adult male pigment or vinyl chloride stabilizer manufacture workers (n = 1573) mean age 45 yr<br>Outcome measures: blood Hgb, Hct, RBC count<br>Analysis: parametric comparison of outcome measures, stratified by blood Pb, linear regression | Blood Pb (µg/dL) mean (SD, range):<br>12.6 (2.0, 1–39)<br><br>Urine Pb (µg/L) mean (SD, range):<br>10.2 (2.7, 1–239) | Significantly higher ($p < 0.001$) Hct, blood Hgb and RBC count in blood Pb category 16–39 µg/dL, compared to 1–15 µg/dL category.<br>Significant positive correlation between blood Pb concentration and Hct: $\forall = 42.95$, $\exists = 0.0586$ ($r = 0.1553$, $p < 0.001$), blood Hgb: $\forall = 14.65$, $\exists = 0.0265$ ($r = 0.1835$, $p < 0.001$) and RBC count $\forall = 457$, $\exists = 0.7120$ ($r = 0.1408$, $p < 0.001$). |
| Morita et al. (1997)<br>Japan<br>NR | Design: cross-sectional cohort<br>Subjects: male Pb workers (n = 76), mean age 42 yr (range 21–62); reference subjects (n = 13, 6 females), mean age, males 41 yr (range 26–52), females 45 yr (range 16–61)<br>Outcome measures: blood NADS, ALAD<br>Analysis: comparison of outcome measures (ANOVA) between blood Pb categories, linear regression | Blood Pb (µg/dL) mean (SD, range)<br>Pb: 34.6 (20.7, 2.2–81.6) | Significantly lower ($p < 0.01$) blood NADS and ALAD in blood Pb categories >20 µg/dL compared to <20 µg/dL, with dose trend in magnitude of difference.<br>Significant associations between increasing blood Pb and decreasing blood NADS and ALAD in Pb workers:<br>NADS: $\forall = 0.843$, $\exists = -0.00971$, $r = -0.867$, $p < 0.001$, $n = 76$<br>log ALAD: $\forall = 1.8535$, $\exists = -0.015$, $r = -0.916$, $p < 0.001$, $n = 58$ |
| Oishi et al. (1996)<br>Japan<br>NR | Design: cross-sectional<br>Subjects: adult glass and pigment manufacture workers (n = 418, 165 females), mean age 33 yr (range 18–58); reference workers (n = 227, 89 females), mean age 30 yr (range 17–59)<br>Outcome measures: plasma ALA, urinary ALA<br>Analysis: linear regression, correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 48.5 (17.0, 10.3–99.4<br>Reference: 9.6 (3.3, 3.8–20.4) | Significant correlation between blood Pb concentration and plasma and urinary ALA (both log-transformed):<br>Plasma ALA: $\forall = 0.327$, $\exists = 0.022$, $r = 0.742$<br>Urinary ALA: $\forall = -0.387$, $\exists = 0.022$, $r = 0.711$<br>Significant correlation between plasma and urinary ALA:<br>$\forall = 6.038$, $\exists = 4.962$, $r = 0.897$ |

## Table 6-9.2 (cont'd). Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Sugawara et al. (1991)<br>Japan<br>NR | Design: cross-sectional cohort<br>Subjects: adult Pb workers and reference group (n = 32, total), ages NR<br>Outcome measures: plasma and erythrocyte lipoperoxide and SOD; erythrocyte CAT, GSH, and methemoglobin<br>Analysis: comparisons of outcome measures between Pb workers and reference group, linear regression and correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 57.1 (17.6, 20–96)<br>Reference: NR | Significantly ($p < 0.01$) higher erythrocyte LPO and lower SOD, CAT and GSH levels in workers compared to reference group.<br>Erythrocyte lipoperoxide ($r = 0.656$) and GSH ($r = -0.631$) were significantly correlated with blood Pb. |
| Kim et al. (2002)<br>Korea<br>1996 | Design: cross-sectional cohort<br>Subjects: adult male secondary Pb smelter workers (n = 83), mean age: 38.7 yr (SD 10.8); reference subjects (n = 24), mean age: 32.0 (SD 10.8)<br>Outcome measures: blood Hgb, blood ALAD, blood EP, blood P5N<br>Analysis: parametric comparison (ANOVA) of outcome measures between Pb workers and reference group, correlation, multivariate linear regression | Blood Pb (µg/dL) mean (SD)<br>Pb: 52.4 (17.7)<br>Reference: 6.2 (2.8) | Significantly ($p < 0.05$) lower blood P5N, ALAD, and Hgb; and higher blood EP in Pb workers compared to controls.<br>Significant ($p < 0.001$) correlations (in Pb worker group) with blood Pb: P5N ($r = -0.704$), log EP ($r = 0.678$), log ALAD ($r = -0.622$).<br>Significant association between increasing EP and decreasing blood Hgb:<br>blood Pb ∃60 µg/dL: ∃ = −1.546 (95% CI: −2.387, −0.704), $r^2 = 0.513$, $p = 0.001$<br>blood Pb <60 µg/dL: ∃ = −1.036 (95% CI: −1.712, −0.361), $r^2 = 0.177$, $p = 0.003$<br>Significant association between increasing P5N and increasing blood Hgb (high blood Pb group only):<br>blood Pb ∃60 µg/dL: ∃ = 0.222 (95% CI: 0.015, 0.419), $r^2 = 0.513$, $p = 0.036$<br>Covariates included in model: P5N, log serum ferritin, log EP |
| Lee et al. (2000)<br>Korea<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb workers (n = 95; secondary smelter, PVC-stabilizer manufacture, battery manufacture); mean age 42.8 yr (SD 9.3, range 19–64); reference group (n = 13), mean age 35.1 yr (SD 9.9, range 22–54)<br>Outcome measures: urinary ALA, EP<br>Analysis: correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 44.6 (12.6, 21.4–78.4)<br>Reference: 5.9 (1.2, 4.0–7.2) | Significant correlation between increasing DMSA-provoked urinary Pb and urinary ALA ($r = 0.31$, $p < 0.002$) and EP ($r = 0.35$, $p < 0.001$). |

## Table 6-9.2 (cont'd). Effects of Lead on Biochemical Effects in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Schwartz et al. (1997)<br>Korea<br>1994-1995 | Design: cross-sectional<br>Subjects: adult male battery manufacture workers (n = 57), mean age 32 yrs (SD 6).<br>Outcome measures: blood Hgb, $Hgb_{A1}$, and $Hgb_{A2}$, ALAD genotype<br>Analysis: comparison of outcome measures between ALAD genotype strata | Blood Pb (µg/dL) mean (SD):<br>ALAD1,1 (n = 38): 26.1 (9.8)<br>ALAD1,2 (n = 19): 24.0 (11.3) | Mean blood Pb (p = 0.48) and blood Hgb levels (p = 0.34) were not different between ALAD genotype strata. |
| Gurer-Orhan et al. (2004)<br>Turkey<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 20), mean age 35 yr (SD 8); reference workers (n = 16), mean age 32 yr (SD 9)<br>Outcome measures: blood ALAD, EP, erythrocyte MDA, CAT, G6PD, blood GSH:GSSG<br>Analysis: comparison of outcome measures between Pb workers and reference group, correlation | Blood Pb (µg/dL) mean (SD):<br>Pb: 54.6 (17)<br>Reference: 11.8 (3.2) | Significant correlation between blood Pb concentration and blood ALAD ($r = -0.85$, $p < 0.0001$) and EP ($r = 0.83$, $p < 0.001$). Significant correlation between blood Pb concentration and erythrocyte MDA ($r = 0.80$, $p = <0.0001$), erythrocyte G6PD ($r = 0.70$, $p < 0.0001$, erythrocyte CAT ($r = 0.62$, $p < 0.001$), blood GSH ($r = 0.64$, $p < 0.0005$), blood GSSG ($r = 0.67$, $p < 0.0001$). GSH: GSSG ratio lower (p = NR) in Pb workers (3.2), compared to controls (8.0). |
| Süzen et al. (2003)<br>Turkey<br>NR | Design: cross-sectional<br>Subjects: Male Pb battery manufacture workers (n = 72), age range 24-45 yrs.<br>Outcome measures: blood ALAD, urine ALA, ALAD genotype<br>Analysis: comparison of outcome measures between ALAD genotype strata | Blood Pb (µg/dL) mean (SD, range):<br>All: 34.5 (12.8, 13.4–71.8)<br>ALAD1,1 (n = 51)<br>34.4 (13.1, 13.4–71.8)<br>ALAD2 (n = 21)<br>34.9 (12.6, 19.2–69.6) | Mean blood Pb concentration (p = 0.88) and blood ALAD activity (p = 0.33) were not different between ALAD genotype strata. Mean urinary ALA was significantly higher ($p < 0.05$) in the ALAD1,1 stratum. |

## Table AX6-9.3. Effects of Lead on Hematopoietic System in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Liebelt et al. (1999)<br>Connecticut<br>NR | Design: cross-sectional<br>Subjects: children (n = 86, 31 female), ages 1–6 yr<br>Outcome measures: serum EPO, blood Hgb<br>Analysis: ANOVA of outcome measures stratified by blood Pb, linear regression | Blood Pb (µg/dL) median (range):<br>18 (2–84)<br>84% <35 | Significant association between increasing blood Pb concentration and decreasing serum EPO concentration ($\exists = -0.03$, $p = 0.02$). Covariates included in model were blood Hgb ($\exists = -1.36$, $p < 0.01$) (age was not included), $r^2 = 0.224$. Predicted decrease in serum EPO per 10 µg/dL was 0.03 mIU/mL. No significant association between blood Pb and blood Hgb. |
| Schwartz et al. (1990)<br>Idaho<br>1974 | Design: cross-sectional<br>Subjects: children (n = 579), ages 1–5 yr, residing near an active smelter (with uncontrolled emissions)<br>Outcome measures: Hct<br>Analysis: logistic regression | Blood Pb (µg/dL) range:<br>11–164 | Significant association between increasing blood Pb concentration and probability of anemia (Hct < 35%) ($\exists_1 = 0.3083$ [SE 0.0061]) and age ($\exists_2 = -0.3831$ [SE 0.1134]). A 10% probability of anemia was predicted to be associated with blood Pb concentration of ~20 µg/dL at age 1 yr, 50 µg/dL at age 3 yr, and 75 µg/dL at age 5 yrs (from Fig. 2 Schwartz et al. (1990).<br>Regression model relating Hct to blood Pb (BL µg/dL) and age (AGE, yr): $Hct = A/[1 + \exp(\exists_0 + \exists_1 BL + \exists_2 AGE)]$:<br>$A = 39.42$ (SE 0.79), $p = 0.0001$<br>$\exists_0 = -3.112$ (SE 0.446), $p = 0.0001$<br>$\exists_1 = 0.0133$ (SE 0.0041), $p = 0.0005$<br>$\exists_2 = -0.2016$ (SE 0.0905), $p = 0.0129$<br>Based on above model, a 10% decrease in hematocrit (from 39.5 to 35.5%) is predicted in association with blood Pb concentrations of 85, 115, and 145 µg/dL, at ages 1, 3, and 5 yrs, respectively. |

## Table AX6-9.3 (cont'd.). Effects of Lead on Hematopoietic System in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** | | | |
| Graziano et al. (2004) (Factor Litvak et al. (1999, 1998) Yugoslavia 1985–1998 | Design: prospective<br>Subjects: children (n = 311; age range 4.5–12 yr) from high-Pb (smelter/refinery) and low-Pb areas<br>Outcome measures: blood Hgb, serum EPO.<br>Analysis: multivariate linear regression (GEE for repeated measures) | Blood Pb (µg/dL) range:<br>4.5 yr: 4.6–73.1<br>6.5 yr: 3.1–71.7<br>9.0 yr: 2.3–58.1<br>Blood Pb (µg/dL) means for ages 4.5–12 yrs:<br>High Pb: 30.6–39.3<br>Low Pb: 6.1–9.0 | Significant association between increasing blood Pb concentration and increasing serum EPO concentration at ages 4.5 ($p < 0.0001$) and 6.5 yr ($p < 0.0007$), with decreasing regression slope with age: 4.5 yr: ∃ = 0.21 (SE 0.043), p = 0.0001; 6.5 yr: ∃ = 0.11 (SE 0.41), p = 0.0103; 9.5 yr: ∃ = 0.029 (SE 0.033), p = 0.39; 12 yr: ∃ = 0.016 (SE 0.031), p = 0.60.<br>Covariates retained in regression model were age (∀), blood Pb (∃), and blood Hgb (() . GEE for repeated measures yielded (Factor-Litvak et al., 1998, updated from personal communication from Graziano 07/2005):<br>(: 0.6097 (95% CI: −0.0915, −0.0479), $p < 0.0001$<br>4.5 yr: ∀ = 1.3421 (95% CI: 1.0348, 1.6194), $p < 0.0001$<br>∃ = 0.2142 (95% CI: 0.1282, 0.3003), $p < 0.0001$<br>6.5 yr: ∀ = 1.6620 (95% CI: 1.3737, 1.9503), $p < 0.0001$<br>∃ = 0.1167 (95% CI: 0.0326, 0.2008), $p < 0.001$<br>9.5 yr: ∀ = 1.7639 (95% CI: 1.4586, 2.0691), $p < 0.0001$<br>∃ = 0.0326 (95% CI: −0.0346, 0.0998), p = 0.1645<br>12 yr: ∀ = 1.8223 (95% CI: 1.524, 2.1121), $p < 0.0001$<br>∃ = 0.0112 (95% CI: −0.0359, 0.0584), p = 0.1645<br>Based on the GEE, the predicted increase in serum EPO per 10 µg/dL increase in blood Pb concentration (at Hgb = 13 g/dL) \ was: 1.25 mIU/mL (36%) at age 4.5 yr and 1.18 (18%) at age 6.5 yr. Blood Hgb levels were not significantly different in children from high-Pb area (mean 25–38 µg/dL) compared to low-Pb area (mean 5–9 µg/dL). |

## Table AX6-9.3 (cont'd). Effects of Lead on Hematopoietic System in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| Perez-Bravo et al. (2004)<br>Chile<br>NR | Design: cross-sectional;<br>Subjects: children (n = 93, 43 males), aged 5-12 yrs who attended school near a powdered Pb storage facility<br>Outcome measures: blood Hgb and Hct, ALAD genotype<br>Analysis: comparison of outcome measures between ALAD genotype strata | Blood Pb (µg/dL) mean (SE):<br>ALAD1 (n = 84): 13.5 (8.7)<br>ALAD2 (n = 9): 19.2 (9.5) | Mean blood Pb, blood Hgb, and Hct not different between ALAD genotypes |

## Table AX6-9.4. Effects of Lead on Hematopoietic System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Hu et al. (1994)<br>U.S.<br>1991 | Design: survey<br>Subjects: adult male carpentry workers (n = 119), mean age: 48.6 yr (range 23–67)<br>Outcome measures: blood Hct, blood Hgb<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) mean (SD, range):<br>8.3 (4.0, 2–25)<br><br>Bone Pb (µg/g) mean (SD, range)<br>Tibia: 9.8 (9.5, −15 to 39)<br>Patella: 13.9 (16.6, −11 to 78) | Significant association between increasing patella bone Pb and decreasing covariate adjusted blood Hgb (∃ = −0.019 [SE 0.0069], p = 0.008, $r^2$ = 0.078) and blood Hct (∃ = −0.052 [SE 0.019], p = 0.009, $r^2$ = 0.061). After adjustment for bone Pb measurement error, a 37 µg/dL increase in patella bone Pb level (from the lowest to highest quintile) was associated with a decrease in blood Hgb and Hct of 11 g/L (95% CI: 2.7, 19.3) and 0.03 (95% CI: 0.01, 0.05), respectively.<br>Covariates considered: age, body mass index, tibia Pb, patella Pb, blood Pb, current smoking status, alcohol consumption<br>Covariates retained: patella bone Pb, alcohol consumption, body mass index. |
| **Europe** | | | |
| Osterode et al. (1999)<br>Austria<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb workers (n = 20), ages 46 yr (SD, 7); age-matched reference group (n = 20)<br>Outcome measures: blood PCV, blood Hgb, serum EPO, blood erythroid progenitor (BFU-E) cell count, blood pluripotent progenitor (CFU-GEMM) cell count, blood granulocyte/macrophage progenitor (CFU-GM) cell count.<br>Analysis: parametric and nonparametric comparison of outcomes between Pb workers and reference group; correlation | Blood Pb (µg/dL) mean (range):<br>Pb: 45.5 (16–91)<br>Reference: 4.1 (3–14)<br><br>Urine Pb (µg/L) mean (range):<br>Pb: 46.6 (7–108)<br>Reference: 3.7 (2–16) | Significantly lower (p < 0.001) BFU-E counts in Pb workers who had blood Pb concentrations ∃60 µg/dL, compared to reference group. Significant negative correlation between blood Pb or urine Pb and CFU-GM and CFU-E. Serum EPO was not correlated with Hct in Pb workers, however, serum EPO increased exponentially with decrease in Hct in reference group. |

## Table AX6-9.4 (cont'd). Effects of Lead on Hematopoietic System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Gennart et al. (1992)<br>Belgium<br>NR | Design: cross-sectional cohort<br>Subjects: adult battery manufacture workers (n = 98), mean age, 37.7 yr (range 22–55); reference group (n = 85), mean age 38.8 yr (24–55)<br>Outcome measures: blood Hgb, RBC count, Hct, blood EP<br>Analysis: linear regression | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 51.0 (8.0, 40–70)<br>Reference: 20.9 (11.1, 4.4–30.0) | Significant association between increasing blood Pb concentration and decreasing blood Hgb ($\exists$ = −0.011, r = 0.22, p = 0.003) or Hct ($\exists$ = -0.035, r = 0.24, p < 0.01).<br>Significant association between increasing blood Pb concentration and increasing blood EP ($\exists$ = 0.0191, r = 0.87, p = 0.0001)<br>(No apparent analysis of covariables). |
| Mohammed-Brahim et al. (1985)<br>Belgium<br>NR | Design: cross-sectional cohort<br>Subjects: adult smelter and ceramics manufacture workers (n = 38, 13 females); reference subjects (n = 100) matched with worker group by age, sex, and socioeconomic status<br>Outcome measures: blood P5N, EP, ALAD, R/ALAD (ratio of ALAD before and after reactivation).<br>Analysis: comparison of outcome measures (ANOVA) between Pb workers and reference group; correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 48.5 (9.1, 27.8–66.6)<br>Reference: 14.3 (6.7, 5.6–33.6)<br><br>Urine Pb (µg/g creatinine) mean (SD, range):<br>Pb: 84.0 (95.9, 21.8–587)<br>Reference: 10.5 (8.2, 1.7–36.9) | Significantly lower (p = NR) P5N in Pb workers (males or females, or combined) compared to corresponding reference groups.<br>Correlations with blood Pb:<br>log P5N r = −0.79 (p < 0.001)<br>log ALAD r = −0.97 (p = NR)<br>R/ALAD r = −0.94 (p < 0.001)<br>log EP r = 0.86 (p = NR)<br>Correlations with urine Pb:<br>log P5N r = −0.74 (p = NR)<br>log ALAD r = −0.79 (p = NR)<br>R/ALAD r = −0.84 (p < 0.001)<br>log EP r = 0.80 (p = NR) |
| Hajem et al. (1990)<br>France<br>NR | Design: cross-sectional<br>Subjects: adult males (n = 129), mean age 36 yr (SD 7.8, range 24–55), with no environmental exposure to Pb<br>Outcome measures: erythrocyte membrane activities of Na+-K+-ATPase, Na+-K+-co-transport, Na+-Li+-antiport, and passive Na+ and K+ permeability<br>Analysis: linear regression, correlation | Blood Pb (µg/dL) geometric mean (95% CI, range):<br>16.0 (15.2–16.8, 8.0–33.0)<br><br>Hair Pb (µg/g) geometric mean (95% CI, range):<br>5.3 (4.44–6.23, 0.9–60) | Na+-K+-co-transport activity negatively correlated with blood Pb concentration (r = −0.23, p = 0.02); linear regression:<br>$\forall$ = 583.19, $\exists$ = −170.70<br>Na+-K+-ATPase activity negatively correlated with hair Pb (r = −0.18, p = 0.04); simple linear regression:<br>$\forall$ = 3.34, $\exists$ = −0.02 |

## Table AX6-9.4 (cont'd). Effects of Lead on Hematopoietic System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Poulos et al. (1986)<br>Greece<br>NR | Design: cross-sectional cohort<br>Subjects: adult male cable production workers who were exposed to Pb (worker 1; n = 50, mean age 37 yr); male cable workers who had not direct contact with Pb (worker 2, n = 75, mean age 36.5 yr); reference group (n = 35, mean age 39 yr)<br>Outcome measures: blood Hgb, Hct<br>Analysis: simple linear regression in the form: mean Hct = a + ∃(individual Hct – group mean Hct) | Blood Pb (µg/dL) mean (SE):<br>Worker 1: 27.0 (0.7)<br>Worker 2: 18.3 (0.6)<br>Reference: 21.5 (1.5) | Significant association between increasing blood Pb and decreasing Hct:<br>Worker 1: ∀ = 46.50, ∃ = −0.170 (SE 0.079), $p < 0.05$<br>Worker 2: ∀ = 44.57, ∃ = −0.180 (SE 0.083), $p < 0.05$<br>Reference: ∀ = 44.69, ∃ = −0.255 (SE 0.044), $p < 0.001$<br>Significant association between increasing blood Pb and decreasing blood Hgb:<br>Worker 1: ∀ = 15.23, ∃ = −0.058 (SE 0.028), $p < 0.05$<br>Worker 2: ∀ = 14.58, ∃ = −0.071 (SE 0.034), $p < 0.05$<br>Reference: ∀ = 14.64, ∃ = −0.087 (SE 0.015), $p < 0.001$ |
| Romeo et al. (1996)<br>Italy<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb workers (n = 28), age range, 17–73; reference group (n = 113), age range, 21–75 yr<br>Outcome measures: serum EPO, blood Hgb<br>Analysis: nonparametric comparison of outcome measures between Pb workers and reference group; correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb 1: 32.3 (5.6, 30–49)<br>Pb 2: 65.1 (16, 50–92)<br>Reference: 10.4 (4.3, 3–20) | Significantly ($p = 0.021$) lower serum EPO in Pb workers compared to reference group. No significant ($p < 0.05$) Pb effect on blood Hgb. |
| Graziano et al. (1990)<br>Yugoslavia<br>1986 | Design: prospective<br>Subjects: pregnant women (n = 1502) from high-Pb (smelter/refinery) and low-Pb areas<br>Outcome measures: Hgb<br>Analysis: comparison of outcome measures between high-and low-Pb groups | Blood Pb (µg/dL) mean (95% CI):<br>High Pb: 17.1 (6.9, 42.6)<br>Low Pb: 5.1 (2.5, 10.6) | Mean blood Hgb levels (g/dL) in high-Pb group (12.4; 95% CI: 10.3, 14.5) not different from low-Pb group (12.3; 95% CI: 10.0, 14.7). |

## Table AX6-9.4 (cont'd). Effects of Lead on Hematopoietic System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Graziano et al. (1990)<br>Yugoslavia<br>1986 | Design: prospective<br>Subjects: pregnant women (n = 48) from high-Pb (smelter/refinery) and low-Pb areas (6 highest and lowest mid-pregnancy blood Pb concentrations), within each of 4 Hgb strata (g/dL): 9.0–9.9, 10.0–10.9, 11.0–11.9, 12.0–12.9<br>Outcome measures: Hgb, EPO<br>Analysis: ANOVA of outcome measures in subjects stratified by blood Pb and blood Hgb | Blood Pb (µg/dL) mean range for Hgb strata<br>High Pb: 16.9–38.6<br>Low Pb: 2.4–3.6 | Significant effect of blood Pb (p = 0.049) and blood Hgb (p = 0.001) on mid-term and term serum EPO (blood Pb p = 0.055, Hgb p = 0.009), with significantly lower serum EPO associated with higher blood Pb. |
| **Asia** | | | |
| Hsiao et al. (2001)<br>China<br>1989–1999 | Design: longitudinal<br>Subjects: adult battery manufacture workers (n = 30, 13 females), mean age 38.3 yr<br>Outcome measures: blood Hgb, Hct, RBC count<br>Analysis: GEE for repeated measures (models: linear correlation, threshold change, synchronous change, lag change); logistic regression | Blood Pb (µg/dL) mean:<br>1989: 60<br>1999: 30 | Significant association between increasing blood Pb and increasing RBC count and Hct:<br>Odds ratios (95% CI):<br>Synchronous change model:<br>Blood Hgb: 0.95 (0.52, 1.78)<br>RBC count: 3.33 (1.78, 6.19)<br>Hct: 2.19 (1.31, 3.66)<br>Lag change:<br>Blood Hgb: 1.70 (0.99, 2.92)<br>RBC count: 2.26 (1.16, 4.41)<br>Hct: 2.08 (1.16, 4.41) |
| Hsieh et al. (2000)<br>China<br>NR | Design: cross-sectional<br>Subjects: Adults in general population (n = 630, 255 females)<br>Outcome measures: blood Hgb, Hct, RBC count, ALAD genotype<br>Analysis: comparison of outcome measures between ALAD genotype strata | Blood Pb ( µg/dL) mean (SD):<br>ALAD1,1 (n = 630): 6.5 (5.0)<br>ALAD1,1/2,2 (n = 30): 7.8 (6.0) | Mean blood Pb not different between ALAD genotype strata (p = 0.17). RBC count, Hgb, Hct not different between ALAD genotype strata (p = 0.7). |

## Table AX6-9.4 (cont'd). Effects of Lead on Hematopoietic System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Froom et al. (1999)<br>Israel<br>1980–1993 | Design: longitudinal survey<br>Subjects: adult male battery manufacturing workers (n = 94), mean age, 38 yr (SD 9, range 26–60)<br>Outcome measures: blood Hgb, blood EP<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) range of 13-yr individual subject means: 20–61 µg/dL | Weak (and probably not significant) covariate-adjusted association between blood Hgb and individual sample blood Pb (∃ = −0.0039 [SE 0.0002]), subject avg blood Pb (∃ = −0.0027 [SE 0.0036]) or blood EP (∃ = −0.001 [SE 0.0007]).<br>Covariates retained in model were age and smoking habits. |
| Solliway et al. (1996)<br>Israel<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 34), mean age: 44 yr (SD 13); reference subjects (n = 56), mean age 43 yr (SD 12); cohorts constructed to have similar age, ethnic characteristics, socioeconomic status, education level, and occupation<br>Outcome measures: blood Hgb, RBC count<br>Analysis: parametric comparison of outcome measures between Pb and reference groups, correlation | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 40.7 (9.8, 23–63)<br>Reference: 6.7 (2.4, 1–13) | Significantly lower ($p < 0.05$) mean RBC count in Pb workers compared to reference group. Significant negative correlation between blood Pb concentration and RBC count ($r = -0.29$, $p < 0.05$). Mean comparison for blood Hgb ($p = 0.4$); correlation with blood Pb concentration ($r = -0.05$, $p = 0.7$). |
| Horiguchi et al. (1991)<br>Japan<br>NR | Design: cross-sectional cohort<br>Subjects: adult male secondary Pb refinery workers (n = 17), mean age: 44.9 yr (range 24–58); reference male subjects (n = 13), mean age: 33.5 yr (range 22–44)<br>Outcome measures: RBC deformability (microfiltration at −20 cm $H_2O$ pressure), RBC count, Hct, blood Hgb<br>Analysis: comparisons of outcome measures between Pb workers and reference group | Blood Pb (µg/dL) mean (SD):<br>Pb: 53.5 (16.1)<br>Reference: NR<br><br>Urine Pb (µg/L) mean (SD):<br>Pb: 141.4 (38.1)<br>Reference: NR | Significantly lower RBC deformability ($p < 0.01$), RBC count ($p < 0.01$) Hct ($p < 0.01$), and blood Hgb ($p > 0.001$) in Pb workers compared to reference group. |

## Table AX6-9.4 (cont'd). Effects of Lead on Hematopoietic System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Makino et al. (1997)<br>Japan<br>1990–1994 | Design: longitudinal survey<br>Subjects: adult male pigment or vinyl chloride stabilizer manufacture workers (n = 1573) mean age 45 yr<br>Outcome measures: blood Hgb, Hct, RBC count<br>Analysis: parametric comparison of outcome measures, stratified by blood Pb, linear regression | Blood Pb (µg/dL) mean (SD, range):<br>12.6 (2.0, 1–39)<br><br>Urine Pb (µg/L) mean (SD, range):<br>10.2 (2.7, 1–239) | Significantly higher ($p < 0.001$) Hct, blood Hgb, and RBC count in blood Pb category 16–39 µg/dL, compared to 1–15 µg/dL category.<br>Significant positive correlation between blood Pb concentration and Hct: $\forall = 42.95$, $\exists = 0.0586$ ($r = 0.1553$, $p < 0.001$), blood Hgb: $\forall = 14.65$, $\exists = 0.0265$ ($r = 0.1835$, $p < 0.001$), and RBC count $\forall = 457$, $\exists = 0.7120$ ($r = 0.1408$, $p < 0.001$). |
| Morita et al. (1997)<br>Japan<br>NR | Design: cross-sectional cohort<br>Subjects: male Pb workers (n = 76), mean age 42 yr (range 21–62); reference subjects (n = 13, 6 females), mean age, males 41 yr (range 26–52), females 45 yr (range 16–61)<br>Outcome measures: blood NADS, ALAD<br>Analysis: comparison of outcome measures (ANOVA) between blood Pb categories, linear regression | Blood Pb (µg/dL) mean (SD, range)<br>Pb: 34.6 (20.7, 2.2–81.6) | Significantly lower ($p < 0.01$) blood NADS and ALAD in blood Pb categories >20 µg/dL compared to <20 µg/dL, with dose trend in magnitude of difference.<br>Significant associations between increasing blood Pb and decreasing blood NADS and ALAD in Pb workers:<br>NADS: $\forall = 0.843$, $\exists = -0.00971$, $r = -0.867$, $p < 0.001$, $n = 76$<br>logALAD: $\forall = 1.8535$, $\exists = -0.015$, $r = -0.916$, $p < 0.001$, $n = 58$ |
| Kim et al. (2002)<br>Korea<br>1996 | Design: cross-sectional cohort<br>Subjects: adult male secondary Pb smelter workers (n = 83), mean age: 38.7 yr (SD 10.8); reference subjects (n = 24), mean age: 32.0 (SD 10.8)<br>Outcome measures: blood Hgb, blood ALAD, blood EP, blood P5N<br>Analysis: parametric comparison (ANOVA) of outcome measures between Pb workers and reference group, correlation, multivariate linear regression | Blood Pb (µg/dL) mean (SD)<br>Pb: 52.4 (17.7)<br>Reference: 6.2 (2.8) | Significantly ($p < 0.05$) lower blood P5N, ALAD, and Hgb; and higher blood EP in Pb workers compared to controls.<br>Significant ($p < 0.001$) correlations (in Pb worker group) with blood Pb: P5N ($r = -0.704$), log EP ($r = 0.678$), log ALAD ($r = -0.622$).<br>Significant association between increasing EP and decreasing blood Hgb:<br>blood Pb ∃60 µg/dL: $\exists = -1.546$ (96% CI: −2.387, −0.704), $r^2 = 0.513$, $p = 0.001$<br>blood Pb <60 µg/dL: $\exists = -1.036$ (96% CI: −1.712, −0.361), $r^2 = 0.177$, $p = 0.003$<br>Significant association between increasing P5N and increasing blood Hgb (high blood Pb group only):<br>blood Pb ∃60 µg/dL: $\exists = 0.222$ (96% CI: 0.015, 0.419), $r^2 = 0.513$, $p = 0.036$<br>Covariates included in model: P5N, log serum ferritin, log EP |

## Table AX6-9.4 (cont'd). Effects of Lead on Hematopoietic System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Schwartz et al. (1997)<br>Korea<br>1994-1995 | Design: cross-sectional<br>Subjects: adult male battery manufacture workers (n = 57), mean age 32 yrs (SD 6).<br>Outcome measures: blood Hgb, $Hgb_{A1}$, and $Hgb_{A2}$, ALAD genotype<br>Analysis: comparison of outcome measures between ALAD genotype strata | Blood Pb (µg/dL) mean (SD):<br>ALAD1,1 (n = 38): 26.1 (9.8)<br>ALAD1,2 (n = 19): 24.0 (11.3) | Mean blood Pb (p = 0.48) and blood Hgb levels (p = 0.34) were not different between ALAD genotype strata. |

## Table AX6-9.5. Effects of Lead on the Endocrine System in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Mahaffey et al. (1982)<br>Wisconsin, New York<br>NR | Design: cross-sectional<br>Subjects: children/adolescents (n = 177), ages 1–16 yr<br>Outcome measures: serum 1,25-OH-D<br>Analysis: comparison of outcome measures between age, location and blood Pb strata, linear regression | Blood Pb (µg/dL) range:<br>12–120 | Serum 1,25-OH-D levels were significantly ($p = 0.05$) higher in the age group 11–16 yr compared to age groups 1–5 or 6–10 yr. Increasing blood Pb (log-transformed) significantly associated with decreasing serum 1,25-OH-D levels in children 1–5 yr of age ($\forall = 74.5$, $\exists = -34.5$, $r = -0.884$, $n = 50$)<br>Dietary calcium: NR |
| Rosen et al. (1980)<br>New York<br>NR | Design: cross-sectional<br>Subjects: children (n = 45), ages 1–5 yr<br>Outcome measures: serum calcium, PTH, 25-OH-D, 1,25-OH-D<br>Analysis: comparison of outcome measures between blood Pb strata, and before and after chelation, correlation | Blood Pb (µg/dL) mean (SE, range):<br>#29 (n = 15): 18 (1, 10–26)<br>30–59 (n = 18): 47 (2, 33–55)<br>∃60 (n = 12): 74 (98, 62–120) | Significantly higher serum PTH levels and lower 25-OH-D in high-Pb group compared to low-Pb group; significantly lower 1,25-OH-D levels in moderate- and high-Pb group compared to low-Pb group. Serum levels of 1,25-OH-D were negatively correlated with blood Pb (high Pb: $r = -0.71$, moderate: $r = -0.63$, $p < 0.01$). After chelation therapy, blood Pb decreased and serum 1,25-OH-D levels increased to levels not significantly different ($p > 0.1$) from low-Pb group, 25-OH-D levels were unchanged.<br>Dietary calcium intake (mg/day) mean (SE):<br>Low Pb: 800 (30)<br>Moderate Pb: 780 (25)<br>High Pb: 580 (15) |
| Sorrell et al. (1977)<br>New York<br>1971–1975 | Design: cross-sectional<br>Subjects: children (124), ages 1–6 yr<br>Outcome measures: serum calcium, phosphate, 25-OH-D<br>Analysis: comparison of outcome measures between blood Pb strata, correlation | Blood Pb (µg/dL) mean (SE):<br>#29 (n = 40): 23 (1)<br>30–59 (n = 35): 48 (1)<br>∃60 (n = 49): 84 (5.0) | Serum calcium and 25-OH-D were significantly lower in high Pb group ($p < 0.001$). Significant negative correlation between blood Pb and serum calcium (high Pb, $r = -0.78$, $p < 0.001$) or calcium intake high Pb, ($r = -0.82$, $p < 0.001$) in all three Pb strata. Serum 25-OH-D was significantly positively correlated with vitamin D intake, but not with blood Pb.<br>Dietary calcium intake (mg/day) mean (SE):<br>Low Pb: 770 (20)<br>Moderate Pb: 760 (28)<br>High Pb: 610 (20) |

## Table AX6-9.5 (cont'd). Effects of Lead on the Endocrine System in Children

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Siegel et al. (1989)<br>Connecticut<br>1987 | Design: cross-sectional<br>Subjects: children (n = 68, 32 female), ages 11 mo to 7 yr<br>Outcome measures: serum FT4, TT4<br>Analysis: linear regression | Blood Pb (µg/dL) mean (range):<br>25 (2–77) | No significant association between blood Pb concentration and thyroid hormone outcomes. Linear regression parameters:<br>FT4: $\forall = 1.55$ (SE 0.05), $\exists = 0.0024$ (SE 0.0016), $r^2 = 0.03$, $p = 0.13$<br>TT4: $\forall = 8.960$ (SE 0.39), $\exists = 0.0210$ (SE 0.0127), $r^2 = 0.04$, $p = 0.10$ |
| Koo et al. (1991)<br>Ohio<br>NR | Design: longitudinal (subset of prospective)<br>Subjects: children (n = 105, 56 females), age 21, 27, 33 mo<br>Outcome measures: serum calcium magnesium, phosphorus, PTH, CAL, 25-OH-D, 1,25-OH-D, and bone mineral content<br>Analysis: structural equation modeling | Blood Pb (µg/dL) geometric mean (GSD, range):<br>Lifetime mean, based on quarterly measurements:<br>9.74 (1.44, 4.8–23.6)<br>Concurrent:<br>15.01 (1.52, 6–44)<br>Maximum observed:<br>18.53 (1.53, 6–63) | Significant association between increasing blood Pb (ln-transformed) and covariate-adjusted decreasing serum phosphorus ($\forall = 1.83$, $\exists = -0.091$). No other covariate-adjusted outcomes were significantly associated with blood Pb.<br>Covariates retained: age, sex, race, and sampling season.<br>Dietary calcium intake (mg/day)<br>#600: n = 4 (4%)<br>600–1200: n = 58 (55%)<br>>1200: n = 43 (41%) |

## Table AX6-9.6. Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** | | | |
| Cullen et al. (1984)<br>Connecticut<br>1979<br>NR | Design: clinical case study<br>Subjects: adult males with neurological symptoms of Pb poisoning<br>Outcome measures: serum, FSH, LH, PRL, TES<br>Analysis: clinical outcomes in terms of abnormal values | Blood Pb (µg/dL) range:<br>66–139 | Five subjects with defects in spermatogenesis (including azospermia), with no change in basal serum FSH, LH, PRL, and TES. |
| Robins et al. (1983<br>Connecticut<br>NR | Design: cross-sectional<br>Subjects: adult male brass foundry workers (n = 47), age range 20–64 yr<br>Outcome measures: FT4<br>Analysis: simple linear regression with stratification by age and race. | Blood Pb (µg/dL) range:<br>16–127 | Significant association between increasing blood Pb concentration and decreasing FT4 ($\forall$ = 1.22, $\exists$ = −0.0042 [95% CI: −0.0002, −0.0082], $r^2$ = 0.085, p = 0.048). Significant interaction between race (black, white) and blood Pb.<br>When stratified by race:<br>Black: $\forall$ = 1.13, $\exists$ = −0.0051 (95% CI: 0.0007, −0.0095), $r^2$ = 0.21, p = 0.03<br>White: $r^2$ = 0.05, p = 0.27<br>Strength of association not changed by including age in the regression model. |
| Braunstein et al. (1978)<br>California<br>NR | Design: clinical<br>Subjects: adult male secondary Pb smelter (n = 12), mean age 38 yr, reference group, (n = 9), mean age 29 yr<br>Outcome measures: serum EST, FSH, LH, TES, HCG-stimulated EST and TES, GnRH-stimulated serum FSH and LH<br>Analysis: comparisons of outcome measures between patients symptomatic for Pb poisoning, Pb-exposed patients not symptomatic, reference group | Blood Pb (µg/dL) mean (SD):<br><br>Symptomatic (n = 9):<br>Time of test: 38.7 (3.0)<br>Highest: 88.2 (4.0)<br><br>Asymptomatic (n = 4):<br>Time of test: 29.0 (5.0)<br>Highest: 80.0 (0.0)<br><br>Reference: 16.1 (1.7) | Statistically significant (p < 0.05) lower basal serum TES, higher TES response to HCG, and significantly reduced LH response to GnRH in workers symptomatic for Pb poisoning (including EDTA-provoked urinary Pb >500 µg/24 hr). |
| Refowitz (1984)<br>NR | Design: cross-sectional survey<br>Subjects: secondary copper smelter workers (n = 58)<br>Outcome measures: FT4, TT4<br>Analysis: linear regression | Blood Pb (µg/dL) range:<br>5–60 | No significant association between blood Pb and hormone levels:<br>FT4: $\forall$ = 2.32, $\exists$ = −0.0067 (95% CI: −0.18, 0.0043)<br>TT4: $\forall$ = NR, $\exists$ = −0.28 (95% CI: −0.059, 0.0002)<br>No significant association when ratified by race (black, white) |

## Table AX6-9.6 (cont'd). Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** | | | |
| Alexander et al. (1998, 1996a)<br>British Columbia<br>1993 | Design: cross-sectional<br>Subjects: adult male primary smelter workers (n = 152), mean age 40 yr<br>Outcome measures: serum FSH, LH, TES<br>Analysis: multivariate linear regression | Blood Pb (µg/dL) range (n = 81): 22.8 (5–58)<br><br>Semen Pb (µg/dL) range: 1.9 (0.1–17.6) | No significant association between covariate-adjusted blood Pb and hormone levels (p ∃ 0.5) or prevalence of abnormal levels.<br>Significant association between covariate-adjusted increasing semen Pb concentration and decreasing serum TES (∃ = −1.57, p = 0.004).<br>Covariates considered: age, smoking, alcohol, other metals in blood (arsenic, cadmium, copper, zinc), abstinence days prior to sample collection, and sperm count. |
| Schumacher et al. (1998)<br>British Columbia<br>1993 | Design: cross-sectional<br>Subjects: adult male smelter workers (n = 151) mean age 40 yr (SD 7.2)<br>Outcome measures: serum FT4, TT4, TSH<br>Analysis: linear regression, ANOVA | Blood Pb (µg/dL) mean: 24.1 (n = 151)<br><15 (n = 36)<br>15–24 (n = 52)<br>25–39 (n = 41)<br>∃40 (n = 22) | No significant effect of blood Pb (categorical) on covariate-adjusted or unadjusted FT4 (p = 0.68), TT4 (p = 0.13), TSH (p = 0.54). No significant association of blood Pb with prevalence of abnormal values of hormones. No significant association between 10-yr avg blood Pb and hormone levels or prevalence of abnormal values.<br>Covariates considered: age and alcohol consumption. |
| **Europe** | | | |
| Gennart et al. (1992)<br>Belgium<br>NR | Design: cross sectional cohort<br>Subjects: adult battery manufacture workers (n = 98), mean age 37.7 yr (SD 8.3, range 22–55); reference worker group (n = 85), mean age 38.8 yr (SD 8.7, range 22–55)<br>Outcome measures: serum TT3, FT4, TT4, TSH, FSH, LH<br>Analysis: comparison of outcome measures between Pb workers and reference group | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 51.0 (8.0, 40.0–75.0)<br>Reference: 20.9 (11.1, 4.4–39.0)<br><br>Urine Pb (µg/g creatinine) mean (range):<br>Pb: 57.8 (1.95, 4.3–399)<br>Reference: 9.75 (2.73, 1.45–77.7) | Mean hormone levels in Pb workers and reference group not different (p = NR); no association between hormone levels and blood Pb or exposure duration quartile. |

## Table AX6-9.6 (cont'd). Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Assennato et al. (1987)<br>Italy<br>NR | Design: cross-sectional<br>Subjects: adult male battery manufacture workers (n = 39), mean age 41 yr (SD 10); reference cement plant workers (n = 18), mean age 40 yr (SD 10)<br>Outcome measures: serum FSH, LH, PRL, TES; urinary 17-ketosteroids<br>Analysis: parametric comparison of outcome measures between Pb and reference groups | Blood Pb (µg/dL) mean (SD):<br>Pb: 61 (20)<br>Reference: 18 (5)<br><br>Urinary Pb (µg/L) mean (SD):<br>Pb: 79 (37)<br>Reference: 18 (8) | No significant association ($p > 0.05$) between blood Pb and hormone levels. |
| Govoni et al. (1987)<br>Italy<br>NR | Design: cross-sectional<br>Subjects: adult male pewter manufacture workers (n = 78), mean age 35 yr (SD 19, range 19–52)<br>Outcome measures: serum PRL<br>Analysis: parametric comparison of outcome measures between blood Pb and ZPP strata | Blood Pb (µg/dL) mean (SD)/blood ZPP (µg/dL) mean (SD):<br>A (n = 22):<br>28.2 (7.1)/24.4 (8.7)<br>B (n = 33):<br>60/3 (19.3)/131 (107)<br>C (n = 13):<br>33.1 (6.7)/77.0 (42.2)<br>D (n = 8):<br>49.1 (4.2)/34.0 (4.8) | Significantly ($p < 0.02$) higher serum PRL in high ZPP strata (B and C, compared to low ZPP strata A). |
| Rodamilans et al. (1988)<br>Spain<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb smelter workers (n = 23), age range 21–44 yr; reference group (n = 20), age range 20–60 yr<br>Outcome measures: serum FSH, LH, TES, FTES, SHBG<br>Analysis: comparison of outcome measures between exposure duration strata | Blood Pb (µg/dL) mean (SD)<br>Pb <1 yr (n = 5): 66 (22)<br>Pb 1–5 yr (n = 8): 73 (24)<br>Pb >5 yr (n = 10): 76 (11)<br>Reference (n = 20): 17.2 (13) | Serum TES ($p = 0.01$) and FTES ($p = 0.001$) significantly lower and SHBG significantly higher ($p < 0.025$) in >5-yr exposure group compared to reference group; serum LH was significantly ($p < 0.01$) higher in all exposure groups compared to reference group. |

## Table AX6-9.6 (cont'd). Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Erfurth et al. (2001)<br>Sweden<br>NR | Design: cross-sectional cohort<br>Subjects: adult male active secondary smelter workers (n = 62), mean age 43 yr (range 21–78) reference worker group (n = 26), mean age 43 yr (range 23–66)<br>Outcome measures: serum FT3, FT4, TSH, TES, SHBG; TRH-stimulated serum TSH; GnRH-stimulated serum FSH, LH, and PRL<br>Analysis: nonparametric comparison of outcome measures between Pb workers and reference group; multivariate linear regression | Blood Pb (µg/dL) median (range):<br>Pb: 31.1 (8.3–93.2)<br>Reference: 4.1 (0.8–6.2)<br><br>Plasma Pb (µg/dL) median (range):<br>Pb: 31.1 (8.3–93.2)<br>Reference: 4.1 (0.8–6.2)<br><br>Urine Pb (µg/g creatinine) median (range):<br>Pb: 19.6 (3.1–80.6)<br>Reference: 4.1 (2.4–7.3)<br><br>Bone (finger) Pb (µg/g) median (range):<br>Pb: 25 (−13 to 99)<br>Reference: 2 (−21 to 14) | Basal hormone levels in workers not different from reference group ($p \exists 0.05$); age-adjusted basal hormone levels not associated with plasma Pb, blood Pb, urine Pb, or bone Pb. In an age-matched subset of the cohorts (n = 9 Pb workers, n = 11 reference), median GnRH-stimulated serum FSH was significantly ($p = 0.014$) lower (77 IU/L H hr) in Pb workers than in reference group (162 IU/L H hr). No association between stimulated TSH, LH, FSH or PRL and Pb measures. |
| Gustafson et al. (1989)<br>Sweden<br>NR | Design: cross-sectional cohort<br>Subjects: adult male secondary smelter workers (n = 21) mean age 36.0 yr (SD 10.4); individually matched for age, sex, and work shift (n = 21)<br>Outcome measures: serum FTES, TTES; FSH, LH, PRL, COR, TSH, TT3, TT4<br>Analysis: nonparametric comparison of outcome measures between Pb workers and reference group, correlation | Blood Pb (µg/dL) mean (SE):<br>Pb: 39.4 (2.1)<br>Reference: 5.0 (0.2) | Significantly higher TT4 ($p < 0.02$) and lower serum FSH ($p = 0.009$) in Pb workers compared to reference group. When restricted to the age range <40 yr, Pb workers had significantly higher TT4 ($p = 0.01$) and lower FSH ($p = 0.03$), LH ($p = 0.04$), and COR ($p = 0.04$), compared to the reference group. |
| Campbell et al. (1985)<br>UK<br>NR | Design: cross-sectional cohort<br>Subjects: adult male welders (n = 25); reference subjects (n = 8) (ages NR)<br>Outcome measures: plasma ACE, AI, PRA, plasma ALD<br>Analysis: linear regression, nonlinear least squares | Blood Pb (µg/dL) mean (SD, range): 35.6 (15.3, 8–62) | Significant positive correlation between blood Pb concentration and plasma ALD level ($r = 0.53$, $p < 0.002$), PRA ($r = -0.76$, $p < 0.001$), AI ($r = 0.68$, $p < 0.002$), and ACE ($r = 0.74$, $p < 0.001$). |

## Table AX6-9.6 (cont'd). Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Europe** (cont'd) | | | |
| Chalkley et al. (1998)<br>UK<br>1979–1984 | Design: cross-sectional<br>Subjects: adult male primary metal (cadmium, Pb, zinc) workers (n = 19), ages NR<br>Outcome measures: blood calcium, serum 25-OH-D, 1,25-OH-D, 24,25-OH-D<br>Analysis: comparison of outcome measures (ANOVA) in group stratified by blood Pb and urinary cadmium | Blood Pb (µg/dL) mean (SD, range): 47 (21–76) | After stratification by blood Pb and urinary cadmium, serum 1,25-OH-D levels in strata were significantly different (p = 0.006), with higher mean values in high blood Pb (>40 µg/dL)/high blood cadmium (>0.9 µg/L)/high urine cadmium >3.1 µg/L) stratum compared to low blood Pb (<40 µg/dL)/high blood cadmium (>0.9 µg/L)/high urine cadmium >3.1 µg/L) stratum. Serum 24,25-OH-D levels decreased with increasing urinary cadmium (p = NR) |
| Mason et al. (1990)<br>UK<br>NR | Design: cross-sectional<br>Subjects: adult male Pb workers (n = 63), age range 21–63 yr; reference male subjects (n = 75), age range 22–64 yr<br>Outcome measures: serum calcium phosphate, PTH, 1,25-OH-D<br>Analysis: comparison of al outcome measures between Pb workers and reference group, multivariate regression | Blood Pb (µg/dL) range:<br>Pb (15–94)<br>Reference: NR<br><br>Tibia Pb (µg/g)<br>Pb: 0–93<br>Reference: NR | Significantly higher (p < 0.025) prevalence of elevated 1,25-OH-D (>2 SD of reference mean) in Pb workers (8/63, 13%) compared to reference group (1/75, 1.3%). Serum levels of 1,25-OH-D significantly (p < 0.05) higher in Pb workers compared to reference group.<br>After stratification of Pb workers into exposure categories (high: blood Pb ∃40 µg/dL and bone Pb ∃40 µg/g, low: blood Pb #40 µg/dL and bone Pb #40 µg/g), serum 1,25-OH-D levels were significantly (p < 0.01) higher in the high Pb group.<br>Increasing blood Pb was significantly (p = NR) associated with increasing 1,25-OH-D levels ($r^2$ = 0.206; with age and bone Pb included, $r^2$ = 0.218). After excluding 12 subjects whose blood Pb concentrations >60 µg/dL, $r^2$ = 0.162 (p = 0.26). |
| McGregor and Mason, (1990)<br>UK<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb workers (n = 90), mean age (31.5 yr (SD 11.9); reference workers (n = 86), mean age 40.6 yr (SD 11.8)<br>Outcome measures: serum FSH, LH, TES, SHBG<br>Analysis: comparison of outcome means between Pb workers and reference groups, multivariate regression, correlation | Blood Pb (µg/dL) range:<br>Pb: 17–77<br>Reference: <12 | Age-adjusted serum FSH was significantly (p = 0.004) higher in Pb workers compared to reference group.<br>Increasing serum FSH significantly (p = NR) associated with blood Pb and age. Increasing serum LH significantly associated with increasing exposure duration (not blood Pb or age).<br>No significant association between serum TES or SHBG and blood Pb or exposure duration.<br>No significant difference in prevalence of abnormal hormone levels between groups. |

## Table AX6-9.6 (cont'd). Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Latin America** | | | |
| L∴pez et al. (2000)<br>Argentina<br>NR | Design: cross sectional<br>Subjects: adult male battery manufacture workers (n = 75), age range 21–56 yr; reference group (n = 62), age NR<br>Outcome measures: serum TT3, FT4, TT4, TSH<br>Analysis: comparison of outcome measures between Pb workers and reference group, correlation | Blood Pb (µg/dL) mean (range):<br>Pb: 50.9 (23.3, 8–98)<br>Reference: 19.1 (7.1, 4–39) | Significantly higher serum FT4 ($p < 0.01$) and TT4 ($p < 0.05$) in Pb workers compared to reference group. Significant positive correlation between blood Pb and serum TT3 ($p < 0.05$), FT4 ($p < 0.01$), TT4 ($p < 0.05$), and TSH ($p < 0.05$), for blood Pb range 8–50 µg/dL; and for TSH ($p < 0.05$) for blood Pb range 8–26 µg/dL. |
| Roses et al. (1989)<br>Brazil<br>NR | Design: adult male Pb workers (n = 70), age range 20–53 yr; reference group (n = 58), age range 25–37 yr.<br>Outcome measures: serum PRL<br>Analysis: comparison of outcome measure between Pb workers and reference group, linear regression | Blood Pb (µg/dL) range:<br>Pb: 9–86<br>Reference: 8–28 | Serum RL levels in Pb workers and reference group not significantly different (p = NR). Correlation between serum PRL and blood Pb ($r = 0.57$, p = NR). |
| **Asia** | | | |
| Dursun and Tutus (1999)<br>Turkey<br>NR | Design: cross-sectional<br>Subjects: adult metal powder manufacture workers (n = 27) mean age 41.1 yr (SD 5.45, range 25–50); reference group (n = 30), mean age 42 yr (SD 3.42, range 28–49)<br>Outcome measures: serum FT4, TT4, FT3, TT3, TSH<br>Analysis: parametric comparison of outcome measures between Pb and reference groups, simple and multivariate linear regression | Blood Pb (µg/dL) mean (range):<br>Pb: 17.1 (9.0, 6–36)<br>Reference: 2.4 (0.1, 1–4) | Significantly ($p < 0.0001$) higher mean TT4, FT4, and FT3 in Pb workers compared to reference group.<br>Significant association between TT4, age ($\exists = 0.23$, $p < 0.006$), and exposure duration ($\exists = -0.20$, $p > 0.01$), but not blood Pb ($\exists = 0.00$, NR) in linear regression model that included age, blood Pb, and exposure duration ($\forall = 2.76$, $r^2 = 0.3$, $p = 0.03$). |

## Table AX6-9.6 (cont'd). Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Kristal-Boneh et al. (1998)<br>Israel<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture/recycling workers (n = 56), mean age 43.4 yr (SD 11.2); reference workers (n = 90), mean age 41.5 yr (SD 9.3)<br>Outcome measures: serum calcium, magnesium, phosphorus, PTH, 25-OH-D, 1,25-OH-D<br>Analysis: parametric comparison of outcome measures between Pb workers and reference group, multivariate linear regression | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 42.6 (14.5, 20–77)<br>Reference: 4.5 (2.6, 1.4–19) | Serum 1,25-OH-D ($p = 0.0001$) and PTH ($p = 0.042$) were significantly higher in Pb workers compared to reference group<br>Increasing blood Pb concentration (ln-transformed) was significantly associated with covariate-adjusted increasing serum PTH and 1,25-OH-D levels:<br>PTH: $\exists = 4.8$ (95% CI: 0.8, 8.8), $r^2 = 0.12$<br>1,25-OH-D: $\exists = 4.8$ (95% CI: 2.7, 6.9), $r^2 = 0.10$<br>Occupational Pb exposure (yes) significantly associated with increasing PTH and 1,25-OH-D levels.<br>Covariates retained: age, alcohol consumption, smoking; calcium, magnesium, and calorie intake:<br>PTH: $\exists = 7.81$ (95% CI: 3.7, 11.5)<br>1,25-OH-D: $\exists = 12.3$ (95% CI: 3.84, 20.8) |
| Horiguchi et al. (1987)<br>Japan<br>NR | Design: cross-sectional<br>Subjects: adult secondary Pb refinery (n = 60, 8 females), mean age 49 yr (range 15–69)<br>Outcome measures: serum TT3, TT4, TSH<br>Analysis: comparison of outcome measures (method NR), between job categories, correlation | Blood Pb (µg/dL) mean (SD):<br>Male: 31.9 (20.4)<br>Female: 13.5 (9.5)<br><br>Urine Pb (µg/L) mean (SD):<br>Male: 59.3 (76.3)<br>Female: 26.0 (19.7) | No significant differences (p = NR) between hormone levels in job Pb categories: mean blood Pb (µg/dL, SD): 17.9 (10.7), 25.6 (15.4), 49.9 (18.7). No significant correlations (p = NR) between hormone levels and blood or urine Pb levels. |
| Ng et al. (1991)<br>China<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 122), mean age 32.6 (SD 8,2, range 17–54); reference group (n = 49), mean age 43.4 yr (SD 13.4, range 18–74)<br>Outcome measures: serum FSH, LH, PRL, TES<br>Analysis: multivariate linear regression ANCOVA | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 35.2 (13.2, 9.6–77.4)<br>Reference: 8.3 (2.8, 2.6–14.8) | When cohorts were stratified by age serum FSH and LH were significantly ($p < 0.02$) higher in Pb workers <40 yrs of age compared to corresponding age strata of the reference group; serum TES was significantly ($p < 0.01$) lower in Pb workers ∃40 yr of age. Covariate-adjusted serum TES were significantly lower ($p < 0.01$) in Pb workers in the ∃10-yr exposure duration category, compared to the reference group. Covariate-adjusted serum FSH and LH were significantly higher ($p < 0.01$) in Pb workers in the <10-yr exposure duration category, compared to the reference group.<br>Covariates: age and tobacco smoking. |

## Table AX6-9.6 (cont'd). Effects of Lead on the Endocrine System in Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Zheng et al. (2001)<br>China<br>NR | Design: retrospective cross-sectional<br>Subjects: adult hospital patients (n = 82, 32 females) mean age 49.6 yr (SD 18.7)<br>Outcome measures: serum and CSF TTR, TT4<br>Analysis: simple and multivariate linear regression | Blood Pb (µg/dL) mean (SD):<br>All: 14.9 (8.3)<br>Female: 14.2 (8.76)<br>Male: 15.4 (8.07) | No significant association between blood Pb and serum TTR ($r = -0.114$, $p = 0.307$), TT4 ($r = -0.160$, $p = 0.152$).<br>Significant association between age-adjusted CSF Pb and CSF TTR ($r = -030$, $p = 0.023$).<br>No significant association between CSF Pb and CSF TT4 ($r = -0.22$, $p = 0.090$). |
| Singh et al. (2000)<br>India<br>NR | Design: cross-sectional cohort<br>Subjects: adult male petrol pump attendants (n = 58), mean age 31.7 yr (SD 10.6); reference group (n = 35), mean age 28.9 yr (SD 4.20)<br>Outcome measures: serum TT3, TT4, TSH<br>Analysis: parametric comparison of outcome measures between Pb workers and reference group, stratified by blood Pb or exposure duration | Blood Pb (µg/dL) mean (SD):<br>Pb: 51.6 (9.3)<br>Reference: 9.5 (8.7) | Serum TSH significantly higher ($p < 0.01$) in Pb workers compared to reference group, significantly higher in high blood Pb category (#70 µg/dL, mean 54.5 µg/dL) compared to low worker group #41 µg/dL, mean 31.3 µg/dL). Serum TSH significantly higher in Pb workers who were exposed for #60 mo, compared to workers exposed for >60 mo. |
| **Africa** | | | |
| Tuppurainen et al. (1988)<br>Kenya<br>1984 | Design: cross-sectional<br>Subjects: adult male battery manufacture workers (n = 176), mean age 34.1 yr (SD 8.1, range 21–54)<br>Outcome measures: serum TT3, FT4, TT4, TSH<br>Analysis: multivariate linear regression and correlation | Blood Pb (µg/dL) mean (SD, range):<br>55.9 (23.8, 14.5–133.6) | Increasing exposure duration significantly associated with decreasing FT4 ($r^2 = 0.071$, $p = 0.001$) and TT4 ($r^2 = 0.059$, $p = 0.021$); regression not improved by including age or blood Pb.<br>Strength of association greater when restricted to workers who had an exposure duration >7.6 yrs: FT4: $r^2 = 0.33$, $p < 0.002$; TT4: $r^2 = 0.21$, $p < 0.001$.<br>No significant association between blood Pb and hormone levels. |

## Table AX6-9.7. Effects of Lead on the Hepatic System in Children and Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| ***Children*** | | | |
| **United States** | | | |
| Saenger et al. (1984)<br>New York<br>NR | Design: clinical cases<br>Subjects: children (n = 26) ages 2–9 yr; age-matched reference group (n = NR)<br>Outcome measures: urinary cortisol and 6∃-OH-cortisol (CYP3A metabolite of cortisol)<br>Analysis: comparison of outcome measure between children who qualified for EDTA treatment (EDTA provocation >500 µg/24 hr) | Blood Pb (µg/dL) mean (SE, range):<br>Chelated: 46 (2, 33–60)<br>Not chelated: 42 (3, 32–60)<br><br>Urinary Pb (µg/24 hr) mean (SE, range), EDTA-provocation:<br>Chelated: 991 (132, 602–2247)<br>Not chelated: 298 (32, 169–476) | Significantly lower (~45% lower) urinary excretion of 6∃-OH-cortisol ($p = 0.001$) and urinary 6∃-OH-cortisol: cortisol ratio ($p < 0.001$) in children who qualified for chelation than in children who did not qualify and significantly lower than age-matched reference group. Urinary 6∃-OH-cortisol: cortisol ratio was significantly correlated with blood Pb ($r = -0.514$, $p < 0.001$), urinary Pb, and EDTA provocation urinary Pb ($r = -0.593$, $p < 0.001$). |
| ***Adults*** | | | |
| **Asia** | | | |
| Al-Neamy et al. (2001)<br>United Arab Emirates<br>1999 | Design: cross-sectional cohort<br>Subjects: adult male (n = 100) workers (e.g., gas pump attendants, garage workers, printing workers, construction workers), mean age 34.6 yr (SD 8.0); reference group (n = 100) matched with Pb workers for age, sex, nationality.<br>Outcome measures: serum protein, albumin, ALT, AP, AST, BUN, (GT, LDH<br>Analysis: comparison of outcome measures between Pb workers and reference group | Blood Pb (µg/dL) mean (SD): Pb: 77.5 (42.8)<br>Reference: 19.8 (12.3) | Significantly higher serum AP ($p = 0.012$) and LDH ($p = 0.029$) in Pb workers compared to reference group (values within normal range). |

## Table AX6-9.7 (cont'd). Effects of Lead on the Hepatic System in Children and Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Hsiao et al. (2001)<br>China<br>1989–1999 | Design: longitudinal<br>Subjects: adult battery manufacture workers (n = 30, 13 females), mean age 38.3 yr<br>Outcome measures: serum ALT<br>Analysis: GEE for repeated measures (models: linear correlation, threshold change, synchronous change, lag change); logistic regression | Blood Pb (µg/dL) mean:<br>1989: 60 (~25–100)<br>1999: 30 (~10–60) | No association between blood Pb and ALT.<br>Odds ratios (95% CI):<br>Synchronous change model: 1.25 (0.69, 2.25)<br>Lag change: 1.76 (0.76, 4.07) |
| Satarug et al. (2004)<br>Thailand<br>NR | Design: cross-sectional<br>Subjects: adults from general population (n = 118, 65 female), age range, 21–57 yr<br>Outcome measures: coumarin-induced urinary 7-OH-coumarin (marker for CYP2A6 activity)<br>Analysis: multivariate linear regression | Urinary Pb (µg/g creatinine) mean (SD, range):<br>Males: 1.3 (1.8, 0.1–12)<br>Females: 2.4 (1.1, 0.6–6.8)<br><br>Serum Pb (µg/L) mean (SD, range):<br>Males: 4.2 (5.4, 1–28)<br>Females: 3.0 (2.2, 1–12) | Significant association between increasing urinary Pb and decreasing covariate-adjusted urinary 7-OH-coumarin ($\exists = -0.29$, $p = 0.003$) in males, but not in females. Covariates retained: age and zinc excretion. Significant association in opposite direction between urinary cadmium and urinary 7-OH-coumarin ($\exists = 0.38$, $p = 0.006$). |

## Table AX6-9.8. Effects of Lead on the Gastrointestinal System

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Canada** | | | |
| Holness and Nethercott (1988)<br>Ontario<br>1982–1984 | Design: longitudinal<br>Subjects: adult male demolition workers (n = 119), age NR<br>Outcome measures: prevalence of symptoms<br>Analysis: comparison of prevalence of symptoms (questionnaire) stratified by job phase or blood Pb | Blood Pb (µg/dL) mean (range):<br>Phase 1: 59 (15–99)<br>Phase 2: 30<br>Phase 3: 19<br>Phase 4: 17 | Prevalence of reporting of symptoms of abdominal cramps or constipation increased with increasing blood Pb concentration ($p < 0.05$):<br><50 µg/dL: 8%, 6%<br>50–70 µg/dL: 37%, 42%<br>>70 µg/dL: 77%, 62% |
| **Caribbean** | | | |
| Matte et al. (1989)<br>Jamaica<br>1987 | Design: survey<br>Subjects: battery manufacture/repair workers (n = 63), mean age ~30 yr (range 11–47)<br>Outcome measures: prevalence of symptoms<br>Analysis: comparison of GI symptoms (questionnaire) between blood Pb strata | Blood Pb (µg/dL) geometric mean site range: 40–64<br>Blood Pb distribution:<br>>60: 60%<br><60: 40% | When stratified by blood Pb, <60 µg/dL (low) or ∃60 µg/dL (high), prevalence ratio (high/low) was not significant for abdominal pain (1.5, [95% CI: 0.5, 4.6]), or for any other Pb symptom (e.g. muscle weakness). |
| **Asia** | | | |
| Bercovitz and Laufer (1991)<br>Israel<br>NR | Design: cross-sectional<br>Subjects: health individuals (n = 12), peptic ulcer patients (n = 11), and individuals with heart disease (n = 11) with environmental exposure<br>Analysis: one-way ANOVA used to compare tooth Pb concentrations in the three groups | Tooth Pb (:g/g dry dentine) mean (SE):<br>Healthy: 25.62 (10.15)<br>Peptic ulcer: 75.02 (8.15)<br>Heart disease: 20.30 (2.70) | Tooth Pb levels in patients with gastrointestinal ulcers (n = 11), were significantly higher than that in healthy subjects ($p = 0.001$)). Ten of the 11 peptic ulcer patients had a higher Pb level than the health subjects. In these 10 patients, increased severity of the ulcer and longevity of suffering was associated with increased tooth Pb levels. There was no significant difference between the tooth Pb levels in the healthy subjects and in the heart disease patients. |

## Table AX6-9.8 (cont'd). Effects of Lead on the Gastrointestinal System

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **Asia** (cont'd) | | | |
| Lee et al. (2000)<br>Korea<br>NR | Design: cross-sectional cohort<br>Subjects: adult male Pb workers (n = 95; secondary smelter, PVC-stabilizer manufacture, battery manufacture); mean age 42.8 yr (SD 9.3, range 19–64); reference group (n = 13), mean age 35.1 yr (SD 9.9, range 22–54)<br>Outcome measures: prevalence of GI symptoms (self-administered questionnaire)<br>Analysis: multivariate logistic regression | Blood Pb (µg/dL) mean (SD, range):<br>Pb: 44.6 (12.6, 21.4–78.4)<br>Reference:<br>5.9 (1.2, 4.0–7.2) | Covariate-adjusted OR for GI symptoms (loss of appetite, constipation or diarrhea, abdominal pain) in workers (referents not included in model) were not significant:<br>Blood Pb (45.7 µg/dL vs. <45.7 µg/dL): OR = 1.8 (95% CI: 0.7, 4.5)<br>DMSA-provoked urinary Pb (>260.5 vs. <260.5 µg): OR = 1.1 (95% CI: 0.4, 2.5)<br>OR for neuromuscular symptoms were significantly associated with DMSA-provoked Pb (OR = 7.8 [95% CI: 2.8, 24.5]), but not with blood Pb.<br>Covariates retained: age, tobacco smoking, and alcohol consumption. |
| **Africa** | | | |
| Awad el Karim et al. (1986)<br>Sudan<br>NR | Design: cross-sectional cohort<br>Subjects: adult male battery manufacture workers (n = 92), mean age 31.1 yr (SD 8.2); reference group (n = 40), mean age 33.7 yr (SD 9.7)<br>Outcome measures: clinical evaluation<br>Analysis: comparison of prevalence of symptoms of Pb poisoning between Pb workers and reference group | Blood Pb distribution for Pb workers<br>>80: 23%<br>40–80: 72%<br><40: 5%<br><br>Blood Pb (µg/dL) mean (SD, range):<br>Pb: 55–81 (mean range for various jobs), range 39–107<br>Reference: 21 (8.5, 7.4–33.1) | Prevalences of abdominal colic (pain) and constipation were 41.3% and 41.4 % in Pb workers and 7.5% and 10%, respectively, in the reference group. |

## Table AX6-9.9. Effects of Lead on Bone and Teeth in Children and Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| ***Children*** | | | |
| **United States** | | | |
| Moss et al. (1999)<br>U.S.<br>1988–1994 | Design: cross-sectional national survey (NHANES III)<br>Subjects: general population (n = 24,901), ages 2–5 yr (n = 3,547), 6–11 yr (n = 2,894), ∃12 yr (18,460)<br>Outcome measures: number of caries (dfs, DFS, DMFS)<br>Analysis: multivariate linear regression and logistic regression | Blood Pb (:g/dL) geometric mean (SE):<br>2–5 yr: 2.90 (0.12)<br>6–11 yr: 2.07 (0.08)<br>∃12 yr: 2.49 (0.06) | Increasing blood Pb concentration (log-transformed) significantly associated with covariate adjusted increases in dfs:<br>2–5 yr: ∃ = 1.78 (SE 0.59), p = 0.004<br>6–11 yr: ∃ = 1.42 (SE 0.51), p = 0.007<br>Increases in DFS:<br>6–11 yr: ∃ = 0.48 (SE 0.22), p = 0.03<br>∃12 yr: ∃ = 2.50 (SE 0.69), p < 0.001<br>Increases in DMFS:<br>∃12 yr: ∃ = 5.48 (SE 1.44), p = 0.01<br><br>Odds ratio (OR) for caries (∃1 DMFS, ages 5–17 yr) and population attributable risk (PAR) in association with 2nd or 3rd blood Pb tertiles, compared to 1st tertile were:<br>1st tertile (#1.66 :g/dL)<br>2nd tertile (1.66–3.52 :g/dL): OR = 1.36 (95% CI: 1.01, 2.83); PAR = 9.6%<br>3rd tertile (>3.52 :g/dL): OR = 1.66 (95% CI: 1.12, 2.48); PAR = 13.5%<br><br>For an increase of blood Pb of 5 :g/dL, OR = 1.8 (95% CI: 1.3, 2.5)<br>Covariates retained were age, gender, race/ethnicity, poverty income ratio, exposure to cigarette smoke, geographic region, educational level of head of household, carbohydrate and calcium intakes, and dental visits. |

## Table AX6-9.9 (cont'd). Effects of Lead on Bone and Teeth in Children and Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| **United States** (cont'd) | | | |
| Schwartz et al. (1986)<br>U.S.<br>1976–1980 | Design: cross-sectional national survey (NHANES II)<br>Subjects: ages <7 yr (n = 2,695)<br>Outcome measures: variables of stature, including height, weight, and chest circumference<br>Analysis: multivariate weighted linear regression | Blood Pb (:g/dL) range: 5-35 | Blood Pb levels were a statistically significant predictor of children's height ($p < 0.0001$), weight ($p < 0.001$), and chest circumference ($p < 0.026$), after controlling for age in mos, race, sex, and nutrition.<br>Height: ∃ = −0.119 (SE 0.0005)<br>Weight: ∃ = −1.0217 (SE 0.08) for log-transformed blood Pb<br>Chest circumference: ∃ = −0.6476 (SE 0.077) for log-transformed blood Pb<br>There are several explanations for the inverse correlation between blood Pb and growth in children. First, blood Pb level may be a composite factor for genetic, ethnic, nutritional, environmental, and sociocultural factors. Second, nutritional deficits that retard growth also enhance Pb absorption. Finally, there may be a direct effect of low level Pb on growth in children. |
| Gemmel et al. (2002)<br>Boston/Cambridge, MA<br>NR | Design: cross-sectional<br>Subjects: children (n = 543), ages 6–10 yr<br>Outcome measures: number of caries (dfs, DFS)<br>Analysis: multivariate linear regression | Blood Pb (:g/dL) mean (SD, max):<br>Urban (n = 290): 2.9 (2.0, 13)<br>Rural (n = 253): 1.7 (1.0, 7) | Increasing blood Pb (ln-transformed) was significantly associated with covariate-adjusted number of caries (dfs + DFS) (ln-transformed) in the urban (∃ = 0.22 [SE 0.08], p = 0.005) group, but not in the rural group (∃ = −0.15 [SE 0.09], p = 0.09). When dfs numbers were stratified by permanent or deciduous teeth, the blood Pb association in the urban group was significant for deciduous teeth.<br>(∃ = 0.28, SE 0.09, p = 0.002), but not for permanent teeth (∃ = 0.02, SE 0.07, p = 0.8).<br>Covariates retained: age, sex, ethnicity, family income, education of female guardian, maternal smoking, frequency of tooth brushing, firmness of toothbrush bristles, and frequency of chewing gum. |
| Campbell et al. (2000)<br>New York<br>1995–1997 | Design: retrospective cohort<br>Subjects: children (n = 154), ages 6.9–12 yr<br>Outcome measures: prevalence of caries (dfs, DMFS)<br>Analysis: multivariate logistic regression | Blood Pb (:g/dL) mean (range): 10.7 (18.0–36.8) (measured at ages 18 and 37 mo) | Covariate-adjusted odds ratios for caries in association with blood Pb <10 or ∃10 :g/dL, were:<br>permanent teeth (DMFS): OR = 0.95 (95% CI: 0.43, 2.09)<br>deciduous teeth (dfs): OR = 1.77 (95% CI: 0.97, 3.24)<br>Covariates retained: age, grade in school, number of tooth surfaces at risk. Other covariates explored, that had no effect on strength of association with blood Pb were: sex, ethnicity, and oral hygiene score. |

## Table AX6-9.9 (cont'd). Effects of Lead on Bone and Teeth in Children and Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| ***Adults*** | | | |
| **United States** | | | |
| Dye et al. (2002)<br>U.S.<br>1988–1994 | Design: cross-sectional national survey (NHANES III)<br>Subjects: adults in general population (n = 10,033; 5,255 females), ages 20–69 yr<br>Outcome measures: symptoms of periodontal bone loss (attachment loss, periodontal pocket depth)<br>Analysis: multivariate linear regression | Blood Pb (:g/dL) geometric mean (SE, range):<br>2.5 (0.08) (2.36% > 10) | Increasing blood Pb (log-transformed) was significantly associated with increasing prevalence of covariate-adjusted dental furcation (∃ = 0.13 [SE 0.05], p = 0.005). Covariates retained: age, sex, race/ethnicity, education, smoking, and age of home. Smoking status interaction was significant when included in the model as an interaction term (∃ = 0.10 [SE 0.05], p = 0.034). When stratified by smoking status, association between dental furcation and blood Pb was significant for current smokers (∃ = 0.21 [SE 0.07], p = 0.004) and former smokers (∃ = 0.17 [SE 0.07], p = 0.015), but not for nonsmokers (∃ = −0.02 [SE 0.07], p = 0.747). |
| **Europe** | | | |
| Tvinnereim et al. (2000)<br>Norway<br>1990–1994 | Design: cross-sectional<br>Subjects: 1,271 teeth samples collected by dentists in all 19 counties in Norway<br>Analysis: Student's t-test comparing metal concentrations in teeth with caries, roots, and in different tooth groups | Tooth Pb (:g/g tooth) geometric mean (SD, range):<br>1.16 (1.72, 0.12–18.76) | Also examined mercury, cadmium, and zinc. All tooth groups had higher Pb concentrations in carious than in non-carious teeth. The geometric mean Pb concentration in carious teeth was 1.36 :g/g compared to 1.10 :g/g (p = 0.001). |

## Table AX6-9.10. Effects of Lead on Ocular Health in Children and Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| ***Children*** | | | |
| **Latin America** | | | |
| Rothenberg et al. (2002b)<br>Mexico<br>1987–1997 | Design = longitudinal (subset of prospective)<br>Subjects: children (n = 45, 24 female), ages 7–10 yr<br>Outcome measures: ERG<br>Analysis: comparison of outcome measures between blood Pb tertiles (ANOVA for repeated measures) | Blood Pb (:g/dL) median (range) at 85–124 mo:<br>1st tertile: 4.0 (2.0–4.5)<br>2nd tertile: 6.0 (5.0–6.5)<br>3rd tertile: 7.5 (7.0–16.0)<br><br>Blood Pb (:g/dL) median (range), maternal at 12 wk of gestation:<br>1st tertile: 4.0 (2.0–5.5)<br>2nd tertile: 8.5 (6.0–10.0)<br>3rd tertile: 14.0 (10.5–32.5) | Significant association between increasing maternal blood Pb at 12 wk of gestation and increasing ERG a-wave (p = 0.025) and b-wave amplitude (p = 0.007), with significant increases in a-wave in the 2nd blood Pb tertile (6.0–10.0 :g/dL), and a-wave and b-wave in the 3rd blood Pb tertile (10.5–32.5 :g/dL), compared to the 1st blood Pb tertile. |
| ***Adults*** | | | |
| **United States** | | | |
| Schaumberg et al. (2004)<br>Massachusetts<br>1991–2002 | Design = longitudinal (subset of Normative Aging Study)<br>Subjects: adult male (n = 642), mean age 69 yr (range 60–93)<br>Outcome measures: cataract diagnosis<br>Analysis: multivariate logistic regression, odds ratio (vs. 1st quintile) | Blood Pb (:g/dL) median (range):<br>5 (0–35)<br><br>Bone Pb (:g/g) median (range):<br>Patella : 29 (0–165)<br>Tibia: 20 (0–126) | Significant covariate adjusted odds ratio (OR) for cataracts in 5th tibia bone Pb quintile (31.0–125 :g/g), OR = 3.19 (95% CI: 1.48, 6.90), p = 0.01. OR for cataracts were not significantly associated with patella bone Pb (5th quintile: 43.0–165 :g/g), OR = 1.88 (95% CI: 0.88, 4.02), or blood Pb (5th quintile: 8.17–35.0 :g/dL), OR = 0.89 (95% CI: 0.46, 1.72).<br>Covariates retained: age, smoking, history of diabetes, daily intake of vitamin C, vitamin E, and carotenoids. |

## Table AX6-9.10 (cont'd). Effects of Lead on Ocular Health in Children and Adults

| Reference, Study Location, and Period | Study Description | Pb Measurement | Findings, Interpretation |
|---|---|---|---|
| ***Adults*** | | | |
| **Europe** | | | |
| Cavalleri et al. (1982)<br>Italy<br>NR | Design = cross-sectional cohort<br>Subjects: adult male vinyl chloride pipe manufacture workers, exposed to Pb stearate (n = 35), mean age 45 yr (SD 14, range 21–59); reference group (n = 35) matched for age, smoking, and alcohol consumption.<br>Outcome measures: visual field<br>Analysis: comparison of outcome measures between Pb workers and reference group | Blood Pb (:g/dL) mean (SD, range):<br>Pb: 46 (14, 21–82)<br>Reference: 23 (4, 21–37)<br><br>Urine Pb (:g/L) mean (SD, range):<br>Pb: 71 (18, 44–118)<br>Reference: 30 (5, 21–42) | Visual sensitivity was significantly (p = 0.003) lower in Pb workers compared to the reference group; however, visual sensitivity index was not significantly associated with blood or urine Pb. Mesopic field scotoma prevalence was 10 of 35 (28%) in Pb workers and 0% in the reference group. |

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