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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
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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	δ-aminolevulinic acid
ALAD	δ-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
β	beta-coefficient; slope of an equation
βFGF	β-fibroblast growth factor
17β–HS	17β-hydroxysteriod
3β-HSD	3β-hydroxysteriod dehydrogenase
17β-HSDH	17β-hydroxysteriod dehydrogenase
6β-OH-cortisol	6-β-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
γ-GT	γ-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	γ-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 × WRAT-R	integrated blood lead index × 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-γ)
Ig	immunoglobulin (e.g., IgA, IgE, IgG, IgM)
IGF-1	insulin-like growth factor 1
IL	interleukin (e.g., IL-1, IL-1β, 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-β-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-$(OH)_2$-D, 1,25-$(OH)_2$ D_3	1,25-dihydroxyvitamin D
24,25-$(OH)_2$-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

AX5. CHAPTER 5 ANNEX

ANNEX TABLES AX5-2

Table AX5-2.1. Effect of Lead on Erythrocyte Morphology, Mobility, and Other Miscellaneous Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
Pb nitrate 0–100 µM, Free Pb^{2+} 0–20 µM, In vitro	(a) Pb recovery studies, 10 min (b) Relationship of free Pb^{2+} to added Pb, 20 min	Erythrocyte cell lysates from humans	—	Uptake and transport of Pb in erythrocyte and across erythrocyte cell membrane under the influence of varying buffers and ions. a. Pb can cross the membrane passively in either direction. Influx and efflux show similar properties b. Passive transport of Pb is strongly stimulated by HCO_3^- (bicarbonate) c. Pb uptake is unaffected by varying the external concentrations of Na^+, K^+, and Ca^{2+} d. In RBC, Pb binds mainly to hemoglobin. The ratio of bound Pb to free Pb^{2+} in the cytosol is estimated 6000:1	Simons (1986a)
Pb nitrate 1.5 mM In vitro	1 h	Human erythrocytes	—	Pb uptake and transport are studied in resealed erythrocyte ghosts. a. Transport of Pb across erythrocyte membranes is passive b. 90% of Pb uptake by erythrocytes is inhibited by drugs that block anion transport, indicating the involvement of anion exchanges c. Pb transport depends upon the presence of a second anion. In the presence of HCO_3^-, the rate is stimulated in the order of ClO_4^- <NO_3^- and $CH_3CO_2^-$ <F^- <Cl^- <Br^- <I^-	Simons (1986b)
10 µM Pb, as Pb acetate, In vitro	20 min	Erythrocyte ghosts and unsealed erythrocytes	—	In erythrocytes, the anion exchange mechanisms and internal thiol groups are critical factors that affect the stimulation of a Ca^{2+}-dependent process by Pb^{2+}.	Lal et al. (1996)
100 µg/dL Pb, 10 mg/dL, Pb, In vitro	1 h	Human erythrocytes	—	Plasma Pb uptake was at the rate of 0.17 µ moles/h.	Sugawara et al. (1990)
	24 h			Uptake comparable in erythrocyte ghosts and in intact cells. No association of Pb with membranes at 24 h.	
2 µM Pb acetate 2 µM Pb	0–1 h	MDCK Kidney epithelial cell line, In vitro	—	Anion exchange (AE) plays a critical role in regulating intracellular pH in erythrocytes and epithelial cells and facilitates Pb uptake.	Bannon et al. (2000)
	0–2 h	Human erythrocytes, in vitro			
10 or 20 mM Pb acetate, i.p. once a week (100 or 200 µmoles)/ kg b.wt.	5 wks	Albino rats	Control: 1-12 µg/100 mL Exposed: 100-800 µg/dL	Exposure to Pb significantly decreased the erythrocyte mobility. The decreases in mobility were either simultaneous or prior to the decreases in hemoglobin (Hb) or hematocrit (Ht). In exposed rats, a significant negative correlation was found between mobility and blood Pb levels. Decreases in ALAD (δ-aminolevulinic acid), was also apparent in exposed animals.	Terayama et al. (1986)

Table AX5-2.1 (cont'd). Effect of Lead on Erythrocyte Morphology, Mobility, and Other Miscellaneous Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
20 mM Pb acetate, i.p. once a week (200 µmoles/kg b.wt)	5 wks	Male Wistar Albino rats	Control: 1–12 µg/100 mL Exposed: 100–800 µg/dL	Exposure to Pb significantly decreased RBC membrane sialic acid content, erythrocyte survival, hemoglobin, and hematocrit. This was evident to a minor extent below blood Pb levels 100 µg/100 mL and was generally present from 100 µg/100 mL and higher.	Terayama and Muratsuga (1988)
200 µM of Pb acetate, i.p.	Once a week for 5 wks	Rat	0–600 µg/dL	Pb exposure significantly decreases RBC count, Hb values, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin, decreases erythrocyte mobility, membrane sialic acid content, and deformability.	Terayama (1993)
Pb, i.p. 20 mg/ kg b.wt.	14 consecutive days	Male Albino rat		Acetyl choline esterase (AchE), NADH dehydrogenase, and Na^{+}-K^{+} ATPase activities in rat erythrocyte membranes were inhibited by Pb exposure. Erythrocyte membrane sialic acid, hexose, hexosamine were inhibited by Pb exposure. Membrane phospholipids and cholesterol were increased.	Jehan and Motlag (1995)
1 µM Pb nitrate	1 h	Erythrocytes from Pb-exposed healthy humans	Controls: 8.3 µg/dL Exposed: 70.5 µg/dL	Pb exposure in healthy human RBC membranes resulted in increased levels of arachidonic acid (AA). The increase in AA correlated in a dose dependent manner with elevation in Pb and with serum iron. On the other hand, a negative correlation was found between Aa and serum calcium. It is inferred that substitution of Pb to calcium, which is essential for the release of phospholipase A2 for AA release may be the reason for increased RBC membrane AA.	Osterode and Ulberth (2000)
1 µM Pb nitrate, In vitro	1 h	Erythrocytes from healthy human volunteers	—	Pb inhibits Gordos effect in human erythrocytes; electron spin labeling studies indicated cell shrinkage and decreased volume.	Eriksson and Beving (1993)
	6 and 12 mo	Erythrocytes from Pb-exposed rats		Cation-osmotic hemolysis (COH) in 12 mo Pb-exposed rats was lower in the areas of lower ionic strength on erythrocyte membranes.	Mojzis and Nistiar (2001)
0.1–200 µM, Pb nitrate in the reaction buffer	1–6 h	In vitro, human erythrocytes	—	Pb crosses the erythrocyte membrane by the anion exchanger and can also leave erythrocytes by a vanadate–sensitive pathway, identified with the calcium pump. The high ratio of erythrocyte to plasma Pb seen in vivo appeared to be due to the presence of a labile Pb2+- binding component present in erythrocyte cytoplasm.	Simons (1993a)
0.1–10 µM Pb ions from 10 mM Pb(NO3)2 solution, In vitro	24 h	Erythrocytes from healthy human volunteers	—	Pb activates erythrocyte K^{+} channels, Ca^{2+} sensitive erythrocyte Scramblase, triggers Phosphatidyl serine receptors and result in cell shrinkage and decreased life span.	Kempe et al. (2005)

Table AX5-2.1 (cont'd). Effect of Lead on Erythrocyte Morphology, Mobility, and Other Miscellaneous Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
20 μM Pb ion, In vitro	2 min–2 h	Erythrocytes from human umbilical cord	—	Pb attenuates prolytic effect on neonatal erythrocytes in iso-or hypotonic low ionic strength media.	Serrani et al. (1997)
				Hemolytic activity of Organo Pbs increases with their hydrophobicity: triethyl Pb chloride < tri-n-propyl Pb chloride < tributyl tin chloride.	Kleszcyńska et al. (1997)
20 μM Pb ions, In vitro	1 h	Human umbilical cord erythrocytes	—	Pb ions increase the resistance to lysis in media of diminishing tonicity. These changes might be mediated by changes in membrane structure.	Corchs et al. (2001)
Erythrocytes from Pb-exposed workers 24–45 yr old white males	Duration of exposure not given. RBCs were isolated. Experiments were performed in ghosts and resealed membranes	Humans	1.17–1.54 μM	Increased blood Pb in exposed workers was associated with a significant decrease in the average microviscosity of resealed and unsealed erythrocyte membranes. Alterations in the microviscosity of the lipid regions of the hydrophobic core of the erythrocyte membrane bilayer and in the phospholipid composition of the membrane may be defects that contribute to the clinical and biochemical alterations/effects.	Cook et al. (1987)
0.1 mM Pb final concentration, In vitro	1 h	Erythrocytes from healthy humans	—	Pb particles adhere to the external and internal surfaces of the human erythrocyte membrane and disturb the lamellar organization of lipid bilayers.	Suwalsky et al. (2003)
1–10 μM Pb acetate, In vitro	3 h	Erythrocytes from healthy humans	—	Low concentrations of Pb alter the physicochemical properties of proteins and lipids in erythrocyte membranes.	Slobozhanina et al. (2005)
0–1200 nM Pb, In vitro	1 h	Erythrocytes from healthy humans	—	Significant increase in the phosphorylation of membrane cytoskeletal proteins in Pb treated human erythrocytes at concentrations above 100 nM mediated by enhanced PKC activity.	Belloni-Olivi et al. (1996)

Table AX5-2.1 (cont'd). Effect of Lead on Erythrocyte Morphology, Mobility, and Other Miscellaneous Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
—	—	a. 24 adult healthy controls (humans) b. 12 patients with Pb poisoning (plumbism) symptoms (Pb controls) c. Patients with chronic renal failure (CRF) Divided into: 1. Normal urinary blood Pb levels 2. High urinary blood Pb levels	Controls: −17.1 µg/dL Pb controls: 80.5 µg/dL CRF −1: 18.4 µg/dL CRF −2: 18.0 µg/dL Urinary Pb CRF 1: −322 µg/72 h CRF 2: 1785 µg/72 h	Increased erythrocyte Zn protoporphyrin to free protoporphyrin ratio in Pb controls and remained in the normal range in CRF patients. CRF patients showed minor abnormalities of erythrocyte heme metabolism, such as low ALAD activity.	Fontanellas et al. (2002)
Occupational, Human exposure	—	a. 28 male workers in a Pb refining factory b. Controls	Exposed: −35.97 µg/100 g Controls: 5.23 µg/100 g	SDS polyacrylamide electrophoresis for erythrocyte membrane proteins showed bands at 3 and 4.1, that significantly decreased while bands 2.3, 6, and 7 significantly increased in the Pb workers compared with controls.	Fukumoto et al. (1983)

RBC—Red blood cells; Hb—Hemoglobin; NADH—Nicotinamide adenine dinucleotide dehydrogenase; PKC—Protein kinase C; AchE—Acetyl choline esterase

Table AX5-2.2. Lead, Erythrocyte Heme Enzymes, and Other Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
Dietary, 0–100 µg/g dry wt. of the diet	35 days	Adult male Zebra finches	0–1.5 µg/mL	Significant negative correlation was observed between blood-Pb concentration and log ALAD activity. RBC ALAD activity ratio is a sensitive indicator of dietary Pb concentration regardless of the mode of exposure.	Scheuhammer et al. (1987)
Pb acetate, oral gavage, 1.5 mg/kg b.wt, Pb acetate	3 or 11 wks	Red-tailed Hawks	0.195–0.752 µg/dL	Erythrocyte phorphobilinogen synthetase was depressed significantly with in the 1st wk of treatment. Rapid but brief increase in free protoporphyrin. Hematocrit, erythrocyte count, Hb were all decreased and blood viscosity increased in exposed group.	Redig et al. (1991)
20 µg/mL as Pb acetate in drinking water	5 wks	Female Wistar Albino rats	37.8 µg/dL	Pb exposure decreases hematocrit, hemoglobin, and the number of erythrocytes and enhances blood viscosity.	Toplan et al. (2004)
17 µM Me/kg Pb acetate, Per OS	5 days	Female Rabbits	—	Pb causes a significant decrease in blood ALAD activity, increases free erythrocyte protoporphyrins, increases aminolevulinic acid and coporphyrin excretion in urine.	Zareba and Chmelnicka (1992)
1.5 mg Pb/kg body wt, oral dose	8 yrs	Cynomolgus Monkey, in vitro	—	Kinetic analyses of erythrocyte δ- aminolevulinic acid revealed differences in P^H optimum and Michaelis constants with Pb exposure. The ALAD enzyme kinetics of Pb exposed monkeys and humans are similar.	Dorward and Yagminas (1994)
		Dogs from urban and rural areas of Greece	326, 97–68 µg/L	Significant negative correlation existed between blood-Pb levels and ALAD activity. 807–992 µmol/PBG/LRBC/h is established as the normal erythrocyte ALAD range for dogs.	Polizopoulou et al. (1994)
Occupational exposure	11–22 yrs	Human erythrocytes from exposed populations	1.39–1.42 µmol/l	Liquid chromatography with inductively coupled plasma spectrometry had revealed ALAD to be the principle Pb binding protein. The percentage of Pb bound to ALAD was influenced by a common polymorphism in the ALAD gene.	Bergdahl et al. (1997)
0–20 mg Pb liter −1	29 days	Juvenile Rainbow trout erythrocytes	—	Significant decreases in the erythrocyte ALAD activity after a 29-days exposure to 121 and 201 mg Pb liter −1.	Burden et al. (1998)

Table AX5-2.2 (cont'd). Lead, Erythrocyte Heme Enzymes, and Other Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
Pb acetate 160 mg/L in water	8 wks	Wistar rats	≥20– ≥40 µg/dL	Pb increases blood and liver Pb, erythrocyte porphyrin content, hypoactivity of both hepatocytic and erythrocytic ALAD.	Santos et al. (1999)
	—	Fish from regions close to the smelters and down stream	—	Smelter site fish had elevated Pb concentrations, decreased ALAD activity and species differences in this inhibitory activity were apparent that could be attributed to Zn levels.	Schmitt et al. (2002)
1.46 µmol/liter, In vitro	48 h	Human whole blood erythrocyte hemolysates, normal and Pb intoxicated individuals	—	The effects of various divalent cations on erythrocyte porphobilinogen are concentration and PH dependent. Zn restores the Pb inhibited activity.	Farant and Wigfield (1987)
Pb 0.34 µM/L– 1.17 µM/L, subcutaneous injection	1 h	Male albino New Zealand rabbits	—	Pb causes the most inhibition and Zn activation of rabbit Erythrocyte porphobilinogen activity.Cu^{2+}, Cd^{2+}, and Hg^{2+} are intermediary. Each divalent ion has a characteristic effect on the PH- activity relationship of PBG-S.	Farant and Wigfield (1990)
0–60 pM Pb ion, In vitro	20 min	Human erythrocyte lysates	—	Human erythrocyte lysate porphobilinogen activity is increased by Zn^{2+} with a Km of 1.6 pM and inhibited by Pb with a Ki of 0.07 pM, Pb reduced the affinity for the substrate 5- aminolevulinate, non-competitively.	Simons (1995)
200–500 ppm Pb in drinking water	14 or 30 days	Male ddY mice	24–51 µg/100 mL	Pb inhibits erythrocyte and bone marrow P5'N activity. Erythrocyte ALAD activity was inhibited by 90%. Elevation of Urinary excretion of ALA with no change in erythrocyte protoporphyrin and urinary co porphyrin as against in the Pb exposed humans indicates that protoporphyrin metabolism might be more resistant to Pb in mice than humans.	Tomokuni et al. (1989)
0.1–100 µM Pb ion, In vitro	5 min	Human erythrocyte ghosts	—	Under normal incubation conditions Pb inhibits, Ca^{2+} -Mg^{2+} ATPase with an IC50 of 6.0µM. Pb inhibits Ca^{2+}- Mg^{2+} ATPase related to sulphahydryl groups above 1.0 µM Pb and by direct action of Pb upon Calmodulin below 1.0 µM.	Mas-Oliva (1989)
20–5 µg/kg body wt 1 mg/ kg body wt	Pregnancy through lactation	Erythrocytes from Sprague-Dawley rats	—	Na^{2+}- K^{+}- ATPase and Ca^{2+}- Mg^{+}- ATPase of erythrocyte membranes from Pb-depleted animals did not change in P0 generation as compared to 1 mg/kg b.wt Pb animals, where as in F1 generation Pb depleted rats showed reduced activity.	Eder et al. (1990)

Table AX5-2.2 (cont'd). Lead, Erythrocyte Heme Enzymes, and Other Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
20 mg Pb acetate/kg b.wt, i.p, In vivo	14 days	Male Albino rats erythrocytes	—	Pb significantly decreases erythrocyte membrane acetyl choline esterase, NADH dehydrogenase, membrane sialic acid, hexose, and hexosamine.	Jehan and Motlag (1995)
				Pb ions inhibit aerobic glycolysis and diminish ATP level in human erythrocytes in vitro. Magnesium partly abolishes these effects by stimulating Magnesium dependent enzymes. Effect is seen both by direct addition of Pb acetate to erythrocyte ghosts as well as in the ghosts obtained after preincubation of erythrocytes with Pb acetate. Ca^{2+}, Mg^{2+} ATPase is less sensitive and Mg ATPase is practically insensitive to Pb under these conditions.	Grabowska and Guminska (1996)
10–200 µg/dL Pb ions (Pb acetate), In vitro	20 h	Human umbilical cord erythrocytes	—	Pb significantly decreased the concentration of ATP, ADP, AMP, adenosine, GTP, GDP, GMP, Guanosine, IMP, inosine, hypoxanthine, NAD and NADP concentrations.	Baranowska-Bosiacka and Hlynczak (2003)
Pb acetate through water or i.p. 1 or 2 mg/Kg b.wt.	Every 4th day for 1 mo	Wistar rats	1.51–35.31 µg/dL	The concentrations of adenosine tri phosphate (ATP), Guanosine triphosphate (GTP), Nicotinamide adenine dinucleotide NAD^{+}, nicotinamide adenine dinucleotide phosphate $NADP^{+}$ adenylate and Guanylate (AEC and GEC) were significantly reduced in erythrocytes of exposed animals. Results indicate Pb ions disrupt erythrocyte energy pathway.	Baranowska-Bosiacka and Hlynczak (2004)

ALAD — Aminolevulinic acid; Cu^{2+}—Copper; Cd^{2+}—Cadmium; Hg^{2+}—Mercury; PBG-S Porphobilinogen synthetase; Zn—Zinc; ATP—Adenosine triphosphate; ADP—Adenosine diphosphate; AMP—Adenosine monophosphate; GTP—Guanosine tri phosphate; GDP—Guanosine diphosphate; GMP—Guanosine monophosphate; IMP—Inosine monophosphate; NAD—Nicotinamide adenine dinucleotide; NADP—Nicotinamide adenine dinucleotide phosphate.

Table AX5-2.3. Lead Binding and Transport in Human Erythrocytes

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
0–60 pM Pb ion, In vitro	20 min	Human erythrocyte lysates	—	Human erythrocyte lysate porphobilinogen activity is increased by Zn^{2+} with a Km of 1.6 pM and inhibited by Pb with a Ki of 0.07 pM, Pb reduced the affinity for the substrate 5- aminolevulinate, non-competitively.	Simons (1995)

Zn—Zinc

Table AX5-2.4. Lead Effects on Hematological Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
4-6 mg/Kg b.wt, i.p., daily	15 and 30 days	Intact and splenctamized rats	—	Pb increases urinary δ-amino levulinic acid (ALA) excretion, depletion in RBC hemoglobin content, and more number of reticulocytes in peripheral blood, and results in accumulation of immature erythrocytes both in intact and splenctomized rats.	Gautam and Chowdhury (1987)
0.82 mg Pb/kg b.wt./d, oral gavage	3 or 11 wks	Red-tailed hawks erythrocytes	0.195–0.375 mg/mL	Activity of porphobilinogen synthase/ALAD was depressed significantly in Pb exposed rats and did not return to normal values until 5 wks after the termination of the treatment. A rapid and relatively brief increase in erythrocyte free proto porphyrin and a slower, prolonged increase in Zn complex.	Redig et al. (1991)
17 µM Me/Kg b.wt Pb acetate or 3.5 mg of Pb/kg body wt, i.p	5 days	Female Rabbits	17.5 µg/dL	Pb causes a significant inhibition of ALAD in the blood , increases free erythrocyte protoporphyrin, and urinary excretion of Aminolevulinic acid and coporphyrin.	Zareba and Chmielnicka (1992)
17 µM Me/Kg b.wt Pb acetate or 3.5 mg of Pb/ kg body wt, i.p. or per OS 17.5 mg/kg b.wt single injection	5 days i.p.	Female Rabbits	—	Pb induced ALAS activity in liver and kidney, both after i.p and p.o. administration; i.p. administration of Pb also induced kidney heme oxygen levels.	Chmielnicka et al. (1994)
Cu deficient 1 mg Cu/Kg	4 wks	Rat	—	Moderately high Zn in the diet reduces plasma copper but not plasma ceruloplasmin.	Panemangalore and Bebe (1996)
Marginal deficient 2 mg/kg				Does not affect the recovery of plasma Cu or activity after oral copper sulphate in Cu deficient diets.	
Control 5 mg Cu/Kg				Does not influence RBC Super oxide dismutase activity.	
High Zn 60 mg/kg.					
0.02–40 ppm Pb, dietary	90 days	Male and female Swiss mice	0.7–13.0 µg/dL	Increased RBC number and increased hemoglobin and decreased hematocrit up on Pb exposure.	Iavicoli et al. (2003)
20 µg/mL, Pb acetate in drinking water	5 wks	Female Wistar Albino rats	37.8 µg/dL	Erythrocyte count, hematocrit and hemoglobin were all decreased and blood viscosity increased in Pb exposed workers.	Toplan et al. (2004)

Table AX5-2.4 (cont'd). Lead Effects on Hematological Parameters

Dose and Route of Exposure	Duration	Species	Blood lead	Effect	Authors
Erythrocytes from humans of occupational Pb exposure and controls In vivo and in vitro	—	Male Pb workers and 13 normal volunteers	Range 20.6–71.3 µg/dL	Nicotinamide adenine dinucleotide synthetase activity in the Pb workers ranged from 0.08 to 1.1 µmol/h per g of hemoglobin. 50% of enzyme inhibition was observed at 40 µg/dL. Aminolevulinic acid dehydratase activity decreased rapidly and reached a plateau at Pb-B levels 40-60 µg/dL. 50% of enzyme activity inhibition was observed at 20 µg/dL.	Morita et al. (1997)
In vivo; exposure In vitro assays on erythrocytes from exposed populations	—	1. Workers exposed to manganese (Mn) and 2. Workers exposed to Pb without clinical manifestations of intoxication	—	Erythrocyte concentrations of adenyl nucleotides (ADP and ATP) were elevated in both groups of workers and that of AMP in Pb-exposed workers. The ratio of ATP/ADP significantly increased in Pb-exposed workers.	Nikolova and Kavaldzhieva et al. (1991)

ALA—Aminolevulinic acid; ALAS—Aminolevulinic acid synthetase; ALAD—Aminolevulinic acid dehydratase, RBC—Red blood cells.

Table AX5-2.5. Lead Interactions with Calcium Potassium in Erythrocytes

Dose and Route of exposure	Duration	Species	Blood lead	Effect	Authors
0–325 µM, Pb nitrate, In vitro	0–60 min	In vitro	—	Pb modifies the threshold sensitivity of individual K^+channels to Ca^{2+} with a biphasic time course. The increase of Pb concentration increased the extent of the initial inhibition and decreased the duration. The inhibitory effect was not observed when addition of Calcium preceded the addition of Pb. Pb decreased the rate of uptake of ^{86}Rb.	Alvarez et al. (1986)
0 µM–5 mM Pb, In vitro	0–100 min	Human erythrocyte hemolysates	—	Pb and Ca transport was carried out by a passive transport system with two kinetic components (Michaelis- Menten and Hill) Pb and Ca were capable of inhibiting the transport of the other metals in a non-competitive way.	Calderon-Salinas et al. (1999b)
1–4 µM Pb acetate, In vitro	0–30 min	Rabbit reticulocytes	—	Pb at low concentrations inhibits the uptake of Fe (II) into all three (heme, cytosolic and stromal) fractions. The saturable components were inhibited at lower concentrations of Pb than the non- saturable components.	Qian and Morgan et al. (1990)
1–50 µM Pb ion, In vitro	20 min	Marine fish erythrocytes	—	Pb activates Ca^{2+} activated potassium channels. Treatment of erythrocytes with 1-2 µM Pb led to a minor intra cellular K loss and at Pb concentrations of 20-50 µM 70% of potassium was lost.	Silkin et al. (2001)
Pb depleted rats Pb concentration <20 µg/kg Diet, oral Pb controls 200,800 µg/kg Pb^{2+} in the form of supra pure Pb acetate. Diet, oral	Gestation through to 15 days of lactation	Sprague-Dawley rats	—	The concentration of CA^{2+} ions in erythrocytes of Pb-depleted rats was elevated in F_1 generation, without changes in P_0 generation. The elevation observed in depleted rats could be because of a reduction in CA^{2+}-Mg^{2+} ATPase.	Loipführer et al. (1993)
Intact or erythrocyte ghosts 0–100 µM Pb ion or Pb nitrate in the reaction mix, In vitro	10 min	Healthy human erythrocytes	—	Modulation of CA^{2+}-activatable K^+ permeability was compared with modulation of a membrane-bound oxidoreductase activity in human erythrocytes. Pb, anitrion, and menadione had parallel effects on the channel protein and the enzyme. The results demonstrate that the K^+ channel and the enzyme are distinct membrane proteins and the enzyme activity may influence channel gating.	Fehlau et al. (1989)

Pb—Lead; K^+—Potassium; Na^{2+}- K^+ ATPase—sodium potassium ATPase; Ca^{2+}- Mg^{2+} ATPase—Calcium, Magnesium ATPase.

Table AX5-2.6. Lead, Heme, and Cytochrome P–450

Dose and Route of exposure	Duration	Species	Blood lead	Effect	Authors
0–75 mg of Pb^{2+}/Kg b. wt. i.p., Single injection	0–30 h	C57 BL/6 male mice	—	Pb causes an increase in δ-amino levulinic acid levels in plasma and a decrease in the heme saturation of hepatic tryptophan -2,3 dioxygenase. P-450- dependent activities, EROD and O-dealkylation of alkoxyresorufins decreased progressively. Pb exposure decreased mRNA levels of the P450 CYp3a11. The decrease in P450 transcription was a mechanism dependent on heme by inhibition of heme synthesis and also by a mechanism independent of heme in which Pb decreases P-450 transcription.	Jover et al. (1996)

EROD—Ethoxy resorufin-O-dealkylase.
CYp3a11—Cytochrome P-450 3a11.

Table AX5-2.7. Lead, Erythrocyte Lipid Peroxidation, and Antioxidant Defense

Dose and Route of exposure	Duration	Species	Blood lead	Effect	Authors
7.5 mg of Pb acetate or 4.09 mg of Pb Kg^{-1} b.wt, oral	28 days, multiple analyses at day 7, 14, 21, and 28	Erythrocytes from male Calves	0.1–1.6 ppm	Pb exposure significantly reduced erythrocyte super oxide dismutase activity until day 21 followed by a marginal increase by day 28. Total, protein-bound and non protein- bound –SH content of erythrocytes declined.	Patra and Swarup et al. (2000)
5.46 mg Pb as Pb acetate, oral	14 days, multiple analyses at day 0, 7, and 14	Erythrocytes from female goats	0.09–1.12 ppm	Pb exposure caused a significant increase of erythrocytic GPx, SOD and CAT activities, total thiol groups and total antioxidant status.	Mousa et al. (2002)
10 mg/kg b.wt Pb acetate, intra muscular, daily Pre treatment with melatonin	7 days	Rat	—	Pb significantly decreased heme synthesis, decreased Hb, decreased liver δ- ALAS and erythrocyte ALAD. Markedly elevates hepatic lipid peroxidation, reduced anti oxidant enzymes such as total sulphahydryl groups and Glutathione. Pre Treatment with melatonin reduced the inhibitory effect of Pb on both enzymatic and non enzymatic antioxidants and reduced the iron deficiency caused by Pb.	El- Missiry (2000)
A. ALA 40 mg/kg b.wt every other day and/or B. Melatonin 10 mg/kg	Every other day 3 times daily for 2 wks	Male Sprague- Dawley rats	—	Melatonin effectively protects nuclear DNA and lipids in rat lung and spleen against the oxidative damage caused by the carcinogen ALA.	Karbownik et al. (2000)
Pb acetate 0.2%, in drinking water, followed by individual or combined treatment of lipoic acid (25 mg/Kg b.wt and DMSA 20 mg/kg b.wt, i.p.)	5 wks	Male Albino rats	97.5 µg/dL	Pb exposure results in decreased blood hemoglobin, hematocrit, enhanced erythrocyte membrane lipid peroxidation, decline in the activities of erythrocyte membrane Na^{+}-K^{+} ATPase, Ca^{2+} ATPase, and Mg^{2+} ATPase. Treatment with lipoic acid and/or DMSA reduced the Pb induced adverse changes in the biochemical parameters.	Sivaprasad et al. (2003)
δ-Aminolevulinic acid, 1-5 mM, In vitro	10 days	CHO cells	—	δ- Aminolevulinic acid treatment induces oxidative stress in Chinese hamster ovary cells by inducing Glutathione, Glutathione disulphide, Malandialdehyde equivalents, and Catalase. N-acetyl cysteine administration reverses the decrease in cell survival and colony formation induced by δ- ALA.	Neal et al. (1997)

SOD—Super oxide dismutase; CAT—Catalase; ALAS—Aminolevulinic acid synthatase, ALAD—Aminolevulinic acid dehydratase; ALA—Aminolevulinic acid; GP_x—Glutathione peroxidase

ANNEX TABLES AX5-3

Table AX5-3.1. Summary of Key Studies on Neurochemical Alterations

Subject	Exposure Protocol	Peak Blood Pb or [Pb] used	Observed Effects	Reference
Rat PND 16–18	Hippocampal cultures	0.1 and 1.0 µM Pb Cl_2	Pb blockage of IPSCs were partially reversible while EPSCs were not.	Braga et al. (2004)
Rat PND 50	1500 ppm $Pb(Ac)_2$ chow 10 days before breeding and maintained to sacrifice	31.9 µg/dL	Decreases the NR1 subunit splice variant mRNA in hippocampus.	Guilarte and McGlothan (2003)
Rat PND 7, 14, 21, 28, and 50	1500 ppm $Pb(Ac)_2$ chow 10 days before breeding and maintained to sacrifice	—	Alters NMDAR subtypes and reduces CREB phosphorylation.	Toscano et al. (2002)
Rat PND 21	750 ppm $Pb(Ac)_2$ chow from GD 0 to PND 21	46.5 µg/dL	Increased expression of nicotinic receptors.	Jett et al. (2002)
	Cultured PC12 cells	0.03–10 µM $Pb(NO_3)_2$	Pb acts as a high affinity substitute for calcium in catecholamine release.	Westerink and Vijverberg (2002)
Adult rat	Water—0.1–1.0% $Pb(Ac)_2$ from GD 15 to adult	61.8 µg/100 mL	Hippocampal GLU and GABA release exhibits biphasic effects from chronic Pb.	Lasley and Gilbert (2002)
Adult rat	Water—0.1–1.0% $Pb(Ac)_2$ from GD 15 to adult	117.6 µg/100 mL	NMDA receptor function is upregulated.	Lasley et al. (2001)
	Cultured PC12 cells	0.53 µM $Pb(Ac)_2$	PKC is involved in TH upregulation but not downregulation of ChAT.	Tian et al. (2000)
Embryonic rat	Hippocampal neurons	100 fM–100 nM	Decreases $[Ca^{2+}]i$ and increases Ca^{2+} efflux by a calmodulin-dependent mechanism.	Ferguson et al. (2000)
Rat	750 or 1500 ppm $Pb(Ac)_2$ chow from 10 days pre-mating to PND 14, 21, and 28	61.1 µg/dL	Dose-response effect between level of Pb and expression of NR1 gene.	Guilarte et al. (2000)
	Cultured PC 12 cells	5–20 µM $Pb(Ac)_2$	Induces expression of immediate early genes but requires PKC.	Kim et al. (2000)

Table AX5-3.1 (cont'd). Summary of Key Studies on Neurochemical Alterations

Subject	Exposure Protocol	Peak Blood Pb or [Pb] used	Observed Effects	Reference
Rat PND 50	750 or 1500 ppm $Pb(Ac)_2$ chow from 10 days pre-mating to PND 50	31.9 µg/dL	Reductions in NMDAR receptors result in deficits in LTP and spatial learning.	Nihei et al. (2000)
	Calcineurin in mixture	10–2000 pM $Pb(NO_3)_2$	Has a stimulatory (low) and inhibitory (high) effect on calcineurin.	Kern and Audesirk (2000)
Adult rat	Cerebrocortical membranes	0.01–4 µM free $Pb(Ac)_2$	Pb binds to the NMDA receptor channel in a site different from zinc.	Lasley and Gilbert (1999)
Adult rat PND 2	0.2% $Pb(Ac)_2$ in water and chow	52.9 µg/100 mL	GLU and GABA release are inhibited independent of Pb exposure period.	Lasley et al. (1999)
Rat	Cultured hippocampal neurons	0.01–10 µM Pb Cl_2	Inhibits glutamatergic and GABAergic transmission via calcium channel.	Braga et al. (1999a)
Rat PND 17	Cultured hippocampal neurons	0.1–10 µM Pb Cl_2	Increases tetrodotoxin-insensitive spontaneous release of GLU and GABA.	Braga et al. (1999b)
Rat PND 7, 14, 21, 28	750 ppm $Pb(Ac)_2$ chow from 14 days pre-mating to experimental use	59.87 µg/dL	NMDAR-2A subunit protein expression is reduced in the hippocampus.	Nihei and Guilarte (1999)
Rat PND 7, 14, 21, 28	750 ppm $Pb(Ac)_2$ chow from 14 days pre-mating to experimental use	59.87 µg/dL	Alters the levels of NMDA receptor subunits mRNA in hippocampus.	Guilarte and McGlothan (1998)
Rat PND 22-adult	Water—0.2% $Pb(Ac)_2$ from GD 16 to PND 21	—	Induces loss of septohippocampal cholinergic projection neurons in neonates lasting into young adulthood.	Bourjeily and Suszkiw (1997)
Rat PND 28 56, 112	Water—1000 ppm $Pb(Ac)_2$ from GD 4-use	39.6 µg/dL	Significant increase in [^{3}H]MK-801 binding after chronic exposure.	Ma et al. (1997)

Table AX5-3.1 (cont'd). Summary of Key Studies on Neurochemical Alterations

Subject	Exposure Protocol	Peak Blood Pb or [Pb] used	Observed Effects	Reference
Rat PND 21–adult	50 or 150 ppm $Pb(Ac)_2$ water for 2 wks–8 mo	28.0 µg/dL	Differential effects in [^{3}H]MK-801 binding with dopamine and D_1 agonists.	Cory-Slechta et al. (1997a)
Adult rat	Water—0.2% $Pb(Ac)_2$ from PND 0–adult	37.2 µg/100 mL	Presynaptic glutamatergic function in dentate gyrus is diminished.	Lasley and Gilbert (1996)
Rat 4 mo	Water—0.2% $Pb(Ac)_2$ from GD 16 to PND 28	22.0 µg/dL	Developmental Pb results in long-lasting hippocampal cholinergic deficit.	Bielarczyk et al. (1996)
Rat PND 111	Water at 50 ppm $Pb(Ac)_2$ for 90 days; start at PND 21	18 µg/dL	Decreases in vivo release of dopamine in the nucleus accumbens.	Kala and Jadhav (1995)
	Cultured bovine chromaffin cells	Variable kind and concentration	Exerts dual stimulatory and inhibitory effects on adrenal PKC.	Tomsig and Suszkiw (1995)
Rat	Homogenized cortex	Ranging $Pb(Ac)_2$	Pb activates PKC in the range of 10^{-11} to 10^{-8} M.	Long et al. (1994)
	Cultured bovine chromaffin cells	Variable kind and concentration	Pb and calcium activate the exocytotic release of norepinephrine.	Tomsig and Suszkiw (1993)
			Review paper discussing Pb-calcium interactions in Pb toxicity.	Simons (1993b)
			Review paper exploring Pb as a calcium substitute.	Goldstein (1993)
Rat PND 14 or 56	Neuronal membranes	Chow containing 750 ppm $Pb(Ac)_2$	Inhibitory effect on [^{3}H]MK-801 binding and loss of binding sites in neonates.	Guilarte and Miceli (1992)
Rat	Cortical synaptosomes	1–50 nM free Pb or 1 µM $Pb(NO_3)_2$	Triggers acetylcholine release more effectively than calcium.	Shao and Suszkiw (1991)

Table AX5-3.1 (cont'd). Summary of Key Studies on Neurochemical Alterations

Subject	Exposure Protocol	Peak Blood Pb or [Pb] used	Observed Effects	Reference
Rat	Hippocampal neurons	2.5–50 μM Pb Cl_2	Pb has a blocking effect on the NMDA subtype of glutamate receptors.	Alkondon et al. (1990)
Rat	Brain protein kinase C	10^{-10} M Pb salts	Stimulates brain protein kinase C and diacylglycerol-activated calcium.	Markovac and Goldstein (1988b)

Abbreviations

GD—gestational day

Table AX5-3.2. Summary of Key Studies on Neurophysiological Assessments

Subject	Exposure Protocol	Peak Blood Pb or [Pb] used	Observed Effects	Reference
Rat PND 22	250 ppm $Pb(Ac)_2$ 3–6 wks (electro) or 7-13 wks (immuno)	30.8 µg/dL	Reduces midbrain dopamine impulse flow and decreases dopamine D_1 receptor sensitivity in nucleus accumbens.	Tavakoli-Nezhad and Pitts (2005)
Rat PND 42–64	100, 250, or 500 ppm $Pb(Ac)_2$ in chow for 3-6 wks	54.0 µg/dL	Decrease in number of spontaneously active midbrain dopamine neurons.	Tavakoli-Nezhad et al. (2001)
			Review paper examining glutamatergic components contributing to impairments in synaptic plasticity.	Lasley and Gilbert (2000)
Rat PND 130–210	0.2% $Pb(Ac)_2$ in water	75.4 µg/dL	Deficits in synaptic plasticity in the dentate gyrus from early exposure.	Gilbert et al. (1999a)
Adult rat	Water—0.1-1.0% $Pb(Ac)_2$ from GD 16 to adult	117.6 µg/dL	Biphasic dose-dependent inhibition of hippocampal LTP.	Gilbert et al. (1999b)
Adult rat	0.2% $Pb(Ac)_2$ in water	30.1 µg/dL	Chronic Pb exposure significantly decreases range of synaptic plasticity.	Zhao et al. (1999)
Adult rat	0.2% $Pb(Ac)_2$ in water PND 0-21	30.1 µg/dL	Impairments in LTP and paired-pulse facilitation in the hippocampal DG.	Ruan et al. (1998)
Rat PND 90–130	750 ppm $Pb(Ac)_2$ chow from 50 days pre-mating to experimental use	16.04 µg/100 mL	NMDA-dependent forms of synaptic plasticity are more vulnerable than NMDA-independent potentiation or paired pulse-facilitation.	Gutowski et al. (1998)
Rat 7–18 mo	Water—0.2% $Pb(Ac)_2$ from GD 16 to experimental use	—	Impairs ability to maintain LTP over time in the dentate gyrus.	Gilbert and Mack (1998)
Rat PND 13–140	750 ppm $Pb(Ac)_2$ chow from 50 days pre-mating to experimental use	28.5 µg/dL	Paired-pulse stimulation of CA3 region shows inhibitory mechanisms.	Gutowski et al. (1997)
Adult rat	Water—0.2% $Pb(Ac)_2$ from PND 0–adult	—	Chronic Pb increases the threshold for LTP in dentate gyrus in vivo.	Gilbert et al. (1996)
Rat PND 4–30	Hippocampal neurons	1–100 µM $Pb\ Cl_2$	Identified the nicotinic acetylcholine receptor as a target for Pb.	Ishihara et al. (1995)
Rat	750 ppm $Pb(Ac)_2$ chow from 50 days pre-mating to experimental use	16.2 µg/100 mL	LTP and learning are impaired if exposed to Pb in the immature brain.	Altmann et al. (1993)

Abbreviations

GD—gestational day

Table AX5-3.3. Summary of Key Studies on Changes in Sensory Function

Subject	Exposure Protocol	Peak Blood Pb or [Pb] used	Observed Effects	Reference
Mice PND 7–90	0.15 % $Pb(Ac)_2$ in dams water from PND 0–21	26 µg/dL	Produces a rod photoreceptor-selective apoptosis inhibited by Bcl-xl overexpression.	He et al. (2003)
	Rat retinas	0.01–10 µM $Pb Cl_2$	Pb and calcium produce rod photoreceptor cell apoptosis via mitochondria.	He et al. (2000)
Rat PND 21 or 90	0.02% and 0.2% $Pb(Ac)_2$ in dams water PND 0–21 and 3 wks as adult	59.0 µg/dL	Functional alterations and apoptotic cell death in the retina.	Fox et al. (1997)
Monkey 13 yrs	2 mg/kg/d $Pb(Ac)_2$ in capsule for 13 y	168.0 µg/dL	Mild increase in detection of pure tones outside of threshold.	Rice (1997)
Monkey	350 or 600 mg $Pb(Ac)_2$ for 9.75 yrs	55 µg/dL	Consistent prolongations of latencies on the brain stem auditory evoked potential.	Lilienthal and Winneke (1996)
	Bovine retinas	50 pM–100 nM $Pb(Ac)_2$	Direct inhibition of purified rod cGMP PDE, magnesium can reverse effect.	Srivastava et al. (1995)
	Rat retinas	10^{-9} to 10^{-4} M	Alters several physiological and biochemical properties of rod photoreceptors.	Fox et al. (1994)
			Review paper examining effects upon auditory and visual function.	Otto and Fox (1993)
Adult rat	0.02% and 0.2% $Pb(Ac)_2$ in dams water PND 0–21	59.4 µg/dL	Inhibits adult rat retinal, but not kidney, Na^+, K^+-ATPase.	Fox et al. (1991b)
Monkey 6 yr	Glycerine capsule with 25 or 2000 µg/kg/d $Pb(Ac)_2$	220 µg/dL	Morphological damage in the visual cortical area V1 and V2.	Reuhl et al. (1989)
Rat PND 90	0.2% $Pb(Ac)_2$ in dams water PND 0–21	0.59 ppm	Long-term selective deficits in rod photoreceptor function and biochemistry.	Fox and Farber (1988)

Table AX5-3.4. Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat, female, 22 wks	75 or 300 ppm $Pb(Ac)_2$	39 µg/dL	Significantly impaired on the alteration task with variable intertrial delays.	Alber and Strupp (1996)
Rat Wistar	750 ppm $Pb(Ac)_2$	15 µg/dL	Pb-induced deficits in AAL in rats exposed to Pb either during pre-weaning or pre- and postweaning: postweaning-only exposure caused reduced deficits in AAL.	Altmann et al. (1993)
Rat, LE, postweaning	50 ppm $Pb(Ac)_2$	15.1 µg/dL	Quinpirole at 0.05 mg/kg reversed the effects of Pb on FI performance; eticlopride had no effect on response rates in Pb-treated animals.	Areola and Jadhav (2001)
Rat, LE, male Postweaning	50 or 150 ppm Pb for 3 mo	10.8 and 28.5 µg/dL	FR: 150-ppm rats—significantly higher response rates and component resets than the low dose group and controls. Waiting behavior: wait time was lower in both treated groups. 150-ppm rats—increased number of reinforcers and a higher response to reinforcement ratio than low dose and controls.	Brockel and Cory-Slechta (1998)
Rat, LE, male Postweaning	50 or 150 ppm Pb for 3 mo	9.7 and 26.2 µg/dL after 3 and 7 mo	D_2 agonist quinpirole reversed the Pb-induced effects on FR-response rate, FR resets, wait reinforcers, and wait time.	Brockel and Cory-Slechta (1999a)
Rat, LE, male Postweaning	50 or 150 ppm Pb for 3 mo	16.0 and 28.0 µg/dL	No Pb-induced effects on sustained attention.	Brockel and Cory-Slechta (1999b)
Rat, SD, adult	500 ppm $Pb(Ac)_2$	20.9 µg/dL	Chronic Pb exposure attenuated the reinforcing effect of brain stimulation.	Burkey and Nation (1994)
Rat, SD	0.2% $Pb(Ac)_2$ during gestation and lactation, postweaning only, or continuously	PND 56: 3.8, 25.3, and 29.9 µg/dL	No Pb-associated effects in learning performance with just maternal or postweaning exposure. Continually exposed rats tended to avoid less frequently and in two-way active avoidance training, did not respond more frequently.	(Chen et al. (1997a)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat, SD	0.2% $Pb(Ac)_2$ during gestation and lactation, postweaning only, or continuously	PND 56: 3.8, 25.3, and 29.9 µg/dL	All Pb-treated groups: impaired learning acquisition but unimpaired memory retention; possible alterations in AMPA receptor binding.	Chen et al. (2001)
Rat, LE, male	50 or 250 ppm $Pb(Ac)_2$ chronically from PND 21	25.1 and 73.5 µg/dL	Pb-induced decrements in accuracy on the learning component, but not on the performance component compared; Pb exposure impaired learning by increasing preseverative responding on a single lever, even though such repetitive responding was not directly reinforced.	Cohn et al. (1993)
Rat, LE, male	50 or 250 ppm $Pb(Ac)_2$ chronically from PND 21	25.1 and 73.5 µg/dL	Pb exposure: attenuated the decline in learning accuracy and the increases in preseverative responding produced by MK-801; dose-effect curves relating MK-801 dose to changes in rates of responding were shifted to the right.	Cohn and Cory-Slechta (1993)
Rat, LE, male	50 or 250 ppm $Pb(Ac)_2$ in water PND 21-use	73.5 µg/dL	Pb-induced potentiation of the accuracy-impairing effects of NMDA by further increasing the frequencies of errors and likewise potentiated the drug's rate-suppressing effect; learning impairments are not caused by changes in dopaminergic function.	Cohn and Cory-Slechta (1994a,b)
Rat, LE, male	50 or 500 ppm from weaning	30.3 and 58–94 µg/dL	50-ppm group: no effects. 500-ppm group: response rates initially decreased, then reached control levels, primarily due to longer interresponse times. FI response rates are more sensitive to perturbation by Pb than FR.	Cory-Slechta (1986)
Rat, LE, male, PND 21	50 ppm PbS 8–11 mo	~20 µg/dL	Decreased FI response rates (i.e., longer IRTs and lower running rates) compared to controls.	Cory-Slechta (1990a)
6–8.5 mo	50 or 500 ppm 3–5 mo		Demonstrated no consistent changes in FI performance, suggesting that once a behavior has been acquired, it may be resistant to the adverse effects of subsequent Pb exposure.	
Rat, LE, male, PND 21	50 or 250 ppm $Pb(Ac)_2$	73.2 µg/dL	Increased sensitivity to the stimulus properties of dopamine D_1 and D_2 agonists.	Cory-Slechta and Widowski (1991)
Rat, F344, PND 21 8 mo, 16 mo	2 or 10 mL/kg/d $Pb(Ac)_2$ for 9.5 mo	13–18 µg/dL steady state	Young and old rats: increased VI and FI response rates; adult rats: decreased response rates on both schedules. Effects on FI seen with 2-mg dose and VI with only the 10-mg dose.	Cory-Slechta and Pokora (1991)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat, F344, male	2 or 10 mg/kg $Pb(Ac)_2$	2 mg: 23; 10 mg: 42 (adult), ~48 (old), ~58 µg/dL (young)	Aging caused impaired accuracy: In both young and old rats: Pb-induced increase in accuracy, at the longest delay periods (12 s) in young rats, and at the short delay periods in old rats. Adults: not affected by Pb exposure.	Cory-Slechta et al. (1991)
Rat, LE, male	100 or 350 ppm $Pb(Ac)_2$ in dam's water PND 0–21	34 µg/dL	Induced functional D_2-D_3 supersensitivity to the stimulus properties of agonist.	Cory-Slechta et al. (1992)
Rat, LE, male	50 or 150 ppm $Pb(Ac)_2$ from weaning	—	Altered cholinergic sensitivity due to Pb and several agonists.	Cory-Slechta and Pokora (1995)
Rat, LE, male	50 or 150 ppm $Pb(Ac)_2$	35.7 µg/dL	Postweaning Pb exposure resulted in an MK-801 subsensitivity.	Cory-Slechta (1995)
Rat, LE, male	50 or 150 ppm $Pb(Ac)_2$ in water PND 21-use	30.6 µg/dL	(1) Enhances the stimulus properties of NMDA via a possible dopaminergic path. (2) Low level Pb exposure is associated with D_1 subsensitivity.	Cory-Slechta et al. (1996a,c)
Rat, LE, male	50 or 150 ppm $Pb(Ac)_2$ from weaning	15–25 30–50 µg/dL	Pb exposures attenuated the decrements in rates produced by the two D_1 agonists SKF38393 and SKF82958, and at 150 ppm, Pb exposure altered the rate change associated with the low dose (0.033 mg/kg) of quinpirole.	Cory-Slechta et al. (1996b)
Rat, LE, male	100 or 350 ppm $Pb(Ac)_2$ from weaning	35.0 µg/dL	Post-washout decrease in sensitivity to MK-801.	Cory-Slechta (1997)
Rat, LE, male	50 or 500 ppm $Pb(Ac)_2$ from weaning	49.1 µg/dL	Increases FI schedule-controlled behavior in nucleus accumbens.	Cory-Slechta et al. (1998)
Rat, LE, male	50 or 500 ppm $Pb(Ac)_2$ from weaning	49.1 µg/dL	Both DA and EEDQ, microinjected into the dorsomedial striatum, caused increases or decreases in FI response rates, which depended on baseline FI overall rates.	Cory-Slechta et al. (2002)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Hamster, Golden	100 ppm $Pb(Ac)_2$ GD8–PND 42	PND 42: 10–15 µg/d	PND 19–20: Pb-exposed hamsters smaller, exhibited less play fighting. PND 45: Pb-induced increase in aggression.	Delville (1999)
Rat, Wistar, female	8, 16, or 24 mg/mL $Pb(Ac)_2$ during pregnancy, pregnancy and lactation, or lactation.	5.7–36.6 µg/dL	PND 7: dose-dependent decrease in ultrasonic vocalization. PND 14: increased vocalization, and higher activity levels.	De Marco et al. (2005)
BK:W mice, male and female	0.13% $Pb(Ac)_2$ chronically started before breeding	Brain and femur: 18 wks: 27.6 and 998 34 wk: 445 and 5, 364 (M) 34 wk: 787 and 4, 026 (F)	Young Pb-exposed female mice habituated more slowly. Young Pb-exposed males habituated more rapidly. Adults: Pb-induced enhancement of social and sexual investigation.	Donald et al. (1986)
BK:W mice, male and female	0.25% $Pb(Ac)_2$ chronically started before breeding		3–4 wks: Pb-induced increase in exploratory behavior and social investigation in exploratory behavior. 15–16 wks: Pb-induced decrease in nonsocial activity in females, increase in males. 17–18 wks: Pb-induced shorter latencies to aggression in males.	Donald et al. (1987)
Monkey, rhesus, 4 yrs	10 mg/kg/d pulses (2) and chronic 0.7 for first yr of life	5 wks: 55 µg/dL first yr: ~36 yr 4: <5	Pb-induced longer latency to enter the open area, increased durations of environmental exploration and activity, and resulted in a failure to habituate.	Ferguson and Bowman (1990)
Rat, SD	350 ppm $Pb(Ac)_2$ from birth until weaning	46 µg/dL	No Pb-related effects in play, burrowing, dominance, residential running wheel, residential figure-8 maze, complex maze, acoustic startle, emergence, prepulse inhibition.	Ferguson et al. (1998)
Rat LE, PND 53	300 or 600 ppm $Pb(Ac)_2$ during gestation and lactation or lactation only	16, 12, and 18 µg/dL	Two-choice olfactory serial reversal task: Pb-treated groups took more trials to reach the point where repeated responding to the previously correct cue ended.	Garavan et al. (2000)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Monkey, cynomolgus, 9–10 yrs of age	50 or 100 µg/kg/d $Pb(Ac)_2$	15.4 and 25.4 µg/dL; 10.9 and 13.1 µg/dL, steady state	Pb-induced impairment in the presence, but not the absence, of irrelevant cues; in the lower-dose group monkeys, impairment ended when the irrelevant stimuli became familiar.	Gilbert and Rice (1987)
Rat, male, adult	500 ppm $Pb(Ac)_2$ in chow for 105 days	28 µg/dL	Chronic Pb exposure attenuates cocaine-induced behavioral activation.	Grover et al. (1993)
Rat, LE	1500 ppm $Pb(Ac)_2$ gestation and lactation	3.9 µg/dL at PND 50	Pb + enriched environment: enhanced performance in water maze; increased gene expression in the hipppocampus of NMDAR subunit 1 and BDNF.	Guilarte et al. (2003)
Rat, Wistar, male	100 mg/kg/body weight by injection	Not reported	Pb-induced deficits in memory component of the radial arm maze test and in retention of passive avoidance learning.	Haider et al. (2005)
Rat, LE, female	75 or 300 ppm $Pb(Ac)_2$ in water GD0 experimental use	51 µg/dL	Impairment of reversal learning as an associative deficit.	Hilson and Strupp (1997)
Rat, LE, male and female	500 ppm Pb choride during lactation	42 µg/dL	PND 11: no Pb-induced sex differences, effects on pup activity, and differences in pup retrieval by dams. PND 26: Pb treatment influenced all social behavior tested (i.e., investigation duration and frequency, crossover frequency, pinning) but did not change activity levels. PND 36: Pb-treated pups demonstrated increased crossover frequencies but no change in activity levels compared to controls.	Holloway and Thor (1987)
Rat, LE	250 ppm $Pb(Ac)_2$ chronically from gestation	Hippocampal Pb levels PND 21: 1.73; PND 56: 1.02; PND 91: 0.91 µg/g	Pb-exposure had no effect on working memory at any age tested, but did affect reference memory (significant in females and nearly significant in males) in the PND 21 rats.	Jett et al. (1997)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat, LE, male	750 ppm $Pb(Ac)_2$ maternally, permanently, or postweaning only	At PND 100 1.8, 21.3, 22.8, and 26.3 µg/dL	Maternal and permanent exposure: impaired water maze performance, with maternal exposure producing both the greatest escape latency and longest escape path length. No effects on performance in the postweaning exposure groups.	Kuhlmann et al. (1997)
Monkey, rhesus	$Pb(Ac)_2$ testing first 4 wks of life	35 µg/dL	Pb-induced greater agitation, climbing, fear, and exploration of the periphery.	Lasky and Laughlin (2001)
Monkey, rhesus	1 mg/kg/d $Pb(Ac)_2$ PND 5–PND 365	First yr ~70 µg/dL 16-mo PE: ~35 µg/dL	First yr: Pb-induced disruption of social play, and increases in both self-stimulation and fearful behavior were observed. 16 mo: continued disruption.	Laughlin et al. (1991)
Monkey, rhesus	$Pb(Ac)_2$ testing first 4 wks of life	35 µg/dL	Few differences between control and Pb-exposed monkeys were seen; less stability in SNAP performance.	Laughlin et al. (1999)
Monkey, rhesus, 5–6 yrs	10 mg/kg/d pulses (2) and chronic 0.7 for first yr of life	250–300 µg/dL peak 80 for rest of yr	Pb-induced deficits occurred most commonly with short intertrial delays; lose-shift errors, possibly due to perseveration.	Levin and Bowman (1986)
Monkey, rhesus, 7–9 yrs	10 mg/kg/d pulses (2) and chronic 0.7 for first yr of life	1–4 wk: 63 µg/dL 5–6 wk: 174 4 yrs: 4 7 yrs: 2	Chronic L-dopa ameliorated the Pb-induced DSA deficits, which returned following cessation of L-dopa administration: implicates DA mechanisms in these impairments.	Levin et al. (1987)
Monkey, rhesus	10 mg/kg/d pulses (2) and chronic 0.7 for first yr of life	wk 5: 56 during; remainder of first 6 mo: 33–43 µg/dL	First 6 wks: Pb-induced lowered muscle tonus and greater agitation, no effects on sensorimotor measures. PND 14: no Pb-related effects on object permanence task. 2 mo: Pb-induced decreased visual attentiveness in visual exploration task.	Levin et al. (1988)
Monkey, rhesus	350 or 600 ppm in utero	50 and 110 µg/dL	At age 12 to 15 mo, the high-dose group exhibited deficits in simple discrimination learning: both groups showed impairments in the more complex learning set formation trials; activity at 12–15 mo showed no Pb-related effects.	Lilienthal et al. (1986)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat, SD, male, PND 60	8 or 16 mg $Pb(Ac)_2$	6.8 µg/dL	Long-lasting changes in drug responsiveness to cocaine and related drugs.	Miller et al. (2001)
Rat, Wistar	500 ppm $Pb(Ac)_2$ through pregnancy and lactation	41.24 µg/dL (dams), 21.24 µg/dL (PND 23), <0.1 µg/dL (PND 70)	PND 23: Pb-induced increased ambulation in the open-field tests, decreased exploratory behavior in the holeboard tests, and no differences from control in the elevated maze tests. PND 70: Pb-induced increase in head dipping in the holeboard test, decrease in social interaction time. No differences in the rotarod tests.	Moreira et al. (2001)
Rat, LE	75 or 300 ppm $Pb(Ac)_2$ continuously	36 µg/dL	Impaired learning of a visual discrimination task.	Morgan et al. (2000)
Rat LE, PND 53	300 or 600 ppm during gestation or gestation and lactation	PND 8: 36–43; PND 24: 27–34; PND 53: 131–158	No Pb-induced differences in learning rate, motivation, or response latency for correct or incorrect responses. Pb-induced: increases in errors of omission when a delay was imposed prior to cue presentation, trials that followed an incorrect response, and response initiation.	Morgan et al. (2001)
Rat, Wistar tested at PND 100 and PND 142	750 ppm though PND 16 maternal exposure or chronically	PND 110: maternally exposed: <3; chronic: 34 µg/dL	Both Pb-treated groups learned the original discrimination comparably to controls, but showed a deficit in retention; Pb-treated female rats took longer to reach criterion in the acquisition learning and longer to eat the pellets in the retention phase.	Munoz et al. (1986)
Rat, Wistar, female	750 ppm $Pb(Ac)_2$	17.3 µg/dL at PND 16 32–39 µg/dL continuous exposure	Pb-induced deficits in acquisition of learning, but not with concurrent hippocampal lesions. Four wks later, both lesioned and Pb-treated animals showed impaired retention.	Munoz et al. (1988)
Rat, Wistar, female	750 ppm $Pb(Ac)_2$	17.3 µg/dL at PND 16 32–39 µg/dL continuous exposure	Pb and lesions of amygdala showed impairments in the acquisition phase of the maze and impaired passive avoidance; neither treatment affected locomotor activity. Continuously exposed rats showed greater deficits.	Munoz et al. (1989)
Rat, Wistar, PND 80	400 mg/L Pb Cl_2 in dam's water PND 1–30	PND 8: 10–15 µg/dL; PND 21: ~45; PND 80: 2–4	48 h PE: no Pb-induced changes in recall; 5 days PE: decline in recall latency.	Murphy and Regan (1999)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat, SD, male, adult	500 ppm $Pb(Ac)_2$	28.91 µg/dL	Decreases sensitization to the locomotor-stimulating effects of cocaine.	Nation et al. (1996)
Rat, SD, PND 120	16 mg $Pb(Ac)_2$ via gavage 30 days pre-pregnancy to PND 21	38.0 µg/dL	Self-administering rats prenatally exposed to Pb demonstrate and increased sensitivity to the relapse phase of cocaine abuse.	Nation et al. (2003)
Rat, SD, PND 70	16 mg $Pb(Ac)_2$ via gavage 30 days pre-pregnancy to PND 21	53.24 µg/dL	Increased sensitivity to cocaine in rats perinatally exposed to Pb.	Nation et al. (2004)
Rabbit, Dutch Belted, male	$Pb(Ac)_2$	20, 40, and 80 µg/dL	Exposed males mated with nonexposed females. Offspring at PND 25 showed Pb-induced effects on exploratory behavior.	Nelson et al. (1997)
Monkey, squirrel	Mother's blood Pb from gestation week 5–birth	21–79 µg/dL	Reduced sensitivity to changes in reinforcement contingencies during behavioral transitions and in steady state.	Newland et al. (1994)
Monkey, squirrel	In utero exposure	21–70 µg/dL maternal	Pb-induced increase in the number of responses that failed to adequately displace the bar in the FR schedule and possible subtle motor impairments.	Newland et al. (1996)
Monkey, cynomolgus	2 mg/kg/d of $Pb(Ac)_2$ continuously	115 µg/dL at PND 100 33 µg/dL by PND 270	At PND 60: Pb-induced increased mean FR pause times, and, decreased FI pause times. At 3 yrs of age: Pb-induced increased FI run rate, pause time, and index of curvature. At both ages, Pb-induced increased variability of performance.	Rice (1988a)
Monkey, cynomolgus	50 or 100 µg/kg/d $Pb(Ac)_2$ chronically beginning at PND 1	PND 100: 15.4 and 25.4 PND 300: 10.9 and 13.1 µg/dL	Delayed alternation at 7–8 yrs of age: Pb-induced impairment of initial acquisition of tasks; longer delays between alternations resulted in poorer performance and perseverative behavior, sometimes lasting for hours.	Rice and Karpinski (1988)
Monkey, cynomolgus, 7–8 yr	1500 µg/kg/d $Pb(Ac)_2$	36 µg/dL	Pb exposure in infancy only impaired spatial discrimination reversal tasks.	Rice (1990)
Monkey, cynomolgus, 7–8 yr	1500 µg/kg/d $Pb(Ac)_2$ continuously from birth, during infancy only, or beginning after infancy	36 µg/dL	All Pb-treated groups: same impairments of initial acquisition, indiscriminate responding, greater impairment with longer delays, and preseverative responses.	Rice and Gilbert (1990b)

Table AX5-3.4 (cont'd). Summary of Key Studies on Neurobehavioral Toxicity

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Monkey, cynomolgus, 5–6 yr	1500 µg/kg/d $Pb(Ac)_2$ continuously from birth, during infancy only, or beginning after infancy	36 µg/dL	Post-infancy exposure impairs nonspatial discrimination reversal while exposure during infancy exacerbates the effect.	Rice and Gilbert (1990a)
Monkey, cynomolgus, 3 or 7 yr	1500 µg/kg/d $Pb(Ac)_2$	36 µg/dL	Pb exposure during different developmental periods produce different effects on F1 performance in juveniles versus adults.	Rice (1992a)
Monkey, cynomolgus, 8–9 yr	1500 µg/kg/d $Pb(Ac)_2$ continuously from birth, during infancy only, or beginning after infancy	36 µg/dL	Pb-treated monkeys in all three exposure groups learned more slowly, with less impairment in infancy-only exposures, and showed perseverative behavior.	Rice (1992c)
Monkey, cynomolgus, 0.5 or 3 yr	2000 µg/kg/d $Pb(Ac)_2$	115 µg/dL	Decreased interresponse times and a greater ratio of responses per reinforcement on the differential reinforcement of low rate schedule.	Rice (1992b)
Rat, adult	16 mg $Pb(Ac)_2$ via gavage 30 days pre-pregnancy to PND 21	83.2 µg/dL	Developmental Pb exposure results in enhanced acquisition of cocaine self-administration.	Rocha et al. (2005)
Rat	0.5, 2.0, or 4.0 mM $Pb(Ac)_2$ in drinking water	11–50 µg/dL	Pb-induced decreased retention in shuttle avoidance task. Pb-associated increase in locomotor activity.	Rodrigues et al. (1996a)
Rat, F344		~42 µg/dL	Pb-induced better performance using extra-maze spatial cues; Pb-treated rats spent less time on the periphery of the maze.	Salinas and Huff (2002)
Rat, LE, male	0.2% $Pb(Ac)_2$ from PND 25 until testing at PND 100	~30 in Pb	Pb-exposure + isolation: spatial learning deficits. Pb-exposure + enrichment: performed better than the isolated Pb group. Pb-induced decreases in hippocampal levels of BDNF, NGF-β, NT-3, and basic FGF.	Schneider et al. (2001)
Rat, Wistar	750 ppm $Pb(Ac)_2$ gestation and lactation	PND 30: 25 µg/dL PND 90: 0.113 µg/dL	At PND 30 and 90: no Pb-associated changes in elevated maze behavior. PND 30: decreased freezing, increased ambulation, and increased grooming. PND 90: Pb-induced decreased freezing and increased ambulation. Offspring of Pb-treated females mated with nonexposed males. F2 generation at PND 30 and 90: increased ambulation and decreased grooming.	Trombini et al. (2001)
Rat, Wistar	0.03%, 0.09%, or 0.27% $Pb(Ac)_2$ gestationally	~30, ~33, and ~42 µg/dL at PND 0, tested at PND 49	Male offspring: all three doses impaired memory retrieval. Female offspring: only the low dose affected memory retrieval. Motor performance and vision were not affected by Pb.	Yang et al. (2003)

Table AX5-3.5. Summary of Key Studies on Cell Morphology and Metal Disposition

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat, PND 110	Water—0.2% $Pb(Ac)_2$ from GD 16-PND 21 or use	—	Reduction in hippocampal neurogenesis with no spatial learning impairments.	Gilbert et al. (2005)
	Rat C6 glioma cells and human astrocytoma cells	5–10 μM $Pb(Ac)_2$	Directly targets GRP78 and induces its compartmentalized redistribution. GRP78 plays a protective role in Pb neurotoxicity.	Qian et al. (2005a)
	Rat pup astroglial cell culture	10 μM $Pb(Ac)_2$	Oxidative stress in astroglia results from Pb impairment of the Cu transporter Atpase (Atp7a).	Qian et al. (2005b)
Rat, PND 60	1500 ppm $Pb(Ac)_2$ for 30–35 days	20.0 μg/dL	Significant deleterious effects on progenitor cell proliferation.	Schneider et al. (2005)
Rat, embryos	Cultured neurospheres	0.1–100 μM $Pb(Ac)_2$	Differentially affects proliferation and differentiation of embryonic neural stem cells originating from different brain regions.	Huang and Schneider (2004)
Young rat	PND 0–20 = 600 μg/dL PND 20–40 = 20–60 μg/dL	131.3 μg/dL	Blood Pb during succimer chelation are not an immediate indicator of brain. Brain Pb values are slower to respond even though blood Pb is normal.	Stangle et al. (2004)
	Cultured oligodendrite progenitor cells—PND 2	1 μM $Pb(Ac)_2$	Pb inhibition of proliferation and differentiation of oligodendrocyte cells requires PKC.	Deng and Poretz (2002)
	Cultured oligodendrite progenitor cells—PND 2	0.1–100 μM $Pb(Ac)_2$	Interferes with maturation of oligodendrocyte progenitor cells.	Deng et al. (2001)
	Cultured cerebellar granule neurons	5–50 μM $Pb(NO_3)_2$ or $Pb(ClO_4)_2$	Specific transport systems carry Pb into neurons.	Mazzolini et al. (2001)
Rat	Cultured C6 glioma cells	1 μM $Pb(Ac)_2$	Induces GRP78 protein expression and GRP78 is a strong Pb chelator.	Qian et al. (2000)
Human, 1–4 yr			Half-life of blood Pb was dependent upon exposure duration, ranging 10–38 mo.	Manton et al. (2000)
Rat and human	Cultured rat astroglial, human neuroblastoma	1 μM $Pb(Ac)_2$	Immature astroglia vs. neuronal cells are most likely to bind Pb in the brain.	Lindahl et al. (1999)
			Review paper addressing Pb-binding proteins in the brain and kidney.	Fowler (1998)
	Cultured GH3, C6, and HEK293 cells	1–10 μM $Pb(NO_3)_2$	Cellular uptake of Pb is activated by depletion of intracellular calcium.	Kerper and Hinkle (1997)
Rat	2 g/l $Pb(Ac)_2$ in weanlings for 3 mo	39 μg/dL	Chronic low Pb levels induces blood brain barrier dysfunction.	Strużyńska et al. (1997)

Table AX5-3.5 (cont'd). Summary of Key Studies on Cell Morphology and Metal Disposition

Subject	Exposure Protocol	Peak Blood Pb or [Pb] Used	Observed Effects	Reference
Rat	50 or 250 µg/mL $Pb(Ac)_2$ for 30, 60, or 90 days	48.9 µg/dL	Low dose, long-term exposure significantly decreases cerebral spinal fluid concentrations of TTR.	Zheng et al. (1996)
Frog tadpoles	Elvax implantation for 6 wks	10^{-10} to 10^{-6} M $Pb Cl_2$	Stunted neuronal growth from low Pb levels are reversible with chelator.	Cline et al. (1996)
Rat	Cultured hippocampal neurons	100 nM $Pb Cl_2$	Possible neurite development inhibition via hyperphosphorylation.	Kern and Audesirk (1995)
Human	Pb-binding proteins isolated from cortex	10–2000 nM $Pb(Ac)_2$	Characterizes two cytosolic Pb-binding proteins-thymosin beta 4 and an unidentified protein.	Quintanilla-Vega et al. (1995)
Rats PND 7–60	100–2000 ppm $Pb(Ac)_2$ in water for adult rats	72.5 µg/dL	Elimination half-life of Pb from all regions of the brain was about 20 days. There was no evidence of selective regional accumulation of Pb.	Widzowski and Cory-Slechta (1994)
Rat, adult	Radiolabeled Pb perfused across whole brain	9.7 mL/100 g	Review paper examining the passage of Pb across the blood-brain barrier. Suggests it is actively transported via Ca-ATP pump.	Bradbury and Deane (1993)
			Review paper indicating that Pb either structurally alters nuclear protein p32/6.3 or inhibits a protease for which it is a substrate.	Shelton et al. (1993)
			Review paper discussing Pb removal from bone; the half-life of Pb in bone is about 20 yr while in blood it is 1 mo.	Wedeen (1992)
Rat, adult	Radiolabeled albumin	—	Discovered that albumin rarely enters brain from blood.	Bradbury et al. (1991)
Guinea pig, chicken, and rat	Mouse neuroblastoma 2a cell line	—	Results indicate a positive correlation between p32/6.3 levels and neuronal maturation.	Klann and Shelton (1990)
Dog and rat	Mouse neuroblastoma 2a cell line	50–100 µM Pb	Examined the relationship between Pb and nuclear protein p32/6.3 and its abundance in intranuclear inclusion bodies.	Klann and Shelton (1989)
Adult rat	Pb binding protein of kidney and brain	0.1–1.6 µM	Attenuation of Pb inhibition of ALAD involves sequestration of Pb and a donation of zinc to the enzyme.	Goering et al. (1986)
Rat	Perfusion of 0.5 MBq of Pb-203 isotope for 0.5–4 h	615 µg/dL	Injections of Pb-203 showed a linear uptake into three regions of the brain, suggesting that the blood-brain barrier is rate-limiting.	Bradbury and Deane (1986)
Human	—	160 µg/100 mL	Blood Pb half-life is affected by duration of exposure, age, and length of follow-up.	Hryhorczuk et al. (1985)
Human	—	>60 µg/dL	Blood Pb half-life is dependent upon the length of exposure.	O'Flaherty et al. (1982)

Table AX5-3.6. Key Studies Evaluating Chelation of Pb in Brain

Subject	Exposure Protocol	Chelator	Observed Effects	Reference
Rat, male, LE, PND 21	Group 1: 50 ppm Pb acetate in drinking water from PND 21 for 3–4 mo, after which they were given i.p. injections of 75 or 150 mg/kg CaEDTA for either 1, 2, 3, 4, or 5 days. Group 2: 25 or 500 ppm Pb acetate followed by a single injection of either 75 or 150 mg/kg CaEDTA. Twenty-four hour urine samples were collected following CaEDTA injections.	CaEDTA	Group 1: Blood Pb declined after the first CaEDTA injection, but did not drop further with subsequent CaEDTA and never dropped below control levels (5 µg/dL). Pb levels in urine increased similarly with both doses of CaEDTA. Pb was found to be mobilized from both bone and kidney and initially redistributed to brain and liver. Subsequent CaEDTA injections caused declines in brain and liver Pb levels, but no net loss of Pb. Group 2: a single injection of 150 mg/kg CaEDTA caused marked elevation of brain Pb, which called into question use of injections of CaEDTA in clinical diagnostic procedures.	Cory-Slechta et al. (1987)
Rat, male, LE, PND 21	50 ppm Pb acetate from weaning until testing 3–4 mo later. The rats received either 25 or 50 mg/kg DMSA for 1, 2, 3, 4, or 5 days and tissues were evaluated 24 h following the last injection.	DMSA	Blood Pb was decreased by DMSA dose-dependently, with levels dropping to <5 µg/dL after 3 injection of the higher dose and 4 injections of the lower dose. Pb levels dropped in brain and kidney immediately, and in liver following a delay. Bone Pb did not decline, which contrasts with earlier studies showing mobilization from bone following DMSA chelation. Another group in this study received the same 5 days of DMSA injections, but was evaluated 4 mo later. Pb concentrations in all tissues were comparable to those seen in the first group, indicating that chelation therapy must be continued to lower tissue Pb levels.	Cory-Slechta (1988)
Rat, female, Wistar	Given ^{206}Pb-enriched drinking water at 210 ng Pb/mL for 36 h. Following an overnight fast, the rats were injected with one 0.25 mL i.p. injection of 0.11 mmol/kg DMSA. Pb levels in blood, kidney, brain, and tibia assessed 24 h later.	DMSA	Blood Pb declined 40%, Pb in urine increased 1500%, and changes in kidney and brain tissue Pb levels varied inconsistently. Chelation did not result in increased excretion of skeletal Pb compared to controls, nor did it show a redistribution of Pb to brain.	Smith and Flegal (1992)

Table AX5-3.6 (cont'd). Key Studies Evaluating Chelation of Pb in Brain

Subject	Exposure Protocol	Chelator	Observed Effects	Reference
Rat, female, Albino	100 ppm Pb acetate in drinking water for 4 wks. During the last 2 days of that exposure, the rats were administered two i.p. injections of 1 µg stable ^{204}Pb tracer. Animals then received 1 to 5 consecutive days of 150 mg/kg CaEDTA ; assayed 24 h following the last injection.	CaEDTA	No redistribution of endogenous Pb into the brain following one CaEDTA dose, no measurable reduction in brain or bone Pb levels, and reductions in both kidney and blood Pb levels. Additionally, over the first day of treatment, CaEDTA reduced the ^{204}Pb tracer more effectively than the Pb from chronic exposure, indicating greater biologically availability of Pb from recent exposures.	Seaton et al. (1999)
Rat, male, SD rats at 6–7 wks	Chelation with ongoing Pb exposure; blood Pb were ~45 µg/dL; 550 ppm Pb acetate in drinking water for 35 days. Group 1: continued on Pb only for 21 days. Group 2: received continued Pb plus oral DMSA at 16, 32, 120, or 240 mg/kg/d for 21 days. Group 3: discontinued on Pb after the first 35 days and received oral DMSA (16, 32, or 240 mg/kg/d).	DMSA	DMSA treatment increased urinary Pb and decreased levels of Pb in blood, brain, bone, kidney, and liver, even with continued Pb exposure.	Pappas et al. (1995)
Rat, male, Wistar	Dosed with 1000 ppm Pb in drinking water for 4 mo, then treated for 5 days with: saline; 25 mg/kg DMSA orally, twice daily; 75 mg/kg CaEDTA i.p. once daily; or 25 mg/kg DMSA twice daily plus 75 mg/kg CaEDTA i.p. once daily. Blood Pb resulting from these treatments were 46, 22, 28, and 13 µg/dL, respectively and brain Pb levels were 49, 38, 26, and 22 µg/g, respectively.	CaEDTA and DMSA	The combined treatments produced an additive response in urinary Pb elimination and elimination from blood, liver, kidney, brain, and femur.	Flora et al. (1995)

Table AX5-3.6 (cont'd). Key Studies Evaluating Chelation of Pb in Brain

Subject	Exposure Protocol	Chelator	Observed Effects	Reference
Rat, female, LE	Group 1: 325 µg/mL Pb acetate maternally through weaning, and then to 30 µg/mL until PND 30. Chelation treatment consisted of 7 days of 30 or 60 mg/kg/d DMSA. Group 2: 325 µg/dL maternally and through PND 40 and then treated to DMSA for 7 or 21 days.	DMSA	Seven days of DMSA effectively removed Pb from both blood and brain. Treatment beyond 7 days further reduced brain Pb, but not blood Pb. Reductions in Pb were greater in the second group, which the authors attribute to the higher exposures used. The authors also hypothesize that DMSA-mediated reduction in blood Pb are a poor indicator of reductions in brain Pb.	Smith et al. (1998)
Rat, LE	Exposed gestationally to 600 µg/mL Pb acetate, then split into high and low dose groups. Low dose group: 20 µg/mL from PND 21–28, followed by 30 µg/mL from PND 29–40. High dose group: 40 µg/mL from PND 21–28, followed by 60 µg/mL from PND 29–40. DMSA treatment consisted of 50 mg/kg/d for 1 wk, then 25 mg/kg/d for 2 wks. Rats received either 1 or 2 treatments at PND 40 or 40 and 70.	DMSA	One treatment lowered both blood Pb and brain Pb, but the brain reductions lagged the blood reductions both temporally and in magnitude. Following the second DMSA treatment, they observed a rebound in blood, but not brain Pb levels.	Stangle et al. (2004)

Table AX5-3.6 (cont'd). Key Studies Evaluating Chelation of Pb in Brain

Subject	Exposure Protocol	Chelator	Observed Effects	Reference
Monkey, Rhesus, 11-yr-old with history of testing for effects of housing and rearing and which were used in drug challenge studies, were used after at least 1.5 yrs had elapsed since the last testing	~50 mg/kg/d Pb acetate, and then doses were adjusted to produce a target blood Pb of 35–40 µg/dL. Following 5 wks of Pb exposure, the monkeys were administered ^{204}Pb tracer starting 4 days before chelation. DMSA was administered for 5 days at 30 mg/kg/d, followed by 14 days at 20 mg/kg/d.	DMSA	Brain levels of Pb and tracer, measured in prefrontal cortex, hippocampus, and striatum, were not different from controls, indicating that DMSA was not effective in reducing brain Pb levels. They also found a poor correlation between brain and blood Pb levels.	Cremin et al. (1999)
Rat, male, LE, PND 55	At PND 55, rats were started on an FI schedule, where a Pb-induced increase in interresponse time was observed. Pb exposure was then terminated and daily injections of 75 or 150 mg/kg CaEDTA were given for 5 consecutive days.	CaEDTA	Chelation treatment failed to reverse the learning deficits in Pb-exposed animals and further increased the proportion of short interresponse times. The authors suggest that this effect may be due to the CaEDTA-mediated redistribution of Pb from bone to brain.	Cory-Slechta and Weiss (1989)
Rat, male, F344, 7-wk-old male	150 or 2000 ppm Pb for 21 days, then distilled water for the next 21 days. Blood Pb peaked at 37 and 82 µg/dL, respectively. Chelation: 50 mg/kg by oral gavage, 3 times a week for up to 21 days; reduced blood Pb to 22 and 56 µg/dL, respectively.	DMSA	Pb-induced increase in rearing behavior was observed. DMSA reduced the Pb-induced effects on activity. Levels of brain glial fibrillary acidic protein (GFAP) were also assessed in these animals. A Pb-induced dose-dependent increase in GFAP was observed in hippocampus, cortex, and cerebellum, which was reversed by DMSA treatment.	Gong and Evans (1997)

ANNEX TABLES AX5-4

Table AX5-4.1. Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Al-Hakkak et al. (1988)	Mouse/BALB/c, weaning	0, 25, 50 mg Pb monoxide alloy/kg in chow for 35–70 days	Reduced number of spermatogenia and spermatocytes in the 50 mg group after 70 days; reduced number of implantations after mating (after 35 days exposure).	PbB not reported
Appleton (1991)	Rat/Long-Evans hooded, adult	Pb acetate single dose by i.v. at 30 mg/kg	Increase in serum calcium and phosphorous; SEM analysis revealed 'Pb line' in tooth that was composed of hypomineralized interglobular dentine.	PbB not reported
Bataineh et al. (1998)	Rat/Sprague-Dawley, adult	1000 ppm Pb acetate in drinking water for 12 wks	Fertility was reduced; total number of resorptions was increased in female rats impregnated by males.	PbB not reported
Berry et al. (2002)	Rat/Sprague-Dawley, 21 days old	Pb nitrate (1000 ppm Pb) in drinking water for 6 wks	Mean plasma growth hormone levels decreased by 44.6%; reduced mean growth hormone amplitude by 37.5%, mean nadir concentration by 60%, and growth hormone peak area by 35%; findings are consistent with decreased hypothalamic growth hormone-releasing factor secretion or reduced somatotrope responsiveness; exogenous growth hormone in Pb-treated and control rats, this response was blunted by the Pb treatment; plasma IGF1 concentration was not significantly affected by Pb treatment.	PbB 37.40 ± 3.60 µg/dL
Bogden et al. (1995)	Rat/Sprague-Dawley, 12 wks old	250 mg/L of Pb acetate in drinking water from GD 1 until after 1 wk after weaning	Dam and pup hemoglobin concentrations, hematocrit, and body weights and lengths were reduced.	PbB <15 µg/dL
Camoratto et al. (1993)	Rat/Sprague-Dawley, adult	0.02% Pb nitrate in drinking water from gestation day 5 of dams until PND 4 of offspring	Female pups exposed to Pb beginning in utero were smaller, no corresponding effect in males; pituitary responsiveness to a hypothalamic stimulus.	PbB 17–43 µg/dL
Corpas (2002a)	Rat/Wistar, adult	Pb acetate 0 or 300 mg/L in drinking water during gestation and lactation	Alterations in hepatic system of neonates (PND 12) and pups (PND 21); reductions in hemoglobin, iron, alkaline and acid phosphatase levels, and hepatic glycogen, and elevated blood glucose.	PbB ~22 µg/dL
Corpas (2002b)	Rat/Albino (NOS), adult	Pb acetate 0 or 300 mg/L in drinking water during gestation and lactation	Effects energy metabolism; decrease in testis and seminal vesicle weights, and an increase in DNA and RNA levels on PN day 21; protein was significantly decreased, alkaline and acid phosphatase levels of the gonads were reduced; reduction of the thickness of the epithelium and seminiferous tubule diameter.	PbB 54–143 µg/dL

Table AX5-4.1 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Cory-Slechta et al. (2004)†	Rat/Long-Evans, adult	Pb acetate in drinking water (150 ppm); 2 mo before breeding until the end of lactation 14 rats no maternal stress Pb exposure, 15 rats no maternal stress with Pb exposure, 18 rats maternal stress without Pb exposure, 23 rats maternal stress and Pb exposure	Pb alone (in male) ($p < 0.05$) and Pb plus stress (in females) ($p < 0.05$) permanently elevated corticosterene levels in offspring.	PbB 30–40 µg/dL
Dey et al. (2001)	Mouse/Albino (NOS), ~100 g	Pb citrate 5 µg/kg-d p.o. from early pregnancy (NOS) until birth	Perforations, tissue damage, cell deformity, disordered organization of collagen bundles found in offspring; reduction in the symmetry of sulphate group of skin pups of mice exposed to Pb citrate (5 µg/kg-d) throughout gestation exhibited a variety of skin anomalies, including perforations, tissue damage, cell deformity, and disordered collagen bundles Pb was found to affect initial genomic expression in embryos fathered by male rats.	PbB not reported
Flora and Tandon (1987)	Rat/Albino (NOS), adult	Pb nitrate dissolved in water 2–20 mg/kg-d i.v. on day 9, 10, 11 of gestation; 6 rats in each group (0, 5, 10, 20, 40 mg/kg Pb)	Dose-dependant increase in external malformations at all doses ($p < 0.001$), particularly tail defects; dose dependant decrease in number of live births at 20 and 400 mg/kg ($p < 0.001$); dose-dependent increase in number of resorptions per dam at ≤10 mg/kg ($p < 0.01$).	PbB 13–45 µg/dL
Fox et al. (1991a)	Rat/Long-Evans hooded, adult	Lactation exposure via dams exposed to 0.02 or 0.2% Pb in drinking water from PND 1 through weaning (PND 21) 8 female pups per litter (number of litter unspecified) control pups, 8 pups for litter (number of litter unspecified) low level exposure pups, 8 pups per litter (number of litter unspecified) moderate level exposure pups	Long-term, dose-dependent decreases retinal Na/K ATPase activity in the female offspring (only female pups were used) (−11%; −26%) ($p < 0.05$).	PbB 18.8 or 59.4 µg/dL at weaning

Table AX5-4.1 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Fox et al. (1997)[†]	Rat/Long-Evans hooded, adult	0.02 or 0.2% Pb acetate in drinking water from PND 0–PND 21; 8 female pups per litter control pups; 8 pups per litter low level exposure; 8 pups per litter moderate level exposure (number of litters per dose unspecified)	Developmental and adult Pb exposure for 6 wks produced age and dose-dependent retinal degeneration such that rods and bipolar cells were selectively lost; at the ultrastructural level, all dying cells exhibit the classical morphological features of apoptotic cell death; decrease in the number of rods was correlated with the loss of rhodopsin content per eye confirming that rods were directly affected by Pb ($p < 0.05$); single-flash rod ERGs and cone ERGs obtained from Pb-exposed rats demonstrated that there were age- and dose-dependent decreases in the rod a-wave and b-wave sensitivity and maximum amplitudes without any effect on cones; in adult rats exposed to Pb for 3 wks, qualitatively similar ERG changes occurred in the absence of cell loss or decrease in rhodopsin content ($p < 0.05$); developmental and adult Pb exposure for three and 6 wks produced age- and dose-dependent decreases in retinal cGMP phosphodiesterase (PDE) activity resulting in increased CGMP levels ($p < 0.05$); retinas of developing and adult rats exposed to Pb exhibit qualitatively similar rod mediated ERG alterations as well as rod and bipolar apoptotic cell death ($p < 0.05$); similar biochemical mechanism such as the inhibition of rod and bipolar cell cGMP PDE, varying only in degree and duration, underlies both the Pb-induced ERG rod-mediated deficits and the rod and bipolar apoptotic cell death ($p < 0.05$).	PbB weanlings 19 ± 3 (low exposure) or 59 ± 8 µg/dL (moderate exposure), adult 7 ± 2 µg/dL (at PND 90)
Gandley et al. (1999)	Rat/Sprague-Dawley, adult	Male rats exposed to 25 or 250 ppm acetate Pb in drinking water for at least 35 days prior to breeding	Fertility was reduced in males with PbB in range 27–60 µg/dL, Pb was found to affect initial genomic expression in embryos fathered by male rats with blood Pb levels as low as 15–23 µg/dL; dose-dependant increases were seen in an unidentified set of proteins with a relative molecular weight of ~70 kDa.	PbB 27–60 µg/dL (fathers) 15–23 µg/dL (offspring)
Govoni et al. (1984)	Rat/Sprague-Dawley, adult	2.5 mg/mL Pb acetate in drinking water from GD 16 to postnatal week 8	Decreased sulpiride binding in the pituitary is consistent with the elevated serum PRL concentrations previously described in Pb-exposed rats; DOPAc concentrations were reduced by 21% in Pb-treated rats.	PbB 71 ± 8 µg/dL
Hamilton et al. (1994)	Rat/Sprague-Dawley, 25 days old	Pb acetate in drinking water at 250, 500 or 1000 ppm; 8 wks prior to mating through GD 21	Altered growth rates; reduced early postnatal growth; decreased fetal body weight.	PbB 40–100 µg/dL
Han et al. (2000)	Rat/Sprague-Dawley, 5 wks old	250 mg/mL Pb acetate in drinking water for 5 wks followed by 4 wks no exposure (mated at end of 4-wk no exposure period)	Pups born to Pb-exposed dams had significantly ($p < 0.0001$) lower mean birth weights and birth lengths.	PbB 10–70 µg/dL
Hanna et al. (1997)	Mouse/Swiss ICR preimplantation embryos	In vitro incubation of two- and four-cell embryos with 0.05–200 µM Pb acetate for 72 hr (time required for blastocyst formation)	Exposure of embryos to Pb was only toxic at 200 µM, which reduced cell proliferation and blastocyst formation.	PbB not reported

Table AX5-4.1 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Iavicoli et al. (2003)	Mouse/Swiss, adult	Pb acetate in food (0.02, 0.06, 0.11, 0.2, 2, 4, 20, 40 ppm) exposure began 1 day after mating until litter was 90 days old one litter of mice exposed to each dietary concentration	Low-level exposure (PbB 2–13 µg/dL) reduced red cell synthesis ($p < 0.05$); high-level exposure (PbB 0.6–2 µg/dL) enhanced red cell synthesis ($p < 0.05$).	PbB 0.6 to <2.0 µg/dL or >2.0–13 µg/dL
Iavicoli et al. (2004)	Mouse/Swiss, adult	Pb acetate in feed; exposure began 1 day after mating until litter was 90 days old	In females: accelerated time to puberty at PbB <3 µg/dL; delayed time to puberty at 3–13 µg/dL.	PbB 0.6 to <2.0 µg/dL or >2.0–13 µg/dL
Lögdberg et al. (1987)	Monkey/ Squirrel, adult	Pb acetate p.o. exposure of gravid squirrel monkeys from week 9 of gestation through PND 0	Increase in pre- and perinatal mortality among squirrel monkeys receiving Pb acetate p.o. during the last two-thirds of pregnancy (45% vs. 7–8% among controls); mean maternal PbB was 54 µg/dL (39–82 µg/dL); statistically significant reductions in mean birth weight were observed in Pb-exposed monkeys as compared to controls; effects occurred without clinical manifestation of toxic effects in the mothers.	PbB 54 µg/dL (39–82 µg/dL)
Lögdberg et al. (1998)	Monkey/ Squirrel, adult	Pb acetate (varying concentrations ≤0.1% in diet); maternal dosing from 5–8.5 wks pregnant to PND 1; 11 control monkeys, 3 low-Pb exposure group (PbB 24 µg/dL), 7 medium Pb group (PbB 40 µg/dL, 5 high-Pb group (PbB 56 µg/dL)	Dose-dependent reduction in placental weight ($p < 0.0007$); various pathological lesions were seen in the placentas ($n = 4$), including hemorrhages, hyalinization of the parenchyma with destruction of the villi and massive vacuolization of chorion epithelium; effects occurred without clinical manifestation of toxic effects in the mothers.	Mean maternal PbB 37 µg/dL (22–82 µg/dL) 24 (22–26) µg/dL (low dose) 40 (35–46) µg/dL (mid dose) 56 (43–82) µg/dL (high dose)
McGivern et al. (1991)[†]	Rat/Sprague-Dawley, adult	0.1% Pb acetate in drinking water from GD 14 to parturition	Male offspring of dams exhibited reduced sperm counts, altered male reproductive behavior, and enlarged prostates later in life; females exhibited delayed puberty, menstrual irregularities, and an absence of observable corpora lutea; males and females exhibited irregular release patterns of both FSH and LH later in life.	PbB 73 µg/dL
Nayak et al. (1989a)	Mouse/Swiss Webster, adult	Pb nitrate dissolved in NaCl solution, administered intravenously, via caudal vein at dose levels of 100, 150, 200 mg/kg; one time exposure on GD 9	Chemical analysis showed Pb was readily transferred across placenta; Pb caused moderate, statistically significant, increase in frequency of SCEs in maternal bone marrow cells and significant reduction in NORs at the 2 highest dose levels (150 and 200 mg/kg); animals showed several specific chromosomal aberrations, mostly deletions, in maternal bone, marrow, and fetal cells; aneupoidy was found to be frequently associated with the lowest dose levels of Pb nitrate (100 mg/kg); increased embryonic resorption and reduced placental weights.	PbB levels at birth in the exposure groups for these studies were >180 µg/dL
Piasek and Kostial (1991)	Rat/Wistar, 10 wks old	7500 ppm Pb acetate in drinking water for 9 wks	Decrease in litter size, pup survival, and birth weight; food consumption, body weight, and fertility were not altered in 20 wk exposure period.	Maternal PbB >300 µg/dL Offspring PbB >220 µg/dL

Table AX5-4.1 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Pinon-Lataillade et al. (1995)	Mouse/NMRI, adult	0–0.5% Pb acetate in drinking water exposed to Pb during gestation until post-GD 60	Pb exposure during gestation reduces litter size; reduced birth weight and growth rates.	PbB <4–132 µg/dL
Pillai and Gupta (2005)	Rat/Charles Foster, 200–220 g	Subcutaneous injection of 0.05 mg/kg-d Pb acetate for 5–7 days prior to mating through PND 21	Long term exposure of rats (premating, gestational, and lactational) to moderate levels of Pb acetate (s.c.) resulted in reduced activities of hepatic steroid (E2) metabolizing enzymes (17-ß-hydroxy steroid oxidoreductase and UDP glucuronyl transferase) and decreased hepatic CYP450 content.	PbB not reported
Ronis et al. (1996)†	Rat/Sprague-Dawley, 22, 55 days or plug-positive time-impregnated	0.6% Pb acetate in drinking water for various durations: PND 24–74 (pubertal exposure), PND 60–74 (post pubertal exposure); 11 males and females in pubertal exposure group (10 each in control pubertal group); 6 males and females post-pubertal exposure and control groups	Reduction in serum testosterone levels in male, not female; in female suppression of circulating E2 ($p < 0.05$) and LH ($p < 0.05$); reduction in male secondary sex organ weight ($p < 0.0005$); delayed vaginal opening and disrupted diestrous in females ($p < 0.005$); increased incidence of stillbirth (2% control vs. 19% Pb) ($p < 0.005$).	In utero PbB 250–300 µg/dL Pre-pubertal PbB 30–60 µg/dL Post-pubertal PbB 30–60 µg/dL PbBs in the dams and offspring in this experiment were >200 µg/dL.
Ronis et al. (1998a)†	Rat/Sprague-Dawley, various ages	0.6% Pb acetate in drinking water ad libitum for various durations: GD 5 to PND 1, GD 5 to weaning, PND 1 to weaning 3 control litters, 2 gestation exposure litters, 2 lactation exposure litters, 2 gestation and lactation exposure litters, 2 postnatal litters, 2 chronic litters (4 male and 4 female pups per litter)	Dose-dependent delay in sexual maturation (delayed vaginal opening) ($p < 0.0002$) following prenatal Pb exposure that continued until adulthood (85 days old); reduced birth weight ($p < 0.05$), more pronounced among male pups.	Group: pup PbB Naïve: ~6 µg/dL Control: <2 µg/dL Gest: ~10 µg/dL Lact: ~3 µg/dL Gest+Lact: ~13 µg/dL Postnatal: ~260 µg/dL Chronic: ~287 µg/dL
Ronis et al. (1998b)†	Rat/Sprague-Dawley, adult	Pb acetate in drinking water (0.05% to 0.45% w/v); dams exposed until weaning, exposure of pups which continued until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Prenatal Pb exposure that continues until adulthood (85 days old) delays sexual maturation in female pups in a dose-related manner ($p < 0.05$); birth weight reduced ($p < 0.05$), more pronounced among male pups; decreased growth rates ($p < 0.05$) in both sexes accompanied by decrease in plasma concentrations of IGF1 through puberty ($p < 0.05$) and a significant increase in pituitary and growth hormone during puberty ($p < 0.05$).	PbBs in the pups between the ages of 21 and 85 days were >100 µg/dL and reached up to 388 µg/dL.

Table AX5-4.1 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Ronis et al. (1998c)	Rat/Sprague-Dawley, adult	Pb acetate 0.05, 0.15, or 0.45% in drinking water beginning GD 5 continuing until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-responsive decrease in birth weight ($p < 0.05$), and crown-to-rump length ($p < 0.05$); dose-responsive delay in sexual maturity in male ($p < 0.05$) and female ($p < 0.05$); neonatal decrease in sex steroids ($p < 0.05$); pubertal decrease in testosterone (male) ($p < 0.05$) and E2 (female) ($p < 0.05$); decrease estrous cyclicity at high dose ($p < 0.05$).	Dams: 0, 48, 88, or 181 µg/dL Pups PND 1: <1, ~40, ~70, or >120 µg/dL Pups PND 21: <1, >50, >160, or ~237 µg/dL Pups PND 35: <1, ~22, >70, or >278 µg/dL Pups PND 55: <1, >68, >137, or ~380 µg/dL Pups PND 85: <1, >43, >122, or >214 µg/dL
Ronis et al. (2001)[†]	Rat/Sprague-Dawley, neonate, male (100 days) and female pup	Pb acetate in drinking water to 825 or 2475 ppm ad libitum from G'D 4 to GD 55 postpartum; 1 male and female pup/litter (5 litters per group) control group, 1 male and female pup/litter (5 litters per group) 825 ppm Pb acetate group, 1 male and female pup/litter (5 litters per group) 2475 ppm Pb acetate group	Dose-dependent decrease of the load of failure in male ($p < 0.05$); no difference in plasma levels of vitamin D metabolites; reduced somatic growth ($p < 0.05$), longitudinal bone growth ($p < 0.05$), and bone strength during the pubertal period ($p < 0.05$); sex steroid replacement did not restore skeletal parameters in Pb exposed rats; L-Dopa increased plasma IGF_1 concentrations, rates of bone growth, and bone strength measures in controls while having no effect in Pb exposed groups; DO gap x-ray density and proximal new endostreal bone formation were decreased in the distration gaps of the Pb-treated animals ($p < 0.01$); distraction initiated at 0.2 mm 30 to 60 days of age.	PbB at 825 ppm was 67–192 µg/dL PbB at 2475 ppm was 120–388 µg/dL
Sant'Ana et al. (2001)	Rat/Wistar, 90 days old	0.1 and 1% Pb in drinking water 7 days	1% Pb exposure reduced offspring body weight during treatment, no changes observed after 0.1% exposure; no altered offspring sexual maturation, higher Pb improved sexual behavior, while 0.1% reduced it; 0.1% Pb caused decrease in testis weight, an increase in seminal vesicle weight, and no changes in plasma testosterone levels, hypothalamic VMA levels were increased compared to control group; reduced birth weight and growth rates.	PbB 36.12 — 9.49 µg/dL or 13.08 ± 9.42 µg/dL
Singh et al. (1993b)	Rat/ITRC, albino (NOS), 6 wks old	250, 500, 1000, and 2000 ppm Pb nitrate in drinking water from GD 6 to GD 14	Significantly reduced litter size, reduced fetal weight, and a reduced crown-to-rump length, increased resorption and a higher blood-Pb uptake in those groups receiving 1000 and 2000 ppm Pb; these also had a higher placental uptake; however the level was the same in both groups; fetal Pb uptake remained the same whether or not 2000 ppm Pb was given to an iron-deficient or normal iron groups of mothers.	PbB not reported
Watson et al. (1997)	Rat/Sprague-Dawley, adult	Pb in drinking water at 34 ppm from weaning of mothers through gestation and weaning of offspring until birth; 6 pups control group, 6 pups experimental group	Reduced body weight ($p = 0.04$); parotid function was decreased by nearly 30% ($p = 0.30$); higher mean caries scores than the control pups ($p = 0.005$); pre- and perinatal Pb exposure had significantly increased susceptibility to dental caries ($p = 0.015$).	PbB 48 ± 13 µg/dL

Table AX5-4.1 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Wiebe et al. (1998)	Rats/Sprague-Dawley, adult	20 or 200 ppm Pb chloride in drinking water; prior to pregnancy, during pregnancy, lactation	Exposure to Pb did not affect tissue weights but did cause a significant decrease in gonadotropin-receptor binding in the prepubertal, pubertal, and adult females; conversion of progesterone to androstenedione and dihydrotestosterone was significantly decreased in 21-day old rats, in 150-day old females, the exposure to Pb resulted in significantly increased conversion to the 5-alpha-reduced steroids, normally high during puberty.	PbB 4.0 ± 1.4 to 6.6 ± 2.3 µg/dL

*Not including effects on the nervous or immune systems.

† Candidate key study.

cGMP, cyclic guanosine—3',5'-monophosphate; DO, distraction osteogenesis; DOPAc, 3,4-dihydroxyphenylacetic acid; E_2, estradiol; ERG, electroretinographic; FSH, follicle stimulating hormone; GD, gestational day; IGF_1, insulin-like growth factor 1; i.v., intravenous; kDA, kilodalton; LH, luteinizing hormone; NOS, not otherwise specified; PbB, blood Pb concentration; PDE, phosphodiesterase; PND, post-natal day; p.o., per os (oral administration); s.c., subcutaneous; SEM, standard error mean; UDP, uridine diphosphate; VMA, vanilmandelic acid

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Acharya et al. (2003)	Mouse/Swiss, 6–8 wks old	200 mg/kg Pb acetate through i.p. injection of Pb; one time injection	Testicular weight loss with constant increase in the incidence of abnormal sperm population; decrease in sperm count; testicular ascorbic acid also declined significantly; significant rise in LPP of tissue; LPP is indicative of oxidative stress in treated mice testes.	Not reported
Adhikari et al. (2000)	Rat/Druckrey, 28 days old	0.0, 0.4, 4.0, 40.0 µM Pb acetate in vitro for 24 and 48 hr	Germ cells progressively detached from Sertoli cell monolayer into medium in a concentration and duration dependent manner Viability of the detached cells showed a decrease with increase in time and concentration of Pb; leakage of LDH recorded at higher dose of 4.0 and 40.0 µM.	PbB not applicable–in vitro study
Adhikari et al. (2001)	Rat/Druckrey, 28 days old	5, 10, and 20 mg/kg Pb in distilled water by gavage for 2 wks	Induced significant numbers of germ cells to undergo apoptosis in the semiferous tubules of rats treated with highest dose; DNA fragmentation was not detected at any of the doses; level of Pb accumulation in testes increased in a dose-dependent manner.	PbB not reported
Alexaki et al. (1990)	Bulls/Holstein, 3–5 yrs old	In vitro fertilization 2.5 or 0.25 µg/mL	Sperm motility reduced significantly at 2.5 µg/mL; lower concentration had no effect on sperm motility.	PbB not applicable–in vitro study
Al-Hakkak et al. (1988)	Mouse/ BALB/c, weaning	0, 25, 50 mg Pb monoxide alloy/kg in chow for 35–70 days	Reduced number of spermatogenia and spermatocytes in the 50 mg group after 70 days; reduced number of implantations after mating (after 35 days exposure).	PbB not reported
Barratt et al. (1989)	Rat/Wistar, 70 days old	0, 0.3, 33, 330 mg Pb acetate/kg-d in drinking water, by gavage for 63 days	Increased number of abnormal post-testicular sperm in the highest exposure group; reduced number of spermatozoa at PbB >4.5 µg/dL.	PbB 2, 4.5, 7, 80 µg/dL PbBs >40 µg/dL
Bataineh et al. (1998)	Rat/Sprague-Dawley, adult	1000 ppm Pb acetate in drinking water for 12 wks	Fertility was reduced in males.	PbB not reported
Batra et al. (2001)	Rat/Portan, 8 wks old	10, 50, 200 mg/kg Pb acetate orally for 3 mo	Pb in testis and epididymis increased with dose; administration of zinc reduced Pb levels; dose related changes in activities of enzyme alkaline phosphatase and Na+-K+-ATPase, which decreased with increased dose of Pb; improvement in activities of enzymes was seen in groups given Pb and zinc; disorganization and disruption of spermatogenesis with accumulation of immature cells in lumen of tubule; highest dose of Pb resulted in arrest of spermatogenesis, and decrease in germ cell layer population; highest dose levels, damage of basement membrane, disorganization of epithelium and vacuolization cells; tubules were found almost empty, indicating arrest of spermatogenesis.	PbB not reported
Batra et al. (2004)	Rat/Portan, 8 wks old	10, 50, 200 mg/kg Pb acetate orally for 3 mo	LH and FSH concentrations were decreased at 200 mg/kg; decrease in fertility status at 200 mg/kg; decline in various cell populations at 200 mg/kg; 50 mg/kg group hormone levels, cell numbers, and fertility status were found close to normal.	PbB not reported
Bizarro et al. (2003)	Mouse/CD-1, adult	0.01 M Pb acetate twice a week for 4 wks	Dose-time relationship was found; ROS role.	PbB not reported
Boscolo et al. (1988)	Rat/Sprague-Dawley, weanling	60 mg Pb acetate/mL in drinking water for 18 mo	Increased vacuolization in Sertoli cells; no other ultrastructural modifications; no impairment of spermatogenesis.	PbB 4–17 µg/dL

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Chowdhuri et al. (2001)	Mouse/ BALB/c, 3 mo old	0.0, 0.2, 0.5, 1.0, 2.0 µg/mL Pb acetate in culture medium for 2 hr (superovulated ova and sperm)	Significant dose dependent decrease in the number of sperm attaching to the ova in both exposed groups; decrease in the incorporation of radio-labeled thymdine, uridine, and methionine.	PbB not applicable–in vitro study
Chowdhury et al. (1984)	Rat/Albino, (NOS), adult	Dietary concentrations of 0.25, 0.50, or 1.0 g/L Pb acetate for 60 days	Testicular atrophy along with cellular degeneration was conspicuous at 1 g/L; high cholesterol concentration and significantly low ascorbic acid concentration were found in the testes at 1 g/L; lowest dose (0.25 g/L) had no significant morphological and biochemical alterations, whereas as 0.5 g/L resulted in partial inhibition of spermatogenesis.	PbB 54–143 µg/dL
Chowdhury et al. (1986)	Rat/NOS, adult	0, 1, 2, 4, 6 mg Pb acetate/kg-d i.p. for 30 days	Dose-related decrease of testis weight; at 187 µg/dL: degenerative changes in testicular tissues; at 325 µg/dL: degenerative changes and inquiry of spermatogenetic cells; edematous dissociation in interstitial tissue.	PbB 20, 62, 87, 187, or 325 µg/dL
Chowdhury et al. (1987)	Rat/Charles Foster, 150 ± 5 g	0, 1, 2, 4, 6 mg Pb acetate/kg-d/i.p. for 30 days	Dose related decrease of testis weight at 56 µg of spermatoids; at 91 µg/dL: inhibition of post-meiotic spermatogenic cell; at 196 µg/dL: decreased spermatogenic cell count (6), detachment of germinal call layers; at 332 µg/dL: Decreased spermatogenic cell count, degenerative changes, Interstitial edema, and atrophy of Leydig cells.	PbB 56–3332 µg/dL
Coffigny et al. (1994)[†]	Rat/Sprague-Dawley, adult	Inhalation exposure to 5 mg/m^3 Pb oxide daily for 13 days during gestation (GD 2, 3, 6–10, 13–17, 20)	Adult male offspring exhibit no change in sperm parameters or sex hormones T, FSH, and LH (because of duration or timing).	PbB 71.1 µg/dL (dam) PbB 83.2 µg/dL (fetal)
Corpas et al. (1995)	Rat/Wistar, adult	300 mg/L Pb acetate via drinking water beginning GD 1 through 5 days postnatal or throughout gestation and early lactation	Testicular weight and gross testicular structure were not altered; seminiferous tubule diameter and the number of prospermatogonia were reduced; total DNA, RNA, and protein content of the testes in treated rats was significantly reduced, DNA:RNA ratio remained unaltered.	PbB 14 µg/dL
Corpas et al. (2002a)	Rat/Wistar, adult	300 mg/L acetate Pb in drinking water beginning at mating until PND 12 and 21	Neither abnormalities in the liver structure nor depositions of Pb, toxicant produced biochemical alterations; pups exhibited decrease in hemoglobin, iron and alkaline, and acid phosphatase levels and an increase in Pb content; protein, DNA, and lipid total amounts were reduced, and hepatic glycogen content was diminished at 12 and 21 PN, with a higher dose of glucose in blood; decrease in alkaline phosphatase in liver of pups at day 21 PN, but acid phosphatase was unaltered.	PbB 22 µg/dL
Corpas et al. (2002b)	Rat/Wistar, adult	300 mg/L acetate Pb in drinking water beginning at mating until PND 12 and 21	Neither abnormalities in the liver structure nor depositions of Pb, toxicant produced biochemical alterations; pups exhibited decrease in hemoglobin, iron and alkaline, and acid phosphatase levels and an increase in Pb content; protein, DNA, and lipid total amounts were reduced, and hepatic glycogen content was diminished at 12 and 21 PN, with a higher dose of glucose in blood; decrease in alkaline phosphatase in liver of pups at day 21 PN, but acid phosphatase was unaltered.	PbB 22 µg/dL

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Cory-Slechta et al. (2004)†	Rat/Long-Evans, adult	Pb acetate in drinking water beginning 2 mo before breeding until the end of lactation	Observed potential effects of Pb and stress in female; Pb alone (in male) and Pb plus stress (in females) permanently elevated corticosterene levels in offspring.	PbB 30–40 µg/dL
Foote (1999)	Rabbit/Dutch-belted, adult	0, 0.005, 0.01, and 0.025 mM PbCl2 in vitro; one time dose	Six out of 22 males tested showed appreciable spontaneous hyperactivation, Pb did not affect hyperactivation, or associated capacitation.	PbB not applicable–in vitro study
Foster et al. (1993)	Monkey/ Cynomolgus, adult	0–1500 µg Pb acetate/kg-d in gelatin capsules p.o. for various durations: 9 control monkeys, 4 monkeys in lifetime group (birth to 9 yrs), 4 in infancy group (first 400 days of life), 4 in post-infancy exposure (from 300 days to 9 yrs)	Suppressed LH response to GnRH stimulation in the lifetime group ($p = 0.0370$); Sertoli cell function (reduction in the inhibin to FSH ratio) ($p = 0.0286$) in lifetime and post-infancy groups.	Lifetime group 3–26 µg/dL at 4–5 yrs; infancy group 5–36 µg/dL at 100–300 days, 3–3 µg/dL at 4–5 yrs; post-infancy group 20–35 µg/dL
Foster et al. (1996a)	Monkey/ Cynomolgus, adult	0–1500 µg Pb acetate/kg-d in gelatin capsules p.o. from birth until 9 yrs of age: 8 control monkeys, 4 monkeys in low group (6-20 µg/dL), 7 monkeys in high group (22–148 µg/dL)	Mean PbB of 56 µg/dL showed no significant alterations in parameters of semen quality (count, viability, motility, or morphology).	PbB 10 ± 3 or 56 ± 49 µg/dL
Foster et al. (1998)	Monkey/ Cynomolgus, adult	0–1500 µg Pb acetate/kg-d in gelatin capsules p.o. for various durations: birth to 10 yrs (lifetime); PND 300 to 10 yrs (post-infancy); birth to 300 days (infancy); 3 control monkeys, 4 lifetime, 4 infancy, 5 post-infancy	Circulating concentrations of FSH, LH, and testosterone were not altered by treatment; semen characteristics (count, motility, morphology) were not affected by treatment possibly because not all Sertoli cells were injured; degeneration of seminiferous epithelium in infancy and lifetime groups (no difference in severity between these groups); ultrastructural alterations in seminal vesicles, most prominent in infancy and post-infancy groups.	PbB ~35 µg/dL
Gandley et al. (1999)	Rat/Sprague-Dawley, adult	Male rats received Pb acetate 25 or 250 ppm in drinking water for 35 days prior to mating	High dose reduced fertility; low dose altered genomic expression in offspring.	PbB 15–23 µg/dL or 27–60 µg/dL
Gorbel et al. (2002)	Rat/(NOS), 90 days old	3 mg (P1) or 6 mg (P2) Pb acetate in drinking water for 15, 30, 45, 60, or 90 days	Male rats, absolute and relative weights of testis, epididymis, prostate and seminal vesicles were found to significantly decrease at day 15 in P2 group and at day 45 in P1 group, at day 60 these absolute values and relative weights returned to control values; at day 15 arrest of cell germ maturation, changes in the Sertoli cells, and presence of apoptotic cells were observed; serum testosterone level was found to be lowered at day 15 in both P1 and P2, and peaked at day 60, then returned to normal values.	PbB not reported

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Graca et al. (2004)	Mouse/CD-1, 2 mo old	Subcutaneous injection of 74 mg/kg-d of Pb chloride for 1 to 3 days	Reversible changes in sperm (count) and ultrastructural changes in testes (reduced diameter of seminiferous tubules).	PbB not reported
Hsu et al. (1997)	Rat/Sprague-Dawley, 7 wks old	10 mg/kg Pb acetate through i.p. injection to males for 6 or 9 wks	Six-week group had unchanged epididymal sperm counts, percent of motile sperms, and motile epididymal sperm counts compared with control group; 9-wk group showed statistically lower epididymal sperm counts, and lower motile epididymal sperm counts; good correlation between blood Pb and sperm Pb; significantly higher counts of chemiluminescence, they were positively associated with sperm Pb level; epididymal sperm counts, motility, and motile epididymal sperm counts were negatively associated with sperm chemiluminescence; SOPR were positively associated with epididymal sperm counts, motility and motile epididymal sperm counts, sperm chemiluminescence was negatively associated with SOPR.	PbB after 6 wks 32 µg/dL, after 9 wks 48 ± 4.3 µg/dL
Hsu et al. (1998a)	Rat/Sprague-Dawley, 100–120 g	20 or 50 mg Pb acetate via i.p. route weekly to males for 6 wks	Serum testosterone levels were reduced; percentage of capacitation and the chemiluminescence were significantly increased in fresh cauda epididymal spermatozoa; serum testosterone levels were negatively associated with the percentage of acrosome-reacted spermatozoa; sperm chemiluminescence was positively correlated with the percentage of both capacitated and acrosome-reacted spermatozoa; SOPR was negatively associated with the percentage of both capacitated and acrosome-reacted spermatozoa.	PbBs >40 µg/dL
Hsu et al. (1998b)	Rat/Sprague-Dawley, 7 wks old	10 mg/kg Pb acetate weekly via i.p. injection to males for 6 wks	Intake of VE and/or VC in Pb exposed rats prevented the Pb associated sperm ROS generation, increased the epididymal sperm motility, enhanced the capacity of sperm to penetrate eggs harvested from unexposed female rats in vitro; protective effect of VE and VC not associated with reduced blood or sperm Pb levels.	PbB 30.1 ± 3.4 to 36.1 ± 4.6 PbBs >40 µg/dL
Huang et al. (2002)	Mouse MA-10 cells	10^{-8} to 10^{-5} M Pb incubated for 3 hr	Higher decreases in human chorionic gonadotropin (hCG)-stimulated progesterone production, expressions of StAR protein, and the activity of 3ß-HSD compared to 2 hr; no affect on P450scc enzyme activity.	PbB not applicable–in vitro study
Johansson (1989)	Mouse, 9 wks old	0–1 g Pb chloride/L in drinking water for 112 days	No effects on frequency of motile spermatozoa, nor on swimming speed; decreased fertilizing capacity of the spermatozoa by in vitro fertilization; premature acrosome reaction .	PbB 0.5–40 µg/dL
Johansson and Pellicciari (1988)	Mouse/NMRI, 9 wks old	1 g/L Pb chloride in drinking water for 16 wks	Decreased uptake of PI was found in spermatozoa from the vas deferens of the Pb-exposed mice; after thermal denaturation of the DNA, the spermatozoa showed a higher uptake of PI in comparison to those of the controls; after reductive cleavage of S-S bonds with DTT and staining with a thiol-specific reagent significantly fewer reactive disulfide bonds were also observed in the spermatozoa; significant delay in the capacity for NCD was noted.	PbB 42 ± 1.6 µg/dL
Johansson and Wide (1986)	Mouse/NMRI, 9 wks old	0–1 g/L Pb chloride in drinking water for 84 days	No effects on sperm count; no effects on serum testosterone; reduced number of implantations after mating.	PbB <0.5–32 µg/dL Mean tissue Pb content difference between Pb treated and controls: testicular 11 µg/g (epididymal 67 µg/g) PbB <0.5 µg/100 mL

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Johansson et al. (1987)	Mouse/NMRI, 9–10 wks old	1 g/L Pb chloride in drinking water for 16 wks	Spermatozoa had significantly lower ability to fertilize mouse eggs; morphologically abnormal embryos were found.	PbB not reported
Kempinas et al. (1988)	Rat/Wistar, adult	0.5 g/L and 1.0 g/L Pb acetate in drinking water for 90 days	PbB exhibited a significant increase in both groups; decrease in hematocrit and hemoglobin, together with a rise in glucose levels; no signs of lesion were detected upon histological examination of testes, caput, and cauda epididymidis; an increase in ductal diameter, and a decrease in epithelial height were observed in the cauda epididymidis; concentration of spermatozoa stored in the caudal region of the epididymis exhibited a significant increase in Pb-treated animals.	PbB 65–103 µg/dL
Kempinas et al. (1990)	Rat/NOS, pubertal	(1.0 g/L) Pb acetate in drinking water in addition to i.v. injections of Pb acetate (0.1 mg/100 g bw) every 10 days, 20 days	Basal levels of testosterone were higher both in the plasma and in the testes of acutely intoxicated animals; levels of LH were not affected in either group, nor was the LHRH content of the median eminence; density of LH/hCG binding sites in testicular homogenates was reduced by saturnism in both groups, apparent affinity constant of the hormone-receptor, complex significantly increased.	PbB ~40 µg/dL
		(1.0 g/L) Pb acetate in drinking water in addition to i.v. injections of Pb acetate (0.1 mg/100 g bw) every 15 days, 9 mo		
Kempinas et al. (1994)	Rat/Wistar, 50 days old	0–1 g Pb acetate/L in drinking water + 0.1 mg/kg i.v. every 10 days for 20 days	Increased plasma and testicular testosterone concentrations; no effects on testicular weight; reduced weight of prostate; increased weight of seminal vesicle and seminal secretions.	PbB 10–41 µg/dL
		0–1 g Pb acetate/L in drinking water + 0.1 µg/kg i.v. every 15 days for 270 days		PbB 8.5–40 µg/dL
Klein et al. (1994)	Rat/Sprague-Dawley, 100 days old	0.1, 0.3, or 0.6% Pb acetate in distilled water for 21 days	2–3-fold enhancement of mRNA levels of GnRH and the tropic hormone LH; 3-fold enhancement of intracellular stores of LH; mRNA levels of LH and GnRH and pituitary levels of stored LH are proportional to blood levels of Pb.	PbB 42–102 µg/dL
Liu et al. (2001)	Mouse, MA-10 cells	10^{-8} to 10^{-5} Pb acetate in vitro for 2 hr	Significantly inhibited hCG- and dbcAMP-stimulated progesterone production in MA-10 cells; steroid production stimulated by hCG or dbcAMP were reduced by Pb; expression of StAR protein and the activities of P450 side-chain cleavage (P450) and 3ß-HSD enzymes detected; expression of StAR protein stimulated by bdcAMP was suppressed by Pb at about 50%; progesterone productions treated with 22R-hydroxycholesterol or pregnenolone were reduced 30–40% in Pb treated MA-10 cells.	PbB not applicable–in vitro study
Liu et al. (2003)	Mouse, MA-10 cells	10^{-8} to 10^{-5} Pb acetate in vitro for 6 hr incubated	Pb significantly inhibited hCG- and dbcAMP-stimulated progesterone production from 20 to 35% in MA-10 cells at 6 hr; Pb suppressed the expression of steriodogenesis acute regulatory (StAR) protein from 30 to 55%; activities P450 side-chain cleavage (P450scc) enzyme and 3ß-HSD were reduced by Pb from 15 to 25%.	PbB not applicable–in vitro study

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Marchlewicz et al. (1993)	Rat/Wistar, 90 days old	0–1% Pb acetate in drinking water for 270 days	No histological or weight changes in testicle or epididymis; fever spermatozoa in all zones of the epididymis.	PbB not reported
McGivern et al. (1991)[†]	Rat/Sprague-Dawley, adult	0.1% Pb acetate in drinking water from GD 14 to parturition: 8 control litters; 6 Pb acetate litters (5 males per litter)	Decreased sperm count (21% at 70 days and 24% at 165 days; $p < 0.05$); reduced male behavior ($p < 0.05$); enlarged prostate (25% increase in weight; $p < 0.07$); irregular release patterns of both FSH and LH ($p < 0.05$).	Control PbB <5 µg/dL at birth Maternal PbB 73 µg/dL at birth Pup PbB 64 µg/dL at birth
McMurry et al. (1995)	Rat/Cotton, adult	0, 100, or 1000 ppm Pb in drinking water for 7 or 13 wks	Immune function was sensitive to Pb exposure; spleen mass was reduced in cotton rats receiving 100 ppm Pb; total leukocytes, lymphocytes, neutrophils, eosinophils, total splenocyte yield, packed cell volume, hemoglobin, and mean corpuscular hemoglobin were sensitive to Pb exposure; reduced mass of liver, seminal vesicles, and epididymis in males after 7 wk exposure.	PbB not reported
Mishra and Acharya (2004)	Mouse/Swiss, 9–10 wks old	10 mg/kg Pb acetate in drinking water for 5 to 8 wks	Stimulates lipid peroxidation in the testicular tissue, associated with increased generation of noxious ROS; reduced sperm count, increased sperm abnormality	PbB not reported
Moorman et al. (1998)	Rabbit/NOS, adult	3.85 mg/kg Pb acetate subcutaneous injection for 15 wks	Increased blood levels associated with adverse changes in the sperm count, ejaculate volume, percent motile sperm, swimming velocities, and morphology; hormonal responses were minimal; dose-dependent inhibition of sperm formation; semen quality, threshold estimates ranged from 16 to 24 µg/dL.	PbB 0, 20, 40, 50, 70, 80, 90, and 110 µg/dL
Murthy et al. (1991)	Rat/ITRC, (NOS), weanling	0–250 ppm Pb acetate in drinking water for 70 days	At 20 µg/dL no impairment of spermatogenesis; vacuolization of Sertoli cell cytoplasm and increase in number and size of lysosomes.	PbB 20.34 ± 1.79 µg/dL
Murthy et al. (1995)	Rat/Druckrey, adult	Pb 5 mg/kg i.p. Pb acetate in drinking water for 16 days	Swelling of nuclei and acrosomes round spermatids; in Sertoli cells, nuclei appeared fragmented, whereas the cytoplasm exhibited a vacuolated appearance and a few structures delimitated by a double membrane that contains microtubules arranged in parallel and cross-striated fin fibrils, cell tight junction remain intact; no significant change in epididymal sperm motility and counts, testicular blood levels were found to be elevated after Pb exposure.	PbB 7.39 µg/dL
Nathan et al. (1992)	Rat/Sprague-Dawley, adult	0, 0.05, 0.1, 0.5, or 1% Pb acetate in drinking water for 70 days	No effects on spermatogenesis in all groups; at 124 µg/dL: decreased seminal vesicle weight; decreased serum testosterone in the 0.5% group at 10 wks; no effects in the other exposure categories; no effects on serum FSH, LH, nor pituitary LH content.	PbB 2.3, 40, 44, 80, or 124 µg/dL
Pace et al. (2005)	Mouse/BALB/c, adult	0.1 ppm Pb acetate in drinking water (lactational exposure as neonates and drinking water from PND 21 to PND 42)	Reduction in fertility when mated with unexposed females; no change in sperm count; increase in number of apoptotic cells in testes.	Neonatal PbB 59.5 µg/dL Post PND 21 PbB 20.3 µg/dL
Piasecka et al. (1995)	Rat/Wistar, adult	1% aqueous solution of Pb acetate for 9 mo	Pb-loaded (electron dense) inclusions were found in the cytoplasm of the epididymal principal cells, especially in the caput of epididymis, also present, but smaller, in smooth muscle cells; inclusions were located in the vacuoles, rarely without any surrounding membrane; similar Pb-containing structures were found in the epididymal lumen.	PbB not reported

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Piasek and Kostial (1987)	Rat/Albino, (NOS), adult	1500, 3500, and 5500 ppm of Pb acetate in drinking water for 18 wks	No overt signs of general toxicity in adult female rats, only at the end of the exposure period the mean body weight of males exposed to two higher levels was slightly lower; no effect of Pb exposure on male fertility either after first or after second mating; values in the pups did not differ from control group.	PbB not reported
Pinon-Lataillade et al. (1993)	Rat/Sprague-Dawley, 90 days old	0–0.3% Pb acetate in drinking water for 70 days 5 mg/m^2 Pb oxide in aerosol for 6 hr/day, 5 days/wk, 90 days	Decreased weight of seminal vesicles in inhalation study; no effects on spermatogenesis (epididymal sperm count, spermatozoal motility or morphology) or plasma testosterone, LH, and FSH; no effects on fertility; decrease in epididymal sperm count of progeny of sires of the inhalation group, however without effect on their fertility.	PbB 58 ± 1.7 µg/dL (oral) PbB 51.1 ± 1.8 µg/dL (inhalation)
Pinon-Lataillade et al. (1995)	Mouse/NMRI, adult	0–0.5% Pb acetate in drinking water, day 1 of gestation until 60 days of age	No effects on testicular histology, nor on number and morphology of epididymal spermatozoa; no effects on plasma FSH, LH, and testosterone, nor on testicular testosterone; decreased weight of testes, epididymis, seminal vesicles, and ventral prostate; no effects on fertility.	PbB <4–132 µg/dL
Rodamilans et al. (1988)	Mouse/BALB/c, 63 days old	0–366 mg Pb acetate/L in drinking water for 30, 60, 90, 120, 150, 180 days	Reduction of intratesticular testosterone concentrations after 30 days; reduction of and renostenedione concentrations after 150 days; no changes in intratesticular progesterone and hydroxy-progesterone.	PbB 48–67 µg/dL
Ronis et al. (1996)†	Rat/Sprague-Dawley, adult	0.6% Pb acetate in drinking water for various durations: PND 24–74 (pubertal exposure); PND 60–74 (post pubertal exposure); 11 males and females in pubertal exposure group (10 each in control pubertal group); 6 males and females post-pubertal exposure and control groups	PbB > 250 µg/dL reduced circulating testosterone levels in male rats 40–50% ($p < 0.05$); reduction in male secondary sex organ weight ($p < 0.005$); delayed vaginal opening ($p < 0.0001$); disrupted estrous cycle in females (50% of rats); increased incidence of stillbirth (2% control vs. 19% Pb) ($p < 0.005$).	Pubertal PbB 30–60 µg/dL Post pubertal PbB 30–60 µg/dL Mean PbBs in male rats 30–60 µg/dL, respectively
Ronis et al. (1998a)	Rat/Sprague-Dawley, adult	0.6% Pb acetate in drinking water ad libitum for various durations as follows: GD 5 to PND 1; GD 5 to weaning; PND 1 to weaning; 3 control litters, 2 gestation exposure litters, 2 lactation exposure litters, 2 gestation and lactation exposure litters, 2 postnatal exposure litters, 2 chronic exposure litters; 4 male and 4 female pups per litter.	Suppression of adult mean serum testosterone levels was only observed in male pups exposed to Pb continuously from GD 5 throughout life ($p < 0.05$).	Group: male PbB Naïve: 5.5 ± 2.0 µg/dL Control: 1.9 ± 0.2 µg/dL Gest: 9.1 ± 0.7 µg/dL Lact: 3.3 ± 0.4 µg/dL Gest+Lact: 16.1 ± 2.3 µg/dL Postnatal: 226.0 ± 29 µg/dL Chronic: 316.0 ± 53 µg/dL

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Ronis et al. (1998b)	Rat/Sprague-Dawley, adult	Pb acetate in drinking water (0.05% to 0.45% w/v); dams exposed until weaning, exposure of pups which continued until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-response reduction in birth weight ($p < 0.05$), more pronounced in male pups; decreased growth rates in both sexes ($p < 0.05$) were accompanied by a statistically significant decrease in plasma concentrations of IGF1 through puberty PND 35 and 55 ($p < 0.05$); increase in pituitary growth hormone during puberty ($p < 0.05$).	Mean PbB in offspring at 0.05% (w/v) 49 ± 6 µg/dL Mean PbB in offspring at 0.15% (w/v) 126 ± 16 µg/dL Mean PbB in offspring at 0.45% (w/v) 263 ± 28 µg/dL
Ronis et al. (1998c)[†]	Rat/Sprague-Dawley, adult	Pb acetate 0.05, 0.15, or 0.45% in drinking water beginning GD 5 continuing until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-responsive decrease in birth weight ($p < 0.05$); dose-responsive decrease in crown-to-rump length ($p < 0.05$); dose-dependent delay in sexual maturity ($p < 0.05$); decrease in prostate weight ($p < 0.05$); decrease in plasma concentration of testosterone during puberty ($p < 0.05$); decrease in plasma LH ($p < 0.05$); elevated pituitary LH content ($p < 0.05$); decrease in plasma testosterone/LH ratio at high dose ($p < 0.05$).	Dams: 0, 48, 88, or 181 µg/dL Pups PND 1: <1, 40, 83, or 120 µg/dL Pups PND 21: <1, 46, 196, or 236 µg/dL Pups PND 35: <1, 20, 70, or 278 µg/dL Pups PND 55: <1, 68, 137, or 379 µg/dL Pups PND 85: <1, 59, 129, or 214 µg/dL
Sant'Ana et al. (2001)	Rat/Wistar, 90 days old	0.1 and 1% Pb acetate in drinking water for 7 days	0.1% Pb caused decrease in testis weight, an increase in seminal vesicle weight and no changes in plasma testosterone levels, hypothalamic VMA levels were increased compared to control group.	PbB 36.12 ± 9.49 µg/dL and 13.08 ± 9.42 µg/dL
Saxena et al. (1984)	Rat/ITRC, albino (NOS), 12 wks old	8 mg/kg Pb acetate i.p. for 15 days	Histoenzymic and histological alterations in the testes; degeneration of seminiferous tubules; patchy areas showing marked loss in the activity of succinic dehydrogenase and adenosine triphosphatase, whereas alkaline phosphatase activity showed only slight inhibition.	PbB not reported
Saxena et al. (1986)	Rat/ITRC, albino (NOS), 40–50 g	5, 8, or 12 mg Pb+2/kg Pb acetate i.p. for 15 days	Increasing dose of Pb resulted in significant loss of body weight, as well as testicular weight in groups 3 and 4; cholesterol in the testis of rats markedly decreased at all given doses of Pb and was statistically significant in groups 3 and 4; in phospholipid contents, the significant decrease was observed only at two highest doses, while at the lowest dose the decrease was not significant; activity of ATPase remained unaffected at all three doses of Pb; no significant increase in Pb content in the testis was noticed at lower dose levels as compared to control; however, significant increase was found in groups 3 and 4 which was dose dependent.	PbB not reported
Saxena et al. (1987)	Rat/Wistar, 40–50 g	8 mg Pb2/kg-d Pb acetate i.p. for 100 days (from PND 21 to PND 120)	Disturbed spermatogenesis; Leydig cell degeneration; altered enzyme activity (G6PDH).	PbB not reported

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Saxena et al. (1990)	ITRC albino, (NOS), adult	8 mg/kg/d Pb acetate for 45 days	Alterations in SDH, G6PDH activity, cholesterol, and ascorbic acid contents and reduced sperm counts associated with marked pathological changes in the testis, after combined treatment with Pb and immobilization stress in comparison to either alone.	PbB >200 µg/dL
Singh et al. (1993a)	Monkey/ Cynomolgus, birth Birth: 300 days:	0–1500 µg Pb acetate/kg-d in gelatin capsules for various durations: 3 control monkeys, 4 monkeys in infancy group (exposure first 400 days), 5 in post-infancy group (exposure 300 days to 9 yrs of age), 4 in lifetime group (exposure from birth until 9 yrs)	Degeneration of seminiferous epithelium in all exposed groups (frequency not specified); ultrastructural alterations in seminal vesicles, most prominent in infancy and post-infancy groups (frequency not specified).	Chronic PbB <40–50 µg/dL
Sokol (1987)	Rat/Wistar, 52 days old	0–0.3% Pb acetate in drinking water for 30 days	Hyper-responsiveness to stimulation with both GnRH and LH (10); blunted response to naloxone stimulation (10).	PbB 30 ± 5 µg/dL
Sokol (1989)	Rat/Wistar, 27 days old	0–0.6% Pb acetate in drinking water for 30 days + 30 days recovery	Suppressed intratesticular sperm counts, sperm production rate, and serum testosterone in both Pb treated groups (10–10); sperm parameters and serum testosterone normalized at the end of the recovery period in the pre-pubertal animals (27 days at start) (10) but not in the pubertal animals (52 days at start) (5).	<3–43 µg/dL (<4–18 µg/dL after recovery period)
	52 days old	0–0.6% Pb acetate in drinking water for 30 days + 30 days recovery		B1 <3–43 µg/dL (<4–18 µg/dL after recovery period)
Sokol (1990)	Rat/Wistar, 52 days old	0–0.6% Pb acetate in drinking water for 7, 14, 30, 60 days	Decreased sperm concentration, sperm production rate and suppressed serum testosterone concentrations after 14 days of exposure; not dose related (NS).	Controls: <8 µg/dL at any time exposed: 42, 60, 58, 75 µg/dL after 7, 14, 30, and 60 days, respectively
Sokol and Berman (1991)	Rat/Wistar, NOS	0, 0.1, or 0.3% Pb acetate in drinking water for 30 days beginning at 42, 52, or 70 days old; 8–11 control rats for each age, 8–11 rats for each age in 0.1% group, 8–11 rats for each age in 0.3% group	Dose-related suppression of spermatogenesis (decreased sperm count and sperm production rate) in the exposed rats of the two highest age groups ($p < 0.05$); dose-related suppression of serum testosterone in 52-day old rats ($p = 0.04$) and in 70-day old rats ($p < 0.003$).	0% All <7 µg/dL 0.1% 42 days 25 µg/dL 0.1% 52 days 35 µg/dL 0.1% 70 days 37 µg/dL 0.3% 42 days 36 µg/dL 0.3% 52 days 60 µg/dL 0.3% 70 days 42 µg/dL

Table AX5-4.2 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Sokol et al. (1985)†	Rat/Wistar, 52 days old	0.1 or 0.3% Pb acetate in drinking water for 30 days	Negative correlations between PbB levels and serum and intratesticular testosterone values; dose-dependent reduction in intratesticular sperm count; FSH values were suppressed; no change in LH; decrease in ventral prostatic weight; no difference in testicular or seminal vesicle weights.	PbB 34 ± 3 µg/dL or PbB 60 ± 4 µg/dL
Sokol et al. (1994)	Rat/Sprague-Dawley, 100 days old	0.3% Pb acetate in drinking water for 14, 30, or 60 days	Pb exposed fertilized fewer eggs; increased duration of exposure did not result in more significant percentage of eggs not fertilized; no ultrastructural changes were noted in the spermatozoa of animals; no difference in histogram patterns of testicular cells.	PbB ~40 µg/dL
Sokol et al. (2002)	Rat/Sprague-Dawley, adult	Pb acetate in water for 1 wk	Dose-related increase in gonadotropin-releasing hormone (GnRH) mRNA; no effect on the serum concentrations of hypothalamic gonadotropin-releasing hormone (GnRH) or LH.	PbB 12–28 µg/dL
Thoreux-Manlay et al. (1995a)	Rat/Sprague-Dawley, 97 days old	0–8 mg Pb acetate/kg i.p. for 5 days/wk, 35 days	No effects on spermatogenesis; decreased plasma and testicular testosterone by 80%; decreased plasma LH by 32%, indications for impaired Leydig cell function, no effects on fertility.	PbB not reported
Thoreux-Manlay et al. (1995b)	Rat/Sprague-Dawley, adult	8 mg/kg-d Pb for 5 days/wk, 35 days	Germ cells and Sertoli cells were not major target of Pb, accessory sex glands were target; epididymal function was unchanged; plasma and testicular testosterone dropped about 80%, plasma LH only dropped 32%.	PbB 1700 µg/dL
Wadi and Ahmad (1999)	Mouse/CF-1, adult	0.25 and 0.5% Pb acetate in drinking water for 6 wks	Low dose significantly reduced number of sperm within epididymis; high dose reduced both the sperm count and percentage of motile sperm and increased the percentage of abnormal sperm within the epididymis; no significant effect on testis weight, high dose significantly decreased the epididymis and seminal vesicles weights as well as overall body weight gain; LH, FSH, and testosterone were not affected.	PbB not reported
Wenda-Rózewicka et al. (1996)	Rat/Wistar, adult	1% aqueous solution of Pb acetate for 9 mo	Electron microscopic studies did not reveal any ultrastructural changes in the semiferous epithelium or in Sertoli cells; macrophages of testicular interstitial tissue contained (electron dense) Pb-loaded inclusions, usually located inside phagolisosome-like vacuoles; x-ray micro-analysis revealed that the inclusions contained Pb.	PbB not reported
Yu et al. (1996)	Rat/Sprague-Dawley, neonates	Neonatal and lactational exposure to 0.3% Pb acetate in drinking water beginning PND 1 to PND 21	Neonatal exposure to Pb decreased cold-water swimming endurance (a standard test for stress endurance) and delayed onset of puberty in males and female offspring, which was exacerbated by swimming stress.	PbB 70 µg/dL

*Not including effects on the nervous or immune systems.

† Candidate key study.

3ß-HSD, 3ß-hydroxysteriod dehydrogenase; dbcAMP, dibutyryl cyclic adenosine-3',5'-monophosphate; DTT, dithiothreitol; FSH, follicle stimulating hormone; G6PDH, glucose-6-phosphate dehydrogenase; GD, gestational day; GnRH, gonadotropin releasing hormone; hCG, human chorionic gonadotropin; IGF_1, insulin-like growth factor 1; i.p., intraperitoneal; LDH, lactate dehydrogenase; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; LPP, lipid peroxidation potential; NCD, nuclear chromatin decondensation rate; NOS, not otherwise specified; PbB, blood lead concentration; PND, post-natal day; p.o., per os (oral administration); ROS, reactive oxygen species; SDH, succinic acid dehydrogenase; SOPR, sperm-oocyte penetration rate; StAR, steroidogenic acute regulatory protein; VC, vitamin C; VE, vitamin E; VMA, vanilmandelic acid

Table AX5-4.3. Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Burright et al. (1989)	Mouse/HET, neonates	0.5% Pb acetate solution via milk, or drinking water chronic beginning PND 1	Plasma prolactin levels implied that Pb exposure alone decreased circulating prolactin in primiparous; low prolactin levels in non-behaviorally tested females suggests that dietary Pb alone may alter plasma-hormone in these lactating HET dams; pattern of plasma prolactin appear to be inconsistent with the observation that Pb exposure decreases dopamine; prolactin levels of Pb exposed dams were very low.	PbB ~100 µg/dL
Coffigny et al. (1994)†	Rat/Sprague-Dawley, adult	Inhalation exposure to 5 mg/m^3 Pb oxide daily for 13 days during gestation (GD 2, 3, 6–10, 13–17, 20)	No effects on the incidence of pregnancy, prenatal death, or malformations when male and female rats from mothers who had been exposed.	PbB 71.1 µg/dL (dam) PbB 83.2 µg/dL (fetal)
Corpas et al. (2002a)	Rat/Wistar, adult	300 mg/L acetate Pb in drinking water from mating until PND 12 or PND 21	Neither abnormalities in the liver structure nor depositions of Pb, toxicant produced biochemical alterations; pups exhibited decrease in hemoglobin, iron and alkaline, and acid phosphatase levels and an increase in Pb content; protein, DNA, and lipid total amounts were reduced, and hepatic glycogen content was diminished at 12 and 21 PN, with a higher dose of glucose in blood; decrease in alkaline phosphatase in liver of pups at day 21 PN, but acid phosphatase was unaltered.	PbB 22 µg/dL
Cory-Slechta et al. (2004)†	Rat/Long-Evans, adult	Pb acetate in drinking water beginning 2 mo before breeding through weaning	Observed potential effects of Pb and stress in female; Pb alone (in male) and Pb plus stress (in females) permanently elevated corticosterene levels in offspring.	PbB 30–40 µg/dL
Dearth et al. (2002)†	Rat/Fisher 344, 150–175 g	12 mg/mL Pb acetate gavage from 30 days prior breeding until pups were weaned 21 days after birth; 10–32 litters per group, control group, gestation and lactation exposure, gestation only exposure, lactation only exposure	Delay in onset of puberty ($p < 0.05$); reduced serum levels of IGF1 ($p < 0.001$), LH ($p < 0.001$), and E2 ($p < 0.001$).	Maternal PbB: ~40 µg/dL Pups PbB as follows: Gest+lact: ~38 µg/dL PND 10 Gest+lact: ~15 µg/dL PND 21 Gest+lact: ~3 µg/dL PND 30 Gest: ~14 µg/dL PND 10 Gest: ~3 µg/dL PND 21 Gest: ~1 µg/dL PND 30 Lact: ~28 µg/dL PND 10 Lact: ~15 µg/dL PND 21 Lact: ~3 µg/dL PND 30
Dearth et al. (2004)	Rat/Sprague-Dawley and Fisher-344, adult	12 mg/mL Pb acetate by gavage 30 days prior to breeding through PND 21 (gestation and lactation exposure)	Pb delayed the timing of puberty in PbB 37.3 µg/dL Pb group and suppressed serum levels of LH and E2, these effects did not occur in PbB 29.9 µg/dL Pb group, when doubling dose to 29.9 µg/dL group the PbB levels rose to 62.6 µg/dL, yet no effect was noted; results indicate that offspring are more sensitive to maternal Pb exposure with regard to puberty related insults than are 29.9 µg/dL rats.	PbB 29.9 µg/dL (Sprague-Dawley) PbB 37.3 µg/dL (Fisher)

Table AX5-4.3 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Foster (1992)	Monkey/ Cynomolgus, 0–10 yrs old	Daily dosing for up to 10 yrs with gelatin capsules containing Pb acetate (1.5 mg/kg); 8 control group monkeys, 8 lifetime exposure (birth–10 yrs), 8 childhood exposure (birth–400 days), and 8 adolescent exposure (postnatal day 300–10 yrs of age)	Statistically significant reductions in circulating levels of LH ($p < 0.042$), FSH ($p < 0.041$), and E2 ($p < 0.0001$) during menstrual cycle; progesterone concentrations were unchanged and menstrual cycle was not significantly affected.	PbB <40 µg/dL
Foster et al. (1992)	Monkey/ Cynomolgus, 10 yrs old	Daily dosing for up to 10 yrs with gelatin capsules containing Pb acetate (1.5 mg/kg); 8 control group monkeys, 8 childhood (birth–400 days), 7 adolescent (postnatal day 300–10 yrs), 7 lifetime (birth–10 yrs)	No effect on endometrial response to gonadal steroids as determined by ultrasound.	PbB <40 µg/dL
Foster et al. (1996b)	Monkey/ Cynomolgus, 15–20 yrs old	Chronic exposure to Pb acetate 50 to 2000 µg/kg-d p.o. beginning at birth for 15–20 yrs; 20 control monkeys, 4 monkeys in 50 µg/kg-d group, 3 monkeys in 100 µg/kg-d, 2 monkeys in 500 µg/kg-d group, and 3 monkeys in 2000 µg/kg-d group	Reduced corpora luteal production of progesterone ($p = 0.04$), without alterations in E2, 20alpha-hydroxyprogesterone, or menstrual cyclicity.	PbB 10–15 µg/dL in low group (50 or 100 µg/kg-d) PbB 25–30 µg/dL in moderate group (500 or 2000 µg/kg-d)
Franks et al. (1989)	Monkey/Rhesus, adult	Pb acetate in drinking water (2–8 mg/kg-d) for 33 mo; 7 control and 10 Pb monkeys	Reduced circulating concentration of progesterone ($p < 0.05$); treatment with Pb did not prevent ovulation, but produced longer and more variable menstrual cycles and shorter menstrual flow.	PbB 68.9 ± 6.54 µg/dL
Fuentes et al. (1996)	Mouse/Swiss, adult	14, 28, 56, and 112 mg/kg Pb acetate via i.p; one time exposure on GD 9	Absolute placental weight at 112 mg/kg and relative placental weight at 14, 56, and 112 mg/kg were diminished significantly; most sections of placenta showed vascular congestion, and increase of intracellular spaces, and deposits of hyaline material of perivascular predominance; trophoblast hyperplasia was also observed, whereas there was a reinforcement of the fibrovascular network in the labyrinth	PbB not reported
Gorbel et al. (2002)	Rat/NOS, 3 mo old	3 mg (P1) or 6 mg (P2) Pb acetate in drinking water for 15, 30, 45, 60, or 90 days	Female rats absolute and relative weights of ovary and uterus were unchanged, vaginal smears practiced in females revealed the estrus phase; fertility was found to be reduced; Pb level in blood was poorly correlated with the level of poisoning.	PbB not reported

Table AX5-4.3 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Iavicoli et al. (2004)	Mouse/Swiss, 33–37 days old	0.02, 0.06, 0.11, 0.20, 2.00, 4.00, 20.00, 40.00 ppm in food Pb acetate concentration beginning GD 1 to 3 mo after birth	Increase in food consumption; however, did low-dose group increase food consumption because of sweet nature of Pb. Body weight may contribute to delay in onset of puberty and confound results.	PbB 0.69, 1.32, 1.58, 1.94, 3.46, 3.80, 8.35, 13.20 µg/dL
Junaid et al. (1997)	Mouse/Swiss, adult	0, 2, 4, or 8 mg/kg-d Pb acetate, subchronic exposure, 5 days/wk, 60 days	Altered follicular development.	PbB 22.3–56.5 µg/dL
Laughlin et al. (1987)	Monkey/Rhesus, adult	Pb acetate in drinking water at 3.6, 5.9, or 8.1 mg/kg-d for 1–2 yrs; 7 control and 10 experimental monkeys per group	Reductions in cycle frequency ($p < 0.01$); fewer days of flow ($p < 0.01$); longer and more variable cycle intervals ($p < 0.025$).	PbB 44–89 µg/dL 51.2 µg/dL (low dose) 80.7 µg/dL (mid dose) 88.4 µg/dL (high dose)
Lögdberg et al. (1987)	Monkey/ Squirrel, adult	Pb acetate in drinking water from 9th week of gestation to PND 1; per oral exposure similar to Laughlin et al. (1987)	Increase in pre- and perinatal mortality during the last two-thirds of pregnancy; statistically significant reduction in mean birth weight was observed in Pb exposed monkeys as compared to controls.	Mean maternal PbB 54 µg/dL (39–82 µg/dL)
Lögdberg et al. (1988)	Monkey/ Squirrel, adult	Pb acetate maternal dosing from 5–8.5 wks pregnant to PND 1 11 control monkeys, 3 low-Pb exposure group (PbB 24 µg/dL), 7 medium Pb group (PbB 40 µg/dL, 5 high-Pb group (PbB 56 µg/dL)	Dose-dependent reduction in placental weight ($p < 0.0007$); various pathological lesions were seen in the placentas, including hemorrhages, hyalinization of the parenchyma with destruction of the villi, and massive vacuolization of chorion epithelium.	PbB 37 µg/dL (22–82 µg/dL) 24 (22–26) µg/dL (low dose) 40 (35–46) µg/dL (mid dose) 56 (43–82) µg/dL (high dose)
McGivern et al. (1991)[†]	Rat/Sprague-Dawley, adult	0.1% Pb acetate in drinking water from GD 14 to parturition	Female rats showed delay in vaginal opening; 50% exhibited prolonged and irregular periods of diestrous and lack observable corpora lutea; both sexes showed irregular release patterns of both FSH and LH.	PbB 73 µg/dL
Nilsson et al. (1991)	Mouse/NMRI, adult	75 µg/g bw Pb chloride via i.v.; one time injection on GD 4	Electron microscopy showed that the uterine lumen, which was closed in control mice, was opened in Pb-injected mice; suggested that Pb caused increase in uterine secretion; study suggested Pb could have a direct effect on the function of the uterine epithelium and that Pb was secreted into the uterine lumen and affect the blastocysts.	PbB not reported
Piasek and Kostial(1991)	Rat/Wistar, 10 wks old	7500 ppm Pb acetate in drinking water for 9 wks	Decrease in litter size, pup survival, and birth weight; food consumption, body weight, and fertility were not altered in 20 wk exposure period.	Maternal PbB >300 µg/dL Offspring PbB >220 µg/dL
Pinon-Lataillade et al. (1995)	Mouse/NMRI, adult	0–0.5% Pb acetate in drinking water exposed to Pb during gestation until post-GD 60	Exhibited reduced fertility as evidenced by smaller litters and fewer implantation sites.	PbB 70 µg/dL

Table AX5-4.3 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Priya et al. (2004)	Rat/Charles Foster, 6–9 mo old	0.03 µM Pb in vitro for 1 h	LH binding was dropped to 84% in Pb treated cells; Pb exposed cells showed 31% reduction in the enzymes 17ß-HSDH and 17ß-HS; Pb can cause a reduction in LH and FSH binding, which significantly alters steroid production in vitro and exerts a direct influence on granulose cell function.	PbB not applicable–in vitro study
Ronis et al. (1996)	Rat/Sprague-Dawley, various ages	Pb acetate in the drinking water or male and female rats for the following durations: PND 24–74 (pubertal exposure); PND 60–74 (post pubertal exposure)	Data suggest that both the temporary and the long-lasting effects of Pb on reproductive endpoints in male and female experimental animals are mediated by the effects of Pb on multiple points along the hypothalamic-pituitary-gonad axis; exposure of male and female Sprague-Dawley rats pre-pubertally (age 24–74 days) to Pb acetate in the drinking water resulted in significant reduction in testis weight and in the weight of secondary sex organs in males; these effects were not observed in rats exposed post-pubertally (day 60–74); there is convincing evidence that pre-pubertal female rats exposed in utero and during lactation have reduced levels of circulating E2 and LH.	Maternal PbB 30–60 µg/dL Offspring PbB >200 µg/dL.
Ronis et al. (1998a)†	Rat/Sprague-Dawley, adult	0.6% Pb acetate in drinking water; ad libitum for various durations as follows: GD 5 to PND 1, GD 5 to weaning, PND 1 to weaning	Female pups exposed to Pb from birth through adulthood or from GD 5 through adulthood were observed to have significantly delayed vaginal opening and disrupted estrus cycling; these effects on female reproductive physiology were not observed in animals where Pb exposure was confined only to pregnancy or lactation.	Pups continuously exposed to Pb 225 to 325 µg/dL
Ronis et al. (1998b)	Rat/Sprague-Dawley, adult	Ad libitum intake of Pb acetate (0.05 to 0.45% w/v); Pb exposure of dams until weaning, exposure of pups until day 21, 35, 55, 85	Prenatal Pb exposure that continues until adulthood (85 days old) delays sexual maturation in female pups in a dose-related manner; dose-dependent delay in sexual maturation (delayed vaginal opening) among female rats following prenatal Pb exposure that continued until adulthood (85 days old); a growth hormone-mediated effect on growth that differs depends upon the developmental state of the animal birth weight was significantly reduced and more pronounced among male pups; decreased growth rates in both sexes were accompanied by a statistically significant decrease in plasma concentrations of IGF1 through puberty and a significant increase in pituitary growth hormone during puberty; growth suppression of male and female rats involves disruption of growth hormone secretion during puberty.	Mean PbB in offspring at 0.05% (w/v) 49 ± 6 µg/dL Mean PbB in offspring at 0.15% (w/v) 126 ± 16 µg/dL Mean PbB in offspring at 0.45% (w/v) 263 ± 28 µg/dL
Ronis et al. (1998c)	Rat/Sprague-Dawley, adult	0.05, 0.15, or 0.45% Pb acetate in drinking water beginning GD 5 for 21, 35, 55, 85 days	Dose-responsive decrease in birth weight and crown-to-rump length was observed in litters; dose-dependent delay in sexual maturity (delay in vaginal opening); decrease in neonatal sex steroid levels and suppression of E2 during puberty; elevation in pituitary LH content was observed during early puberty; E2 cycle was significantly disrupted at the highest Pb dose; data suggests that the reproductive axis is particularly sensitive to Pb during specific developmental periods, resulting in delayed sexual maturation produced by sex steroid biosynthesis.	PbB in dams 181 ± 14 µg/dL PbB in pups ranged from 197 ± 82 to 263 ± 38 µg/dL, increasing with age of pups
Sierra and Tiffany-Castiglioni (1992)	Guinea pig/NOS, adult	0, 5.5, or 11 mg/kg Pb acetate, oral dose from GD 22 until GD 52 or 62	Hypothalamic levels of SRIF; lower serum concentrations of progesterone at higher dose only; hypothalamic levels of GnRH and SRIF were reduced in a dose-dependent manner by Pb treatment in both dams and fetuses; reduction of SRIF levels in 52-days old fetus was particularly severe (92%) in the 11 mg group.	PbB not reported
Srivastava et al. (2004)	Rat/Fisher 344, adult	12 mg/mL Pb acetate by gavage for 30 days prior to breeding until weaning	Pb decreased StAR protein expression and lowered E2 levels; suggested that the primary action of Pb to suppress E2 is through its known action to suppress the serum levels of LH and not due to decreased responsiveness of StAR synthesizing machinery.	PbB of dams 39 ± 3.5 SEM µg/dL and offspring PbB 2.9 ± 0.28 SEM µg/dL

Table AX5-4.3 (cont'd). Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Taupeau et al. (2001)	Mouse/C57blxCBA, 8 wks old	10 mg/kg-d Pb nitrate via i.v. for 15 days	Low Pb concentration in the ovary caused dysfunction of folliculogenesis, with fewer primordial follicles and an increase in atretic antral follicles.	PbB not reported
Tchernitchin et al. (1998a)	Rat/Sprague-Dawley, 14 days old	172 µg/g bw Pb from day 14 every 2nd day until day 20	Pb inhibits estrogen-induced uterine eosinophilia at 6 and 24 hr after treatment; Pb also inhibits estrogen-induced edema in deep and superficial endometrial stoma at 24 hr but not 6 hr after treatment; myometrial hypertrophy is inhibited under the effect of exposure at 24 hr of treatment.	PbB 47 µg/dL
Tchernitchin et al. (1998b)	Rat/Sprague-Dawley, 20 or 21 days old	(75 mg/g bw) Pb via i.v. one time exposure at 1 or 24 before hormone stimulation	Enhanced some parameters of estrogen stimulation and inhibited other estrogenic responses; interaction with responses to estrogen was different depending on whether Pb pretreatment was 1 or 24 hr before hormone stimulation; estrogenic responses mostly affected were uterine eosinophilia, endometrial edema, uterine liminal epithelial, hypertrophy, and mitosis in various, but not all, uterine cell types, in some cell types, estrogen-induced mitotic response developed earlier under the effect of Pb exposure.	PbB not reported
Wide (1985)	Mouse/NMRI, 10 wks old	20 µg/dL/g bw Pb chloride via i.v. single exposure on days 8, 12, or 16 after mating	Litter size and fetal survival varied significantly; small litters and increased numbers of fetal deaths were observed in mice exposed to Pb on day 8 of intrauterine life; live fetuses were normal with respect to weight and morphological appearance; ovarian follicle counts revealed a significantly smaller number of primordial follicles in the latter group, it suggested that the exposure to Pb at a time of early organogenesis caused the observed fertility decrease by interfering with the development of the female germ cells.	PbB not reported
Wide and D'Argy (1986)	Mouse/NMRI, adult	20 µg/g bw by i.v. single injection on GD 8	Primordial germ cells showed a normal body distribution but were significantly fewer at all four stages compared with those of control embryos of corresponding age; Pb had interfered with the production or activity of alkaline phosphatase.	PbB not reported
Wiebe and Barr (1988)	Rat/Sprague-Dawley, adult	20 or 200 ppm Pb chloride in drinking water; 3 exposure durations; prior to mating through weaning, GD 7 to weaning, PND 21 to PND 35	Treatment with Pb prior to mating resulted in significant increase in E2-receptor affinity in 21-day old offspring without a change in E2 receptor number; treatment from day 7 of pregnancy until weaning of the pups resulted in ~35% decrease in E2 receptors per mg uterine protein when these offspring reached 150 days of age; Pb treatment from 21–35 days old or until 150 days resulted in a significant decrease in uterine E2 receptor number at 35 and 150 day, respectively.	PbB likely 4.0 ± 1.4 to 6.6 ± 2.3 µg/dL (similar design as Wiebe et al. (1988)
Wiebe et al. (1988)	Rat/Sprague-Dawley, adult	20 or 200 ppm Pb chloride in drinking water; 4 exposure durations; prior to mating through weaning, GD 7 to weaning, PND 21 to PND 35, prior to mating only	Exposure to Pb did not affect tissue weights but did cause a significant decrease in gonadotropin-receptor binding in the pre-pubertal, pubertal, and adult females; conversion of progesterone to androstenedione and dihydrotestosterone was significantly decreased in 21-day old rats and in 150-day old females; significantly increased conversion to the 5-alpha-reduced steroids, normally high during puberty.	PbB range 4.0 ± 1.4 to 6.6 ± 2.3 µg/dL
Yu et al. (1996)	Rat/Sprague-Dawley, adult	Neonatal and lactational exposure to 0.3% Pb acetate in drinking water (PND 30)	Neonatal exposure to Pb decreased cold-water swimming endurance (a standard test for stress endurance); delayed onset of puberty in males and female offspring, which was exacerbated by swimming stress.	PbB 70 µg/dL

*Not including effects on the nervous or immune systems.

† Candidate key study.

E_2, estradiol; FSH, follicle stimulating hormone; GD, gestational day; GnRH, gonadotropin releasing hormone; HET, Binghamton Heterogeneous Stock; IGF_1, insulin-like growth factor 1; i.p., intraperitoneal; LH, luteinizing hormone; NOS, not otherwise specified; PbB, blood lead concentration; PND, post-natal day; p.o., per os (oral administration); SRIF, somatostatin; StAR, steroidogenic acute regulatory protein.

ANNEX TABLES AX5-5

Table AX5-5.1. In Vivo and In Vitro Studies of the Effects of Lead Exposure on Production and Metabolism of Reactive Oxygen Species, Nitric Oxide, and Soluble Guanylate Cyclase

				Pb Exposure			Measured Parameters			
Reference	Species/ Tissue	Age/Weight	n	Dosage	Duration	Pb Level	CVS	Other	Interventions	Results
Khalil-Manesh et al. (1994)	Male SD rats	200 g	N/A	Pb-acetate, 100 ppm in water	6 mo	7 ± 3.6 µg/d	BP, tail art. ring response to NE	ET-3, cGMP	DMSA R_X	Pb caused HTN, ↑ET_3, ↓U cGMP (NS) (no effect on NE reactivity). DMSA R_x lowered BP and Vasc response to NE and raised cGMP
Gonick et al. (1997)	Male SD rats	2 mo 200 g	6	Pb-acetate, 100 ppm in water	3 mo	12.4 ± 1.8 µg/dL	BP	cGMP, NO_2 + NO_3, ET-1, ET-3, MDA, eNOS, iNOS	—	HTN, ↑MDA, ↑eNOS, ↑iNOS (protein and activity in kidney)
Ding et al. (1998)	Male SD rats	2 mo	N/A	Pb-acetate, 100 ppm in water	3 mo	3.2 ± 0.2 µg/dL	BP	Urine NO_2 + NO_3, plasma MDA	DMSA (0.5% H_2O) × 2 wks, i.v. infusions of L. Arg., SOD and SNP	Pb caused HTN, ↓urine NO_2+NO_3, ↑plasma MDA. DMSA lowered BP, blood Pb and MDA + raised urine NO_2 + NO_3. L-Arg lowered BP and MDA, raised NO_2+NO_3, SNP lowered BP
Vaziri (1997)	Male SD rats	190 g	12	Pb-acetate, 100 ppm in water	3 mo	17 ± 9 µg/dL	BP	Plasma MDA urine NO_2 + NO_3	Antioxidant R_x (Lazaroid)	Pb caused HTN, ↑MDA, ↓urine NO_2+NO_3 in untreated animals. Antioxidant R_x improved HTN, urine NO_2 + NO_3 and lowered MDA without changes in blood Pb level
Dursun (2005)	Male SD rats		24	Pb acetate 8 mg/kg IP	2 wks		BP, RBF	Ur Na, Ur NO_2 + NO_3, 24 hr UrNa (Na^+ intake Not given)		↑BP, ↓RBF, ↓UrNO_2 + NO_3, unchanged UrNa^+

Table AX5-5.1 (cont'd). In Vivo and In Vitro Studies of the Effects of Lead Exposure on Production and Metabolism of Reactive Oxygen Species, Nitric Oxide, and Soluble Guanylate Cyclase

				Pb Exposure			Measured Parameters			
Reference	Species/ Tissue	Age/Weight	n	Dosage	Duration	Pb Level	CVS	Other	Interventions	Results
Vaziri et al. (1999b)	Male SD rats	200 g	6 per group per time point	Pb-acetate, 100 ppm in water	3 mo	8.2 ± .8 and 10.8 ± 1 µg per g. Kidney tissue in untreated and antiox-treated groups	BP	Aorta and kidney eNOS protein abundance, Ur NO_2 + NO	Subgroups treated with high-dose vitamin E	Pb exposure resulted in a time-dependent rise in BP, aorta and kidney eNOS and iNOS. This was associated w/a paradoxical fall in NO availability (Ur NO_2 ± NO_3). Antioxidant R_x attenuated upregulation of iNOS and eNOS and raised NO availability.
Vaziri et al. (2001)	Male SD rats	200 g	6 per group	Pb acetate	3 mo	N/A	BP	Aorta, heart, kidney and brain NOS isoforms, urine NO_2 + NO_3	Subgroups studied after 2 wks of R_x w/tempol and those studied 2 wks after cessation of tempol R_x	Pb exposure resulted in rises in BP, eNOS, iNOS and nNOS in the tested tissues + ↓urine NO_x. Tempol administration attenuated HTN, reduced NOS expressions and increased urine NO_x. The effects of tempol disappeared within 2 wks of its discontinuation.
Vaziri and Ding (2001)	Human coronary endothelial cells	N/A	≥4 per experiment	0 and 1 ppm Pb acetate	24 hrs w/Pb or Na acetate followed by 24 hrs w/tempol or vehicle	1 ppm medium	N/A	eNOS expression	Co-treatment w/$O_2^{\cdot}$ scavenger, tempol	Pb exposure for 48 hr upregulated eNOS expression. Co-treatment w/ tempol resulted in dose-dependent reversal of Pb-induced upregulation of eNOS but had no effect on control cells.

Table AX5-5.1 (cont'd). In Vivo and In Vitro Studies of the Effects of Lead Exposure on Production and Metabolism of Reactive Oxygen Species, Nitric Oxide, and Soluble Guanylate Cyclase

Reference	Species/ Tissue	Age/Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Vaziri et al. (1999a)	Male SD rats	200 g	6 per group	100 ppm in water	3 mo	8.3–10.8 μg/g kidney tissue	BP	Urine NO_2 + NO_3, tissue and plasma nitrotyrosine (marker of NO-ROS interaction).	Antioxidant R_x (Vit E)	Pb exposure raised BP, reduced Ur NO_2 + NO_3 and increased nitrotyrosine abundance in plasma, heart, kidney, brain and liver. Anti ox R_x ameliorated HTN, lowered nitrotyrosine and raised Ur NO_2 + NO_3.
Vaziri et al. (2003)	Male SD rats	200 g	6 per group	100 ppm in water	3 mo	N/A	BP	Urine NO_2 + NO_3, kidney, heart, brain SOD, catalase, GPX, NAD(P)H oxidase abundance	Tempol ($O_2^{\bullet}$ scavenger infusion)	Pb caused HTN, ↑NAD(P)H oxidase ($gp91^{phox}$), ↑SOD, un-changed catalase and GPX, ↓UrNO_2 + NO_3. Tempol resulted in ↓BP + ↑urine NO_2 + NO_3 in Pb-exposed but not control rats.
Ni et al. (2004)	Cultured human coronary endothelial and VSM cells.	N/A	≥4 per experiment	0,1 and 10 ppm Pb acetate	Short exposure (5–30 min) and long exposure (60 hr)	0, 1, 10 ppm	N/A	$O_2^{\bullet}$ and H_2O_2 productions SOD, catalase, GPX and NAD(P)H oxidase ($gp91^{phox}$)	None	Short-term incubation with Pb at 1 and 10 ppm raised $O_2^{\bullet}$ and H_2O_2 productions by both endothelial and VSM cells, long-term incubation resulted in further rise in H_2O_2 generation and normalization of detectable $O_{2y}^{\bullet}$. This was associated with increases in NAD(P)H oxidase and SOD and reduced or unchanged catalase and GPX.

Table AX5-5.1 (cont'd). In Vivo and In Vitro Studies of the Effects of Lead Exposure on Production and Metabolism of Reactive Oxygen Species, Nitric Oxide, and Soluble Guanylate Cyclase

Reference	Species/ Tissue	Age/Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Ding et al. (2001)	Male SD rats	2 mo 200 g	N/A	100 ppm	3 mo	Blood Pb 12.4 ± 1.8 µg/dL vs. 1 mg/dL in controls	BP	Response to DMTU administration, tissue nitrotyrosine, hydroxyl radical	i.v. infusion of DMTU	Pb caused HTN, ↑plasma nitrotyrosine, ↑plasma.OH concentration all reversed with .OH-scavenger, DMTU infusion
Ding et al. (2000)	Cultured rat aorta endothelial cells	N/A	≥4 experiment	0–1 ppm	1, 2, 24, 84 hr	0–1 ppm culture media	N/A	Hydroxyl radical production using the following reaction (Na Salicylate + OH → 2,3dihydroxy benzoic acid), MDA	None	Pb exposure resulted in conc-dependent rise in MDA and OH production by cultured endothelial cells.
Attri (2003)	Male Wistar Kyoto rats	150–200 g	10 per group	Pb acetate, 100 ppm in water ± Vit C 20 mg/d/rat	1–3 mo	Blood Pb 1.5 mg/dL at 1 mo 2.4 mg/dL at 2 mo 4.1 mg/dL at 3 mo	BP	Total antioxidant capacity, ferric-reducing antioxidant power, NO metabolites, MDA, 8-hydroxyguanosine	Response to vitamin C.	Pb caused ↑BP, ↑MDA, ↑DNA damage/ oxidation, ↓NO_x, ↓antioxidant and ferric-reducing antioxidant. Concomitant R_x with Vit-C ameliorated all abnormalities.
Malvezzi (2001)	Male Wistar rats	5–6 wks (170 g)	4–10 per group	Pb acetate 750 ppm in water	100 days	Blood, bone, kidney, aorta, liver	BP	—	Response to L. arg, DMSA, L. arg .+ DMSA (given together w/Pb in last 30 days	↑BP w/Pb, partial ↓BP w/L. Arg or DMSA, greater reduction w/both, blood and aorta PB remained ↑ in all but DMSA + L. Arg group. Significant Pb mobilization shown in other organs.

Table AX5-5.1 (cont'd). In Vivo and In Vitro Studies of the Effects of Lead Exposure on Production and Metabolism of Reactive Oxygen Species, Nitric Oxide, and Soluble Guanylate Cyclase

Reference	Species/ Tissue	Age/Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Khalil-Manesh et al. (1993b)	Male SD rats	8 wks	N/A	Pb acetate 100 or 5000 ppm in water	1–12 mo	29 ± 4 µg/dL	BP, vascular contractility to NE in vitro	cGMP, ET-3, ANP	—	Pb caused HTN, ↓serum and urine cGMP, ↑serum ET-3 without changing ANP or response to NE
Marques et al. (2001)	Male Wistar rats	3 mo	20	Pb acetate 5 ppm ± Vit C (3 mmol/L) in water	30 days	N/A	BP, arch-, SNP-vasorelaxation response in aorta rings	sGC protein mRNA and activity. cGMP production, eNOS protein	CoT_x with Vit C	Pb caused HTN, ↓relaxation to Ach and SNP, ↑eNOS, ↓sGC protein mRNA and activity. These abnormalities were prevented by antioxidant R_x.
Farmand et al. (2005)	Male SD rats	200 g	8	Pb acetate 100 ppm in water	3 mo	N/A	BP	Aorta sGC, SOD, catalase, glutathione peroxidase	—	↓sGC, ↑CuZn SOD activity, unchanged catalase and GPX activities.
Courtois et al. (2003)	Rat thoracic aorta	N/A	6/ experiment	0–1 ppm	24 hr	0–1 ppm	cGMP production	sGC expression, superoxide production, COX-2	Vit C, COX-2 inhibitor	Pb caused ↓sGC, ↓cGMP, ↑O_2, ↑COX-2. All abnormalities improved by Vit C. COX-2 inhibitor improved sGC expression but not O_2 production.

Table AX5-5.2. Studies of the Effects of Lead Exposure on PKC Activity, NF_kB Activation, and Apoptosis

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Watts et al. (1995)	Isolated rabbit mesenteric artery	N/A	5–6 sets per experiment	Pb acetate 10^{-10}–10^{-3}M	Immediate (contraction)	5^{-10}–10^{-3}M medium	Vascular contraction		Preincubation w/PKC activators, PKC inhibitor or verapamil for 30–60 min + endothelium denudation	Pb acetate induced contraction which was potentiated by PKC activators and attenuated by PKC inhibitor (role of PKC). CCB attenuated Pb-induced contraction (contribution of Ca^{2+} entry). Removal of endothelium did not affect Pb-induced vasoconstriction.
Rodríguez-Iturbe et al. (2005)	Male SD rats	200 g	8 Pb group 9 controls	Pb acetate 100 ppm in drinking water	3 mo	N/A		NF_kB activation, apoptosis, Ang II positive cells, macrophage/T cell infiltration and nitrotyrosine staining in renal tissue		Pb-exposed animals showed tubuloniterstitial accumulation of activated T-cells, macrophages and Ang II positive cells, NF_kB activation increased apoptosis and nitrotyrosine staining in the kidney.

Table AX5-5.3. Studies of the Effects of Lead Exposure on Blood Pressure and Adrenergic System

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Measured Parameters			Reference	Species/Tissue
				Dosage	Duration	Pb Level	CVS	Other		
Chang et al. (1997)	Wistar rats	190–200 g	20	Pb acetate 0.5% in drinking water	2 mo	Blood 29.1 ± 1.9 µg/dL aorta; 1.9 ± 0.2 µg/g	BP	Plasma catecholamines + aorta; β receptor binding assay and cAMP generation	—	Pb exposure caused HTN, elevated plasma NE (unchanged plasma Epi). ↓ isoproterenol-stimulated plasma cAMP, ↓ β receptor density in aorta.
Tsao et al. (2000)	Wistar rats	190–200 g	70	Pb acetate 0–2% in drinking water	2 mo	Blood, heart, aorta, kidney	BP, β agonist-stimulated cAMP production (10 µM isoproterenol in vitro)	pl NEpi, cAMP β receptor densities	—	Pb exposure raised BP and pl NE + lowered aorta and heart β receptor density, basal and stimulated cAMP productions + increased kidney β receptor density and basal and stimulated cAMP productions.
Carmignani et al. (2000)	Male SD rats	3 mo	24	60 ppm	10 mo	Blood 22.8 ± 1.2 µg/dL	BP, HR, cardiac contractility (dP/dt), blood flow	Plasma NE, Epi, dopamine, monoamine oxidase (MAO) activity, histology	—	Pb exposure raised BP and dp/dt, lowered carotid blood flow, (no change in HR) raised plasma NE and Epi and MAO (all tissues) lowered plasma NOx + ↓aorta media thickness, ↑lymphocyte infiltration in periaortic fat, nonspecific change in kidney (congestion, edema, rare prox. tubular cell necrosis).

Table AX5-5.3 (cont'd). Studies of the Effects of Lead Exposure on Blood Pressure and Adrenergic System

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Lai et al. (2002)	Male SD rats	300 g	Acute response	In vivo: Intrathecal injection of PbCl2, 10–100 µM. In vitro: Thoracic cord slices exposed to 5–50 µM PbCl2	—	—	BP, HR, (In vivo) w/without ganglionic blockade (Hexomethonium)	Electophysiologic measures (In vitro) before/after saline washout	—	In vivo: IT injection of PbCl2 raised BP and HR. This was reversed by ganglionic blockade. In vitro: Pb raised excitatory and lowered inhibitory postsynaptic potentials which were reversed by removal of Pb (saline washout)
Chang et al. (2005)	Male Wistar rats	10 wks	70	2% Pb acetate (drinking water)	2 mo, observed for 7 mo after cessation	Blood: 85 µg/dL Aorta: 8 µ/g/g Heart: 1 µg/g Kidney: 60 µg/g	BP	Plasma NE, β recaptor density (aorta, heart, kidney)	Cessation of Pb exposure	Pb exposure raised BP, plasma NE, and renal tissue β receptor and lowered aorta/heart β receptor density. Plasma and tissue Pb fell to near-control values within 7 mo. after Pb cessation. This was associated with significant reductions (not normalization) of BP, plasma NE and partial correction of tissue β receptor densities (Bone Pb was not measured).

Table AX5-5.4. Studies of the Effects of Lead Exposure on Renin-angiotensin System, Kallikrein-Kinin System, Prostaglandins, Endothelin, and Atrial Natriuretic Peptide (ANP)

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Carmignani et al. (1999)	Male SD rats	Weaning	16	Pb acetate 60 ppm drinking water	10 mo	Blood 24.2 ± 1.8 µg/dL	BP, HR, carotid blood flow	Plasma ACE, Kininase Kallikrein activities dp/dt	—	Pb exposure raised BP and dp/dt, lowered carotid blood flow without changing HR. This was associated with marked increase in plasma ACE, Kininase II and Kininase I activities.
Sharifi et al. (2004)	Male SD rats	200 g	32	Pb acetate 100 ppm drinking water	2–8 wks	—	BP	ACE activity in plasma, aorta, heart, kidney	—	Pb exposure raised BP, ACE activity in plasma and tested tissues markedly increased peaking within 2–4 wks followed by a decline to subnormal values.
Gonick at al. (1998)	Male SD rats	2 mo	21	Pb acetate 100 ppm drinking water	12 wks	—	BP	Urinary Tx B2, 6-keto PGF1	—	Pb exposure raised BP but did not affect urinary PG metabolite excretion rates.
Dorman and Freeman (2002)	VSMC (rat aorta)	—	—	0.0, 0.02, 0.2, 2.0 mg/dL	up to 48 hrs	0.0 to 2 mg/dL	—	Arachidonic acid (AA), DNA synthesis, cell proliferation + cell viability	Ang II, FCS	Pb augmented Ang II stimulated AA release in a concentration-dependent fashion. At low concentrations, Pb augmented Ang II-stimulated DNA synthesis and lowered cell count in unstimulated cells.
Giridhar and Isom (1990)	Male SD rats	150–175 g	20	Pb acetate 0.01, 0.01, 0.5, 1.0 mg/Kg, BiW, IP	30 days	—	—	ANF	—	Pb exposure resulted in fluid retention (↓urine flow + unchanged fluid intake + weight gain). This was associated with decreased plasma and hypothalamic ANF levels .

Table AX5-5.5. Studies of Effect of Lead on Vascular Contractility

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Shelkovnikov and Gonick (2001)	Rat aorta rings			Pb acetate 10^{-8} to 10^{-4}	Short incubations	—		Vasoconstriction/ vasodilation		Pb acetated did not cause vasoconstriction and did not modify the response to NE, isoproterenol, phorbol ester or acetylcholine but raised contractile response to submaximal Ca^{2+} concentration
Purdy et al. (1997)	Male SD rats	8 wks		Pb acetate 100 ppm in water	3 mo	—	BP	Aorta ring response to NE, phenylephrine, acetylcholine, and nitroprusside		Pb exposure raised BP. Aorta ring vasoconstrictive response to NE and phenylephrine and vasodilatory response to acetylcholine and nitroprusside were unchanged.
Oishi et al. (1996)	Male Wistar rats			Pb acetate	1–3 mo			Mesenteric art and aorta response to acetylcholine in presence or absence of NOS inhibitor (L-NAME)		Vasorelaxation response to acetylcholine in presence of L-NAME was significantly reduced in mesenteric art, but not aorta of Pb-exposed animals (Inhibition of hyperpolarizing factor)
Valencia et al. (2001)	Wistar rat thoracic aorta rings	7 wks	6 sets/ experiment	Pb acetate 0.1–3.1 mM	Rapid response in vitro	—		In vitro contractile response		Pb induced a concentration-dependent vasoconstriction in intact and endothelial-denuded rings in presence or absence of α-1 blocker, PKC inhibitor, L. type Ca^{2+} channel blocker or intra- and extracellular Ca^{2+} depletion. However, the response was abrogated by lanthanum (a general Ca channel blocker)

Table AX5-5.6. Effects of Lead on Cultured Endothelial Cell Proliferation, Angiogenesis, and Production of Heparan Sulfate Proteoglycans and tPA

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Kaji et al. (1995a)	Bovine aorta endothelial cells	—	4 sets per experiment	Pb nitrate 5–50 μM	24 hrs		—	Endothelial damage	Co-incubation with cadmium	Addition of Pb alone resulted in mild deendothelialization of the monolayers and markedly increased cadmium-associated endothelial damage.
Kaji et al. (1995b)		—	4–5 sets per experiment	Pb nitrate 0.5–5 μM	24 hrs		—	$_3$H-thymidine incorporation, cell count, morphology, LDH release	Stimulation w/βFGF and αFGF	Incubation w/Pb resulted in a concentration-dependent reduction of DNA synthesis and cell count, caused some shape change (polygonal →spindle) and reduced βFGF- and αFGF-mediated proliferation.
Fujiwara et al. (1998)	Bovine aorta endothelial cells	—	6 set per experiment	Pb nitrate 5 and 10 μM	48 hrs		—	Appearance of cells in denuded areas of monolayer, DNA synth	Stimulation w/Zn	Pb inhibited appearance of endothelial cells in the denuded section of monolayer and attenuated the healing response to Zinc.
Kishimoto et al. (1995)	Human-umbilical vein endothelia cells	—	3 sets per experiment	Pb acetate 1–100 μM	24 hrs		—	Formation of tube-like structures (angio-genesis assay, on Matrigel (BM)	—	Pb inhibited tube formation concentration-dependently and tube lengthening time dependently.
Ueda D. et al. (1997)	Human umbilical vein endothelial cells	—	3 sets per experiment	Pb acetate 1–100 μM	24 hrs		—	Tube formation on Matrigel matrix	PKC activator and inhibitor	Pb inhibited tube formation concentration-dependently and tube lengthening time dependently. These effects were independent of PKC.

Table AX5-5.6 (cont'd). Effects of Lead on Cultured Endothelial Cell Proliferation, Angiogenesis, and Production of Heparan Sulfate Proteoglycans and tPA

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Fujiwara and Kaji (1999)	Bovine aorta endothelial cells	—	4 sets per experiment	Pb nitrate 0.5, 1, 2 μM	12–48 hrs			βFGF production/ distribution Heparan sulfate production (sulfate incorporation) DNA synthesis (cell proliferation) βFGF binding assay	Heparin, Anti-βFGF antibody	Pb and anti-βFGF alone or together equally reduced DNA synthesis. PB did not change endogenous βFGF production but reduced its HSPG-bound component. This was due to diminished heparan sulfate synthesis as opposed to interference with βFGF binding property.
Kaji et al. (1991)	Bovine aorta endothelial cells	—	4–5 sets per experiment	Pb nitrate 0, 1–20 μM	24–48 hrs			Glycosaminoglycan (GAG) synthesis (sulfate incorporation)		At 10 μM, Pb significantly reduced production of total GAGs. Heparan sulfate was reduced more severely than other GAGs. Cell surface GAG was reduced more severely than found in the medium.
Kaji et al. (1997)	Bovine aorta endothelial cells (confluent)	—	N/A	Pb chloride 10 M	24 hrs	N/A		Synthesis of heparan sulfate proteoglycans (HSPGs) and their core proteins		In confluent cells, Pb suppressed incorporation of precursors into HSPG in the cell layer to a greater extent than chondroitin/dermatan sulfate proteoglycans. Pb suppressed low-molecular weight HSPGs more than the high-molecular weight subclass. The core proteins were slightly increased by Pb exposure.

Table AX5-5.6 (cont'd). Effects of Lead on Cultured Endothelial Cell Proliferation, Angiogenesis, and Production of Heparan Sulfate Proteoglycans and tPA

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Interventions	Results
				Dosage	Duration		CVS	Other		
Fujiwara and Kaji (1999)	Bovine aorta endothelial cells (growing 10% BCS)	—	4 sets per experiment	Pb nitrate 0.1 μM	48 hrs			Sulfate and glucosamine incorporation in GAGs, quantification of high and low MW-HSPG, identification of perlecan core protein		In growing cells, Pb depressed high-MW HSPGs production but had little effect on low-MW HSPGx (~50 KD). The core protein of perlecan (400 KD) was significantly reduced by Pb exposure.
Kaji et al. (1992)	Human umbilical vein endothelial cells (confluent)	—	5 sets per experiment	0.01–1 μM				t-PA release, DNA synth, protein synth (leucine incorporation)	Thrombin and ET-1 stimulations	Pb exposure reduced basal and thrombin-stimulation t-PA release and worsened ET-1 induced inhibition of t-PA release.

Table AX5-5.7. Studies of the Effect of Lead on Cultured Vascular Smooth Muscle Cells

Reference	Species/ Tissue	Age/ Weight	n	Pb Exposure		Pb Level	Measured Parameters		Reference	Species/Tissue
				Dosage	Duration		CVS	Other		
Fugiwara et al. (1995)	Bovine aorta vascular smooth muscle cell		4 sets per experiment	Pb nitrate 0.5–10 μM	24 hrs		—	DNA synthesis	Coincubation w/βFGF, αFGF. pDGF	Pb caused a concentration-dependent increase in DNA synthesis. Co-incubation w/βFGF and Pb resulted in an additive stimulation of VSMC DNA synth. However, Pb inhibited PDGF and αFGF-induced DNA synthesis.
Carsia et al. (1995)	Rat aorta VSMC cells (80–90% confluent)		≥3 sets per experiment	Pb citrate 100 and 500 μg/L	Time to confluence (~90% for control experiments)			Cell density (cell #/Cm^2), cell morphology, membrane lipid analysis, receptor densities (Ang-II, α, β, ANP		At low concentration, Pb caused VSMC hyperplasia, phenotypic transformation from spindle-to-cobblestone (neointima-like) shape, reduced Ang II receptor density without changing α, β, ANP receptors, increased arachidonic acid content of cell membrane.
Yamamoto et al. (1997)	Human aorta VSMC and fetal lung fibroblasts (confluent)		5 sets per experiment	Pb chloride 0.5–10 μM	24 hrs			t-PA and PAI-1 release		At 2 μM or higher concentrations, Pb resulted in a concentration-dependent decline in t-PA release in both cell types. Pb increased PAI-1 release in fibroblasts but lowered PAI-1 in VSMC.

ANNEX TABLES AX5-6

Table AX5-6.1. Genotoxic/Carcinogenic Effects of Lead—Laboratory Animal Studies

Compound	Dose and Duration	Cell Type	Co-exposure	Effects	Reference
Pb acetate	0.5, 5, or 25 ppm given in drinking water–duration not given. Number of animals per group was not given.	Female C3HSt mice infected with MMTV (Murine mammary tumor virus)–age not given	Selenium, 0.15–1 ppm (duration not given) in diet (Se prevents spontaneous tumors in these mice)	Pb acetate exposed mice exhibited greater mortality unrelated to the tumor formation. 25 ppm suppressed tumor formation, but increased the aggressiveness of the tumors. 5 ppm increased tumor formation, but had no effect on growth rates. 0.5 ppm with low selenium exhibited 80% tumor formation and reduced weight gains that recovered. 0.5 ppm with high selenium exhibited normal weight gain, but tumor incidence still reached 80%. Control data described as "significantly lower" but not given. Methods poorly described and data not shown.	Schrauzer (1987)
Pb acetate	0–4000 ppm given in drinking water for 104 wks.	Wild type (WT) and metallothionine null (MT null) mice	None	Renal proliferative lesions were much more common and severe in MT null mice than WT mice. MT null mice could not form renal inclusion bodies even with prolonged Pb exposure and this could have contributed to increase in the carcinogenic potential of Pb.	Waalkes et al. (2004)
Pb acetate	50, 250, or 1000 ppm given in drinking water for 15 wks. Number of mice per group in initial exposures not given. Number of mice at analysis ranged from 19–25.	Female albino Swiss Mice–3 wks old	Urethane 1.5 mg/g given i.p.	No signs of Pb poisoning. No Pb effects on growth or weight gain. Urethane added to induce lung tumors. Pb did not affect urethane metabolism. Pb did not affect number of tumors or affect tumor size. Pb alone was not evaluated. Pb levels did increase in tissues.	Blakley (1987)

Table AX5-6.1 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Laboratory Animal Studies

Compound	Dose and Duration	Cell Type	Co-exposure	Effects	Reference
Pb acetate	50 or 1000 ppm 50 or 1000 ppm given in drinking water for 280 days. Number of mice pre group in initial exposures not given. Number of mice at end were 50 per dose.	Female albino Swiss Mice–8 wks old	None	Mice have high rate of spontaneous leukemia from endemic viral infection. No signs of Pb poisoning. No Pb effects on growth or weight gain. Pb did increase leukemia-related mortality possibly due to immunosuppression. Pb levels did increase in tissues. Data indicate that Pb may be immunosuppressive, though the exact mechanism is not understood.	Blakley (1987)
Pb acetate	60 mg/kg injected s.c. weekly for 5 wks followed by observation for 80 wks. 13 treated and 14 control rats.	Fisher F344/NSle rats–3 wks old	None	Pb induced tumors at the site of injection in 42% of rats though data was not shown. Control data not indicated or shown. Pb accumulated in tumor tissue, tooth, and bone. This data was shown.	Teraki and Uchiumi (1990)
Pb acetate	1 or 100 µg/L given in the drinking water for 31 wks 8 animals per group	Male Wistar Rats—weanlings	0.2–4 % calcium carbonate given in the diet for 31 wks.	No differences in drinking water or food consumption. High Pb and high calcium reduced growth. No deaths in low calcium groups. 10/24 rats from high calcium diet died (4 from controls and 3 each from Pb groups). All 10 had kidney or bladder stones. 0/8 rats in low calcium no Pb had kidney pathology 2/8 rats in low calcium low Pb had nephrocalcinosis. 7/8 rats in low calcium high Pb had nephrocalcinosis. 3/4 rats in high calcium no Pb had nephrocalcinosis. 1/5 rats in high calcium low Pb had a renal pelvic carcinoma. 3/5 rats had nephrocalcinosis. 3/5 rats in high calcium high Pb had transitional cell hyperplasia. 2/5 rats had invasive renal pelvic carcinoma. Pb tissue levels were same regardless of dietary calcium levels.	Bogden et al. (1991)

Table AX5-6.2. Genotoxic/Carcinogenic Effects of Lead—Human Cell Cultures

Compound	Dose and Duration	Cell Type	Co-exposure	Effects	Reference
Pb chromate	Anchorage Independence (0.1–1 μM for 48 h)	Human Foreskin Fibroblasts In H-MEM +15% FCS	None	Pb chromate-induced concentration-dependent increase in anchorage independence.	Biedermann and Landolph (1987)
Pb chromate	Anchorage Independence (0.1–1 μM for 48 h)	Human Foreskin Fibroblasts In H-MEM +15% FCS	None	Pb chromate-induced concentration-dependent increase in anchorage independence.	Biedermann and Landolph (1990)
Pb chromate	Morphological Transformation (2 μg/mL for 24 h, performed 3 times immediately after passage) Anchorage Independence (0.2–2 μg/mL or cells isolated during morphological transformation) Neoplastic Transformation (cells isolated during morphological transformation)	HOS TE 85 in DMEM + 10% FBS	None	Pb chromate induced foci of morphological transformation after repeated exposure and passaging. Pb chromate did not induce anchorage independence, but cells from the foci obtained during morphological transformation. Pb chromate did not induce neoplastic transformation in the cells from the foci obtained during morphological transformation. Studied as a chromate compound. Role of Pb not mentioned or considered.	Sidhu et al. (1991)
Pb acetate	Anchorage Independence (500–2000 μM for 24 h)	Human Foreskin Fibroblasts (Chinese) In DMEM +10% FCS	3-aminotriazole (3-AT) (80 mM to inhibit catalase)	Pb acetate-induced concentration-dependent increase in anchorage independence. Anchorage independence not affected by 3-AT.	Hwua and Yang (1998)

Table AX5-6.3. Genotoxic/Carcinogenic Effects of Lead—Carcinogenesis Animal Cell Cultures

Compound	Dose and Duration	Cell Type	Co-exposure	Effects	Reference
Pb acetate	Morphological Transformation (10–50 μM for 48 h)	Primary SHE cells in AMEM + 10% FBS	None	Pb acetate was weakly positive inducing a 0.19–1.6% increase in transformation. There was a weak dose response. There were no statistical analyses of these data.	Zelikoff et al. (1988)
Pb chloride	Morphological Transformation (doses not given)	C3H10T1/2 cells in EMEM +10% FBS	None	Pb chloride did not induce morphological transformation.	Patierno et al. (1988), Patierno and Landolph (1989) (both papers present the same data)
Pb chromate	Enhancement of Simian Adenovirus (SA7) induced morphological transformation. (80–1,240 μM for 20 h)	Primary SHE cells in DMEM + 10% FBS	None	Pb chromate enhanced SA7-induced morphological transformation. Studied as a chromate compound. Role of Pb not mentioned or considered.	Schechtman et al. (1986)
Pb chromate	Morphological Transformation (10–50 μM for 24 h) Anchorage Independence for cells isolated during morphological transformation Neoplastic Transformation for cells isolated during morphological transformation.	C3H10T1/2 cells in EMEM + 10% FBS	None	Pb chromate induced morphological and neoplastic transformation. Cells exhibiting morphological transformation grew in soft agar and grew in nude mice. Studied as a chromate compound.	Patierno et al. (1988) Patierno and Landolph (1989) (both papers present the same data)
Pb chromate (and pigments containing Pb chromate)	Morphological Transformation (0.04–8 μg/mL as Cr for 7 days) Anchorage Independence for cells isolated during morphological transformation Neoplastic Transformation for cells isolated during morphological transformation	Primary SHE cells in DMEM + 10% FCS	None	Pb chromate induced morphological and neoplastic transformation. Cells exhibiting morphological transformation grew in soft agar and grew in nude mice. Studied as a chromate compound.	Elias et al. (1989)
Pb chromate	Morphological Transformation (0.02–0.88 μg/mL as Cr for 7 days)	Primary SHE cells in DMEM + 10% FCS	None	Pb chromate induced morphological transformation more potently (9-fold) than other chromate compounds.	Elias et al. (1991)

Table AX5-6.3 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Carcinogenesis Animal Cell Cultures

Compound	Dose and Duration	Cell Type	Co-exposure	Effects	Reference
Pb nitrate	Morphological Transformation (0.04–8 μg/mL as Cr for 7 days)	Primary SHE cells in DMEM + 10% FCS	Calcium chromate	Pb nitrate alone did not induce significant levels of transformation. Pb nitrate plus calcium chromate increased the potency of calcium chromate to that of Pb chromate. Data suggest Pb ions are synergistic with chromate ions in inducing neoplastic transformation.	Elias et al. (1991)

Abbreviations

Cells
SHE—Syrian hamster embryo;
C3H10T/12 cells are a mouse embryo cell line

Medium and Components
AMEM—Alpha Minimal Essential Medium;
DMEM—Dulbecco's Minimal Essential Medium;
EMEM—Eagle's Minimal Essential Medium;
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum
H-MEM—Minimum essential medium/nutrient mixture–F12-Ham
HOS TE—Human osteosarcoma cell line TE

Differences between the serum are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.4. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Laboratory Animal Studies.

Compound	Dose and Duration	Species	Co-exposure	Effects	Reference
Pb acetate	2.5 mg/100 g given i.p. as daily injection for 5–15 days or 10–20 mg/100 g given i.p. as single injection and animals studied after 15 days 5 animals per group. Chromosome damage in bone marrow	Female Norway Rat	Selenium (0.012–0.047 mg/100g or 0.094–0.188 mg/100 g given i.p. with Pb)	Pb induced chromosome damage after chronic treatment. It was not dose dependent as only 1 dose was studied. The effects of selenium on Pb effects are unclear as selenium alone induced substantial chromosome damage. The single dose exposure also induced chromosome damage, but untreated controls were not done in this regimen. There is some mention that this dose regimen is toxic to the animals as selenium modulated the lethal effects, but no explanation of how many animals died.	Chakraborty et al. (1987)
Pb acetate	25–400 mg/kg given i.p. as single injection and animals studied after 24 h For some chromosome damage studies animals were treated with 25–200 mg/kg given i.p. as a series of 3, 5, or 7 daily injections and animals studied after 24 h after the last injection. 5 animals per group. Chromosome damage, sister chromatid exchange, in bone marrow and spermatocytes.	Male Swiss Mice, 9–12 wks old	None	Pb induced chromosome damage in a dose dependent manner at 100–400 mg/kg after a single dose or repeated does exposure in bone marrow cells. In spermatocytes, Pb also induced chromosome damage in a dose dependent manner at 50–400 mg/kg after a single dose or repeated dose exposure in bone marrow cells. Pb induced SCE at 50 and 100 mg/kg. A lower dose was negative and higher doses were not done.	Fahmy (1999)
Pb acetate	200 or 400 mg/kg given by gavage daily for 5 days 5 animals per group Chromosome aberrations in bone marrow and spermatocytes.	Male Swiss Mice, 9–12 wks old	Calcium chloride (40 or 80 mg/kg by gavage daily for 3 days given 2 wks after Pb exposure)	Pb induced chromosome damage at both 200 and 400 mg/kg in bone marrow cells and spermatocytes. Calcium appeared to block this effect.	Aboul-Ela (2002)

Table AX5-6.4 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Laboratory Animal Studies.

Compound	Dose and Duration	Species	Co-exposure	Effects	Reference
Pb nitrate	100–200 mg/kg given i.v. on 9th day of gestation onwards for 9 days. Mothers and fetuses analyzed on G18. Group size not given. Resorptions, fetal viability and chromosome damage, SCE and NOR in the mother and fetus were examined. Mother–bone marrow; fetus liver or lung 3 mothers and fetuses per dose were analyzed.	ICR Swiss Webster Mice, 6–8 wk old	None	Pb levels were found in both mother and fetus indicating no problems crossing the placenta. All doses indicated increased resorption and decreased placental weights. No effects on fetal weight. Significant increase in SCE in mothers at 150 and 200 mg/kg. No increase in SCE in fetuses. Significant decrease in NOR in both mother and fetuses. No gaps or breaks in mothers or fetuses. Some weak aneuploidy at lowest dose. Some karyotypic chromosome damage was seen. No explanation of how many cells analyzed per animal (3 animals per dose were analyzed) as only 20– 40 cells were analyzed. There was no dose response and no statistical analyses for chromosome damage. No details on how many animals analyzed for metaphase damage or how many cells per animal. Data interpretation is also complicated as too few metaphases were analyzed 10–25 for SCE. Not given for CA. No detail on potential maternal toxicity.	Nayak et al. (1989b)
Pb nitrate	10, 20, or 40 mg/kg given i.p. 24 h 6 animals per group. Chromosome damage and Mitotic Index in bone marrow	Swiss Albino Mice, 8 wks old	Phyllanthus fruit extract (685 mg/kg) or ascorbic acid (16.66 mg/kg) given by gavage for 7 days	Pb nitrate increased the amount of chromosome damage at each dose. But there was no dose response and a similar level of damage was seen for each dose. Phyllanthus fruit extract reduced the amount of damage at each dose. Ascorbic acid reduced the damage at the lowest dose but increased it at the higher doses. Higher concentrations of Pb nitrate reduced the mitotic index. This effect was reversed by ascorbate and Phyllanthus only at the moderate dose.	Dhir et al. (1990)
Pb nitrate	5, 10, or 20 mg/kg given i.p. 24 h 6 animals per group. Chromosome damage in bone marrow. 50 metaphases per animal for a total of 300 (X6).	Swiss Albino Mice, 8 wks old	Ferric chloride (18 mg/kg) given i.p. for 24 h administered 1 h before, 1 h after, or together with Pb nitrate	Pb nitrate increased the amount of chromosome damage in a dose-dependent manner. Iron exhibited some modifications of Pb induced damage: If administered 1 h before Pb plus simultaneously it reduced the damage. If administered with Pb only at same time it reduced damage in the lower doses. If Pb was started 1 h before iron there was no effect. Thus iron may antagonize Pb perhaps by blocking uptake.	Dhir et al. (1992a)

Table AX5-6.4 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Laboratory Animal Studies.

Compound	Dose and Duration	Species	Co-exposure	Effects	Reference
Pb nitrate	5 or 10 mg/kg given by gavage for 24 h 6 animals per group. Chromosome aberrations in bone marrow	Swiss Albino Mice, 7–8 wks old	Zirconium oxychloride (110 or 220 mg/kg) given by gavage for 24 h administered 2 h before, 2 h after or together with Pb nitrate	Pb nitrate increased the amount of chromosome damage in a dose-associated manner. Zirconium induced a dose-associated increase in chromosome damage. Zirconium exhibited minimal modification of Pb nitrate-induced damage when administered 2 h before or after Pb nitrate. Administering the two together increased the damage.	Dhir et al. (1992b)
Pb nitrate	10, or 20 mg/kg given i.p. 48 h 12 animals per group. Micronucleus formation in bone marrow	Swiss Albino Mice, 6 wks old	Phyllanthus fruit extract (685 mg/kg) or ascorbic acid (16.66 mg/kg) given by gavage for 7 days	Pb nitrate increased the amount of micronuclei at both doses in a dose-associated manner. The 48 h recovery time was lower than 24 h but still elevated. Phyllanthus fruit extract reduced the amount of damage at both doses. Ascorbic acid reduced the damage at the lowest dose but increased it at the higher dose.	Roy et al. (1992)
Pb nitrate	10, 20, or 40 mg/kg given i.p. 24 h 5 animals per group. SCE in bone marrow	Swiss Albino Mice, 6–8 wks old	Phyllanthus fruit extract (685 mg/kg) or ascorbic acid (16.66 mg/kg) given by gavage for 7 days	Pb nitrate increased the amount of SCE in a dose-dependent manner. Pb nitrate had no effect of the proliferative rate index (consideration of metaphases in different division numbers) Phyllanthus fruit extract and ascorbic acid reduced the amount of damage at each dose.	Dhir et al. (1993)
Pb nitrate	0.625–80 mg/kg given i.p. for 12, 24 or 36 h 12 animals per group Micronucleus formation in bone marrow. 4000 erythorocytes scored per animal	Swiss Albino Mice, 6–8 wks old	None	Pb nitrate induced micronuclei but they did not increase with dose. Pb induced more micronuclei in males than in females. The ratio of polychromatic to normochromatic erythrocytes was elevated in Pb nitrate treated cells, but again did not increase with dose.	Jagetia and Aruna (1998)
Pb nitrate	0.7–89.6 mg/kg given by gavage for 24, 48, or 72 h, or 1 or 2 wks 5 animals per group. Cell viability by trypan blue Single strand breaks in white blood cells	Swiss Albino Mice, 4 wks old	None	Viability was high (92–96%) at all doses. Pb nitrate induced single strand breaks but they did not increase with dose. In fact the 3 highest doses were all similar in magnitude and less than the 5 lowest doses. The 5 lowest doses were also similar in magnitude.	Devi et al. (2000)

Table AX5-6.4 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Laboratory Animal Studies.

Compound	Dose and Duration	Species	Co-exposure	Effects	Reference
Pb acetate	10 mg/kg given by gavage 5 times a week for 4 wks. 10 animals per group Chromosome Aberrations with 20 metaphases scored per animal	Male Wistar rats, 30 days old	Cypermethrin	No effects on weight gain. Pb acetate induced an increase in aneuploidy, and the percent of cells with damage, but did not increase structural damage or alterations in organ weight. Cypermethrin and Pb together increased structural aberrations that were predominately acentric fragments. However, this was compared to untreated controls and not the individual treatments. Considering the individual treatments, the two together are less than additive.	Nehez et al. (2000)

Table AX5-6.5. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Human Cell Cultures Mutagenesis

Compound	Dose and Duration	Cell Type	Co-exposure	Effects	Reference
Pb acetate, In vitro	Cytotoxicity–tritium incorporation (0.1–100 μM/mL for 2–24 h) Mutagenesis–HPRT modified to labeling of 6-thioguanine resistant cells (0.1–100 μM/mL for 2–24 h)	Human Keratinocytes pooled in MEM and low calcium MEM + 2% FBS	None	Decrease in tritium incorporation at 10–100 μM/mL. 6 μM/L was selected as the concentration to study as tritium-incorporation was highest and greater than control. Tritium incorporation in the presence of 6-thioguanine (TG) was optimal after 4 h Pb acetate exposure and 5 days of expression time. It was concluded that the significant increase relative to control indicated mutations. The argument made was that because these cells are TG resistant they must be mutated. However, this argument was not proven by sequencing or colony formation in TG.	Ye (1993)
Pb acetate	Cytotoxicity (500–2,000 μM for 24 h) Mutagenicity–HPRT assay (500–2,000 μM for 24 h)	Human Foreskin Fibroblasts (Chinese) in DMEM +10% FCS	3-aminotriazole (3-AT) (80 mM to inhibit catalase)	LC50 = 500 μM. Cytotoxicity not affected by 3-AT. Pb acetate was not mutagenic. Mutagenicity not affected by 3-AT.	Hwua and Yang (1998)
Pb chromate	Mutagenicity as 6-thioguanine resistance (0.25–1 μM for 24 h)	Human Foreskin Fibroblasts In EMEM +15% FCS	None	Pb chromate was not mutagenic.	Biedermann and Landolph (1990)

Abbreviations

Medium and Components

MEM—Minimal Essential Medium;
DMEM—Dulbecco's Minimal Essential Medium;
EMEM—Eagle's Minimal Essential Medium;
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.6. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Human Cell Cultures Clastogenicity

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb chromate	Chromosome aberrations (0.08–2 μg/cm^2 for 24 h)	Human Foreskin Fibroblasts (Caucasian) in EMEM + 15% FBS	None	Pb chromate induced chromosome damage in a concentration dependent manner. This study was focused on chromate.	Wise et al. (1992)
Pb chromate	Chromosome aberrations (0.1–5 μg/cm^2 for 24 h)	Primary Human Lung Cells in DMEM/F12 + 15% FBS	None	Pb chromate induced chromosome damage in a concentration dependent manner. This study was focused on chromate.	Wise et al. (2002)
Pb chromate	Chromosome aberrations (0.1–5 μg/cm^2 for 24 h)	Primary Human Lung Cells and WTHBF-6—human lung cells with hTERT in DMEM/F12 + 15% FBS	None	Pb chromate induced chromosome damage in a concentration dependent manner. Effects were similar in both cell types establishing the WTHBF-6 cells as a useful model. This study was focused on chromate.	Wise et al., (2004a)
Pb chromate	Chromosome aberrations (0.1–5 μg/cm^2 for 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 15% CCS	Vitamin C (2 mM co-exposure for 24 h)	Pb chromate induced chromosome damage in a concentration dependent manner. Vitamin C blocked Cr ion uptake and the chromosome damage after Pb chromate exposure. This study was focused on chromate.	Xie et al. (2004)
Pb chromate	Chromosome aberrations (0.05–5 μg/cm^2 for 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 15% CCS	Vitamin C (2 mM co-exposure for 24 h)	Pb chromate induced chromosome damage in a concentration dependent manner. This study was focused on showing chromate and not Pb ions were the clastogenic species.	Wise et al. (2004b)
Pb chromate	Chromosome aberrations (0.05–5 μg/cm^2 for 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 15% CCS	None	Pb chromate induced chromosome damage in a concentration dependent manner. This study was focused on comparing particulate chromate compounds.	Wise et al. (2005)

Table AX5-6.6 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Human Cell Cultures Clastogenicity

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb glutamate	Pb ion uptake–ICPMS (250–2,000 µM for 24 h) Chromosome Aberrations (250–2,000 µM for 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 15% CCS	None	Pb glutamate induced a concentration-dependent increase in intracellular Pb ions. Pb glutamate did not induce chromosome damage.	Wise et al. (2005)
Pb glutamate	Pb ion uptake–ICPMS (250–2,000 µM for 24 h) Mitotic Index (250–2,000 µM for 24 h) Growth Curve (250–2,000 µM for 24 h) Cell cycle Analysis (250–2,000 µM for 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 15% CCS	None	Pb glutamate induced a concentration-dependent increase in intracellular Pb ions. Pb glutamate increased the mitotic index, but inhibited growth and did not induce chromosome damage.	
Radioactive Pb ions No further specification	LET = 13,600keV/µM Fluence of 2×10^6 particles/ cm^2 Chromosome Aberrations	Human Foreskin Fibroblasts in DF-12 + 10% FCS	None	Pb induced chromosome damage that recurred with time and cell passaging. Analysis limited to ~25 metaphases. Focused on radioactive effects of Pb	Martins et al. (1993)

Abbreviations
hTERT is the catalytic subunit of human telomerase

Medium and Components
EMEM—Eagle's Minimal Essential Medium
DMEM/F12—Dulbecco's Minimal Essential Medium/Ham's F12
CCS—Cosmic Calf Serum
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.7. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Human Cell Cultures DNA Damage

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	DNA strand breaks as nucleiod sedimentation (500 μM for 20–25 h)	HeLa Cells in AMEM + 5% FBS	None See also Table AX5-6.16	Pb acetate alone did not induce single strand breaks.	Hartwig et al. (1990)
Pb acetate	DNA strand breaks as nucleoid sedimentation assay (100 μM for 30 min–4 h)	HeLa Cells in HEPES/ glucose buffer	Buthionine sulfoximine (BSO) to deplete cells of thiols	Pb acetate did not induce DNA strand breaks.	Snyder and Lachmann (1989)
Pb chromate	DNA adducts (0.4–0.8 μg/cm^2 for 24 h)	Primary Human Small Airway Cells in Clonetics growth medium	None	Pb chromate induced Pb inclusion bodies and Cr-DNA adducts and Pb-DNA adducts in a concentration-dependent manner.	Singh et al. (1999)
Pb chromate	DNA double strand breaks (0.1–5 μg/cm^2 for 24 h) by Comet assay and H2A.X foci formation	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 15% CCS	None	Pb chromate induced DNA double strand breaks in a concentration dependent manner. This study showed the damage was due to chromate and not Pb.	Xie et al. (2005)
Pb acetate	DNA strand breaks and DNA protein crosslinks and oxidative lesions by comet assay (1–100 μM for 1 h)	Primary lymphocytes in RPMI 1640 without serum	Vitamins A (10 μM), C (10 μM), E (25 μM), calcium chloride (100 μM) magnesium chloride (100 μM) or zinc chloride (100 μM)	Pb acetate induced an increase in DNA single strand breaks at 1 μM that went down with increasing dose. The highest concentration was significantly less than the damage in untreated controls. For double strand breaks, all concentrations had more damage than the controls, but there was less damage in the highest concentrations than the two lower ones. Pb only induced a slight increase in the amount of DNA-protein crosslinks at the highest concentration. Co-exposure to magnesium had no effect. Co-exposure to vitamins A, C, and E or zinc exacerbated the DNA single strand break effects at the highest concentration. Co-exposure to calcium exacerbated the single strand break effect at all concentrations.	Woźniak and Blasiak (2003)

Table AX5-6.7 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Human Cell Cultures DNA Damage

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb nitrate	DNA-protein crosslinks by SDS precipitation (1–10 mM for 6 h)	Human Burkitt's lymphoma cells–EBV transformed in RPMI 1640 + 10% FCS	None	Pb nitrate did not induced DNA protein crosslinks. Independent samples were analyzed by 5 different laboratories.	Costa et al. (1996)

Abbreviations
hTERT is the catalytic subunit of human telomerase.

Medium and Components
AMEM—Alpha Minimal Essential Medium;
EMEM—Eagle's Minimal Essential Medium;
DMEM/F12—Dulbecco's Minimal Essential Medium/Ham's F12;
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.8. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Animal Cell Cultures Mutagenicity

Compound	Assay and Duration	Cell Type	Co-exposure	Effects	Reference
Pb acetate	Cytotoxicity (1–25 μM for 24 h) Mutagenesis—HPRT (0.5–5 μM for 44 h)	V79 in AMEM + 10% FBS	None See also Table AX5-6.16	LC50 = 3 μM Pb acetate alone was not mutagenic.	Hartwig et al. (1990)
Pb acetate —insoluble precipitate at high dose.	Cytotoxicity (0.5–2000 μM for 5 days) Mutagenesis—gpt (0.5–1700 μM for 5 days)	G12–CHV79 cells with 1 copy gpt gene in Ham's F12 + 5% FBS	See also Table AX5-6.17	LC50 = 1700 μM Pb acetate was mutagenic, but only at toxic concentration (1700 μM) where precipitate formed not at lower concentrations (500 or 1000 μM). There were no statistical analyses of these data.	Roy and Rossman (1992)
Pb chloride	Cytotoxicity (0.1–1 μM for 1 h) Mutagenicity—gpt assay (0.1–1 μM for 1 h)	AS52-CHO-gpt, lack hprt in HBSS followed by Ham's F12 + 5% FBS	None	LC74 = 1 μM (maximum concentration tested) Pb chloride induced a dose-dependent increase in the number of 6 thioguanine resistant mutants. Did not adjust and compare as previous studies.	Ariza et al. (1996)
Pb chloride	Cytotoxicity (0.1–1 μM for 1 h) Mutagenicity—gpt assay (0.1–1 μM for 1 h)	AS52-CHO-gpt, lack hprt in HBSS followed by Ham's F12 + 5% FBS	Allopurinol (50 μM) to inhibit xanthine oxidase	LC74 = 1 μM. Allopurinol had no effect on cytotoxicity. Pb chloride was mutagenic (0.8 and 1 μM). Allopurinol reduced mutagenesis.	Ariza et al. (1998)
Pb chloride	Mutagenicity—gpt assay (0.1–1 μM for 1 h) PCR/Southern to analyze mutants for sequence	AS52-CHO-gpt, lack hprt in HBSS followed by Ham's F12 + 5% FBS	None	Pb chloride (0.1–0.4 μM) caused mostly point mutations. Higher concentrations (0.5–1 μM) caused more deletions. There were no statistical analyses of these data. Usually examined fewer mutations than control.	Ariza and Williams (1999)
Pb chromate	Cytotoxicity (10–100 μM for 24 h) HGPRT assay (10–100 μM for 24 h)	V79 CHL–HPRT low clone in MEM + 10% FCS	NTA	Mutagenesis was assessed with HGPRT assay. Pb chromate was not mutagenic. Co-exposure to NTA caused Pb chromate to become mutagenic through increased solubilization. This mutagenic effect was completely attributed to the Cr(VI) ions.	Celotti et al. (1987)
Pb chromate	Mutagenicity as Sodium/potassium ATPase (ouabain resistance) or 6-thioguanine resistance (25–100 μM for 5 h)	C3H10T1/2 cells in EMEM + 10% FBS	None	Pb chromate was not mutagenic.	Patierno et al. (1988) and Patierno and Landolph (1989) (both papers present the same data)

Table AX5-6.8 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Animal Cell Cultures Mutagenicity

Compound	Assay and Duration	Cell Type	Co-exposure	Effects	Reference
Pb nitrate Precipitate at 1000 µM and higher.	Cytotoxicity (50–5,000 µM for 5 days) Mutagenesis at HPRT locus (50–2,000 µM for 5 days)	V79 CHL–HPRT low clone in Ham's F12 +10% FBS	None	LC50 = 2950 µM Pb nitrate was mutagenic at 500 µM, but there was no dose response as higher doses less mutagenic though still 2–4-fold higher. There were no statistical analyses of these data.	Zelikoff et al. (1988)
Pb nitrate -no insoluble precipitate	Cytotoxicity (0.5–2000 µM for 5 days) Mutagenesis—gpt (0.5–1700 µM for 5 days)	G12–CHV79 cells with 1 copy gpt gene in Ham's F12 + 5% FBS	See also Table AX5-6.17	LC 50 = 1500 µM Pb nitrate was not mutagenic. There were no statistical analyses of these data.	Roy and Rossman (1992)
Pb sulfide	Cytotoxicity (100–1,000 µM for 24 h) Mutagenicity at HPRT locus (100–1,000 µM for 24 h)	V79 CHL–HPRT low clone in Ham's F12 +10% FBS	None	LC50 = 580 µM; did not increase with longer exposures. Mutagenic at 376 and 563 µM. Not mutagenic lower or higher. Suggested cytotoxicity prevented mutagenesis at higher concentrations. There were no statistical analyses of these data.	Zelikoff et al. (1988)

Abbreviations

V79 are a Chinese Hamster Lung Cell Line;
G12–CHV79 are derived from V79;
CHO are a Chinese Hamster Ovary Cell Line ;
AS52 are derived from CHO;
C3H10T/12 cells are a mouse embryo cell line

Medium and Components
AMEM—Alpha Minimal Essential Medium;
EMEM—Eagle's Minimal Essential Medium;
HBSS—Hank's Balanced Salt Solution
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.9. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Animal Cell Cultures Clastogenicity

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb chromate	Chromosome Aberrations (0.4–8 μg/cm^2 for 24 h)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	None	Pb chromate induced chromosome damage in a concentration dependent manner. This study was focused on chromate.	Wise et al. (1992)
Pb chromate	Chromosome Aberrations (0.8–8 μg/cm^2 for 24 h)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	Vitamin C (1 mM for 24 h as co-exposure to block Cr uptake)	Pb chromate induced chromosome damage in a concentration dependent manner. This effect and uptake of Cr ions were blocked by vitamin C. This study was focused on chromate.	Wise et al. (1993)
Pb chromate	Chromosome Aberrations (0.8 or 8 μg/cm^2 for 24 h)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	Vitamin E (25 μM as pretreatment for 24 h)	Pb chromate induced chromosome damage in a concentration dependent manner. Vitamin E blocked clastogenic activity of Pb chromate, but had no effect on other Pb compounds. This study found that the chromosome damage was mediated by chromate ions and not Pb ions	Wise et al. (1994)
Pb chromate	Chromosome Aberrations (0.8–8 μg/cm^2 for 24 h)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	Vitamin C (1 mM as pretreatment for 24 h) Vitamin E (25 μM as pretreatment for 24 h)	Pb chromate induced chromosome damage in a concentration dependent manner. Vitamins C and E blocked clastogenic activity of Pb chromate. This study was focused on chromate.	Blankenship et al. (1997)
Pb glutamate	Chromosome Aberrations (500–2,000 μM for 24 h)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	Vitamin E (25 μM as pretreatment for 24 h)	Pb glutamate induced chromosome damage at 1 mM but not at higher or lower concentrations. Vitamin E did not modify this effect.	Wise et al. (1994)
Pb nitrate	Chromosome Aberrations (500–2,000 μM for 24 h) Insoluble precipitate at all concentrations	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	Vitamin E (25 μM as pretreatment for 24 h)	Pb nitrate did not induce chromosome damage.	Wise et al. (1994)
Pb nitrate	Chromosome Aberrations (3–30 μM for 2 h +16 h recovery)	Chinese Hamster Ovary cells in EMEM + 10% FBS	None	Pb nitrate did not induce chromosome damage.	Lin et al. (1994)
Pb nitrate	Chromosome aberrations (0.05–1 μM for 3–12 h)	Chinese Hamster Ovary AA8 cells in DMEM +10% NCS	Crown ethers to modify effect through chelation and uptake	Pb nitrate did not induce chromosome damage.	Cai and Arenaz (1998)

Table AX5-6.9 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Animal Cell Cultures Clastogenicity

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	SCE (1–10 μM for 26 h+)	V79 in AMEM + 10% FBS	None See also Table AX5-6.17	Pb acetate alone did not induce SCE. Only 25 cells per treatment analyzed.	Hartwig et al. (1990)
Pb acetate	Micronucleus assay (0.01–10 μM for 18 h)	Chinese Hamster V79 cells in DMEM + 10% FCS	None	Pb acetate induced an increase in micronuclei that increased with concentration and reached a plateau. Two experiments were done and presented separately as a Figure and a Table. The magnitude of the effects was small to modest and statistics were not done.	Bonacker et al. (2005)
Pb nitrate	SCE Formation (500–3,000 μM for 24 h) Precipitate at 1000 μM and higher.	V79 CHL–HPRT low clone in Ham's F12 +10% FBS	None	No SCE. Only 30 cells analyzed per treatment.	Zelikoff et al. (1988)
Pb nitrate	Micronucleus formation (3–30 μM for 2 h +16 h recovery) SCE (3–30 μM for 2 h +16 h recovery)	CHO cells in EMEM + 10% FBS	None	Pb nitrate did not induce micronuclei formation Pb nitrate induces a concentration-dependent increase in SCE (3, 10, 30 μM).	Lin et al. (1994)
Pb nitrate	SCE (0.05–1 μM for 3–12 h)	CHO AA8 in DMEM +10% NCS	Crown ethers to modify effect through chelation and uptake	Pb nitrate caused a weak concentration-dependent increase in SCE. These data were not statistically analyzed. The effect was reduced by a crown ether probably because a similar reduction was seen in spontaneous SCE.	Cai and Arenaz (1998)

Table AX5-6.9 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Animal Cell Cultures Clastogenicity

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb sulfide	SCE Formation (100–1,000 μM for 24 h)	V79 CHL–HPRT low clone in Ham's F12 +10% FBS	None	No SCE. Only 30 cells analyzed per treatment.	Zelikoff et al. (1988)

Abbreviations
V79 are a Chinese Hamster Lung Cell Line;
CHO are a Chinese Hamster Ovary Cell Line ;
Medium and Components
AMEM—Alpha Minimal Essential Medium;
DMEM—Dulbecco's Minimal Essential Medium;
EMEM—Eagle's Minimal Essential Medium;
HBSS—Hank's Balanced Salt Solution
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum
NCS—Newborn Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.10. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Animal Cell Cultures DNA Damage

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	DNA damage as alkaline elution (exposure time and dose not given) Precipitate at 1000 μM and higher.	V79 CHL–HPRT low clone in Ham's F12 +10% FBS	None	No DNA damage (Single strand breaks, DNA-protein crosslinks or DNA-DNA crosslinks). However, the data was not shown	Zelikoff et al. (1988)
Pb acetate	DNA strand breaks as nick translation (1700 μM for 5 days) Or supercoiled relaxation (1000 μM for 5 days) Insoluble precipitate at high dose.	G12–CHV79 cells with 1 copy gpt gene in Ham's F12 + 5% FBS	See also Table AX5-6.17	Pb acetate did not induce SSB. Pb acetate (1700 μM) did increase nick translation when an exogenous polymerase was added. There were no statistical analyses of these data.	Roy and Rossman (1992)
Pb chromate	DNA damage as alkaline elution (0.4–8 $\mu g/cm^2$ for 24 h plus 24 recovery)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	None	Pb chromate induced DNA single strand breaks in a concentration dependent manner, which were all repaired by 24 h post-treatment. Pb chromate induced DNA protein crosslinks in a concentration dependent manner, which persisted at 24 h post-treatment. Pb chromate did not induce DNA-DNA crosslinks. This study was focused on chromate.	Xu et al. (1992)
Pb chromate	DNA adducts (0.8 or 8 $\mu g/cm^2$ for 24 h)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	Vitamin C (1 mM as pretreatment for 24 h) Vitamin E (25 μM as pretreatment for 24 h)	Pb chromate induced DNA adducts in a concentration dependent manner. Vitamins C and E blocked DNA adducts induced by Pb chromate. This study was focused on chromate.	Blankenship et al. (1997)
Pb nitrate	DNA Protein Crosslinks as SDS precipitation (50–5,000 μM for 4 h)	Novikoff ascites hepatoma cells	None	Pb nitrate induced DNA protein crosslinks in a concentration dependent manner.	Wedrychowski et al. (1986)

Table AX5-6.10 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Animal Cell Cultures DNA Damage

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb nitrate	DNA strand breaks as nick translation (1700 μM for 5 days)	G12–CHV79 cells with 1 copy gpt gene in Ham's F12 + 5% FBS	See also Table AX5-6.17	Pb nitrate (1700 μM) did increase nick translation when an exogenous polymerase was added. There were no statistical analyses of these data.	Roy and Rossman (1992)

Abbreviations

G12–CHV79 are derived from V79;
V79 are a Chinese Hamster Lung Cell Line;
CHO are a Chinese Hamster Ovary Cell Line ;

Medium and Components
AMEM—Alpha Minimal Essential Medium;
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.11. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity Non-mammalian Cultures

Compound	Assay and Concentration	Cell Type	Co-exposure	Effects	Reference
Pb chromate (and 13 pigments containing Pb chromate)	Mutation Frequency (50–500 µg/plate) Anchorage Independence for cells isolated during morphological transformation Neoplastic Transformation for cells isolated during morphological transformation	Salmonella typhimurium +/- S9 fraction	Nitrilotriacetic acid (NTA to dissolve insoluble compounds) and Silica Encapsulation	Pb chromate and its related pigments did not induce mutagenicity. A few did when dissolved in NTA. Encapsulation prevented mutagenesis in those that were positive when dissolved in NTA. S9 had no effect. Studied as a chromate compound.	Connor and Pier (1990)

Table AX5-6.12. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity as it Pertains to Potential Developmental Effects

Compound	Assay and Concentration	Species	Co-exposure	Effects	Reference
Pb acetate	25–400 mg/kg given i.p as single injection and animals studied after 24 h Sperm morphology	Male Swiss Mice—9–12 wks old	None	Pb induced sperm head abnormalities at 50–100 mg/kg. A lower dose was negative and higher doses were not done.	Fahmy (1999)
Pb acetate	200 or 400 mg/kg given by gavage daily for 5 days 5 animals per group Sperm Morphology	Male Swiss Mice—9–12 wks old	Calcium chloride (40 or 80 mg/kg by gavage daily for 3 days given 2 wks after Pb exposure)	Pb induced sperm abnormalities at 200 and 400 mg/kg. A lower dose was negative and higher doses were not done. Calcium appeared to block this effect.	Aboul-Ela (2002)

Table AX5-6.13. Genotoxic/Carcinogenic Effects of Lead—Genotoxicity as it Pertains to Potential Developmental Effects—Children

Compound	Exposure Regimen	Species	Co-exposure	Effects	Reference
Pb chloride	Administered in drinking water 1.33 g/L for 6 wks	Male NMRI Mice—9 wks old	Cyclophosphamide—120 mg/kg b.w. given i.p 7 days prior to start of breeding	Pb did not increase resorptions indicating no dominant lethal mutagenic effect. Pb appeared to have a small, but statistically insignificant reduction in the number of resorptions. Cyclophosphamide reduced live implants in female mice.	Kristensen et al. (1993).
Pb nitrate	12.5–75 mg/kg given i.v. on 9th day of gestation for 9 days. Mothers and fetuses analyzed on G18. 5 animals per group Resorptions, fetal viability, and chromosome damage in the mother and fetus were examined.	ICR Swiss Webster Mice—6–8 wks old	None	12.5–50 mg/kg had no effect on resorption or fetal viability. 75 mg/kg demonstrated some increased resorption though statistics were not done. No chromosome damage was seen in untreated controls. A low level 1-3 and 2-5 aberrations were seen in mothers and fetuses respectively. There was no dose response and no statistical analyses. Data interpretation is also complicated as too few metaphases were analyzed 20–40 total. No descriptions of potential effects on maternal health parameters or fetal weights. No indication of how many animals included in the chromosomal analysis.	Nayak et al. (1989a)
Pb nitrate	100–200 mg/kg given i.v. on 9th day of gestation for 9 days. Mothers and fetuses analyzed on G18. Group size not given. Resorptions, fetal viability and chromosome damage, SCE and NOR in the mother and fetus were examined. Mother–bone marrow; fetus liver or lung 3 mothers and fetuses per dose were analyzed.	ICR Swiss Webster Mice—6–8 wks old	None	Pb levels were found in both mother and fetus indicating no problems crossing the placenta. All doses indicated increased resorption and decreased placental weights. No effects on fetal weight. Significant increase in SCE in mothers at 150 and 200 mg/kg. No increase in SCE in fetuses. Significant decrease in NOR in both mother and fetuses. No gaps or breaks in mothers or fetuses. Some weak aneuploidy at lowest dose. Some karyotypic chromosome damage was seen. No explanation of how many cells analyzed per animal (3 animals per dose were analyzed) as only 20–40 cells were analyzed. There was no dose response and no statistical analyses for chromosome damage. No details on how many animals analyzed for metaphase damage or how many cells per animal. Data interpretation is also complicated as too few metaphases were analyzed 10–25 for SCE. Not given for CA. No detail on potential maternal toxicity.	Nayak et al. (1989b)

Table AX5-6.14. Genotoxic/Carcinogenic Effects of Lead—Epigenetic Effects and Mixture Interactions—Animal

Compound	Exposure Regimen	Species	Co-exposure	Effects	Reference
Pb acetate	Administered as an i.p. injection of 100 µl/kg. Animals were studied either 24 h after a daily dose for 3 days or for various times (5 min–48 h) after a single dose.	Male Wistar Rats—10 wks old	Actinomycin D (0.8 mg/kg) administered i.p. for 4 h before a single dose of Pb acetate.	Pb acetate induced GST-P, which required the cis element, GPEI (GST-P enhancer I). Actinomycin D blocked the effects indicating that regulation was at the mRNA level. Pb acetate induced c-jun, which exhibited three peaks of exposure over 48 h. Pb acetate was more potent than Pb nitrate.	Suzuki et al. (1996)
Pb nitrate	Administered as an i.p. injection of 100 µmol/kg. Animals were studied either 24 h after a daily dose for 3 days or for various times (5 min–48 h) after a single dose.	Male Wistar Rats—10 wks old	Actinomycin D (0.8 mg/kg) administered i.p. for 4 h before a single dose of Pb acetate.	Pb nitrate induced GST-P, which required the cis element, GPEI (GST-P enhancer I). Actinomycin D blocked the effects indicating that regulation was the mRNA level. Pb nitrate induced c-jun, which exhibited three peaks of exposure over 48 h. Pb nitrate was less potent than Pb acetate.	Suzuki et al. (1996)
Pb nitrate	Administered as an i.p. injection of 100 µmol/kg. Some rats were partially hepatectomized. Animals were studied 48 h after injection.	Male Sprague Dawley rats	Partial Hepatectomy	Pb nitrate induced GSH and GST 7-7 activity. Partial hepatectomy did not induce GSH or GST 7-7.	Dock (1989)
Pb nitrate	Administered as an i.v. injection of 20, 50, or 100 µmol/kg. Animals were studied 24 h after injection.	Male Fisher 344 rats—7 wks old	2-methoxy-4-aminobenzene to induce P4501A2 or 3-methylcholanthrene to induce 4501A1	Pb nitrate selectively inhibited P4501A2 and its induction by 2-methoxy-4-aminobenzene at the mRNA and protein level in a dose-dependent manner. Pb nitrate had minimal effect on P4501A1 and its induction by 3-methyl cholanthrene. Pb nitrate did not affect microsomal activity. Pb nitrate induced GST-P in a dose-dependent manner.	Degawa et al. (1993)

Table AX5-6.15. Genotoxic/Carcinogenic Effects of Lead—Epigenetic Effects and Mixture Interactions—Human

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	Tyrosine aminotransferase expression and activity (0.3–10 μM for 24–48 h) PKC activity: 10 μM for 48 h	H4-IIE-C3—human hepatoma cells in DMEM + 2.5% FCS	Dexamethasone (0.1 μM for 16 h), or calcium chloride (10 μM) or genistein (100 μM to block PKC activity)	Pb acetate inhibited glucocorticoid –induction of tyrosine aminotransferase in a time- and dose-dependent manner. Co-treatment with calcium reduced the effects of Pb. Co-treatment with genistein increased the effects of Pb. Pb acetate decreases PKC activity and its translocation from the cytosol to the particulate cellular fraction.	Tonner and Heiman (1997)
Pb nitrate	EROD/MROD activity (10–100 μM for 24 h) NAD(P)H: quinone oxidoreductase activity (10–100 μM for 24 h) Glutathione-S-transferase Ya activity (10–100 μM for 24 h)	Hepa 1c1c7 wild type cells in DMEM + 10% FBS	TCDD (0.1 nM), 3-methyl cholanthrene (0.25 μM), beta-naptflavone (10 μM), benzo(a)pyrene (1 μM)	Pb did not affect EROD/MROD activity. Pb reduced CYP1A1 induction by TCDD, 3-methyl cholanthrene, beta-naptflavone, benzo(a)pyrene. Pb increased NAD(P)H: quinone oxidoreductase activity Pb increased NAD(P)H: quinone oxidoreductase activity induction by TCDD, 3-methyl cholanthrene, beta-naptflavone, benzo(a)pyrene. 10 μM increased Glutathione-S-transferase Ya activity. 25 and 100 μM increased Glutathione-S-transferase Ya activity. Pb nitrate did not affect Glutathione-S-transferase Ya induction by TCDD, 3-methyl cholanthrene, beta-naptflavone, benzo(a)pyrene.	Korashy and El-Kadi (2004)
Pb nitrate	NAD(P)H: quinone oxidoreductase activity (25 μM for 24 h) Glutathione-S-transferase Ya activity (25 μM for 24 h)	C12- AHR-deficient Hepa 1c1c7 cells in DMEM + 10% FBS	TCDD (0.1 nM), 3-methyl cholanthrene (0.25 μM), beta-naptflavone (10 μM), benzo(a)pyrene (1 μM)	Pb nitrate did not increase NAD(P)H: quinone oxidoreductase and Glutathione-S-transferase Ya activity Pb increased NAD(P)H: quinone oxidoreductase activity induction by TCDD, 3-methyl cholanthrene, beta-naptflavone, benzo(a)pyrene. Pb did not affect Glutathione-S-transferase Ya induction by TCDD, 3-methyl cholanthrene, beta-naptflavone, benzo(a)pyrene.	Korashy and El Kadi (2004)

Abbreviations

Medium and Components

DMEM—Dulbecco's Minimal Essential Medium;
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.16. Genotoxic/Carcinogenic Effects of Lead—Epigenetic Effects and Mixture Interactions—DNA Repair—Human

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	DNA strand breaks as nucleoid sedimentation (500 µM for 20–25 h)	HeLa Cells in AMEM + 5% FBS	UV (5 J/m^2)	Pb acetate alone did not induce single strand breaks. UV did induce strand breaks. Co-exposure of Pb and UV cause DNA strand breaks to persist longer suggesting an inhibition of repair.	Hartwig et al. (1990)

Abbreviations
Medium and Components
AMEM—Alpha Minimal Essential Medium;
FBS—Fetal Bovine Serum

Table AX5-6.17. Genotoxic/Carcinogenic Effects of Lead—Epigenetic Effects and Mixture Interactions—DNA Repair—Animal

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	Cytotoxicity (0.5–5 μM for 24 h) Mutagenesis—HPRT (0.5–5 μM for 44h) SCE (1–10 μM for 26 h+)	V79 in AMEM + 10% FBS	UV (5 J/m^2)	Pb acetate (3 and 5 μM) increased UV-induced increased cytotoxicity with no dose response (plateau). There were no statistical analyses of these data. Pb acetate (0.5–5 μM) increased UV mutagenicity though with no dose response (plateau). There were no statistical analyses of these data Pb acetate (1–10 μM) increased UV-induced SCE. Significant at $p < 0.01$. Only 25 cells per treatment analyzed.	Hartwig et al. (1990)
Pb acetate	Mutagenesis—gpt (0.5–1700 mM for 24 h) DNA strand breaks as supercoiled relaxation (1000 mM for 24 h)	G12–CHV79 cells with 1 copy gpt gene in Ham's F12 + 5% FBS	UV (2 J/m^2), or MNNG (0.5 μg/L)	Pb acetate was co-mutagenic with UV and MNNG increasing frequency 2-fold. Pb acetate does not increase strand breaks induced by UV.	Roy and Rossman (1992)

Abbreviations

G12–CHV79 are derived from V79;
V79 are a Chinese Hamster Lung Cell Line;

Medium and Components
AMEM—Alpha Minimal Essential Medium;
FBS—Fetal Bovine Serum

Table AX5-6.18. Genotoxic/Carcinogenic Effects of Lead—Mitogenesis—Animal

Compound	Exposure Regimen	Species	Co-exposure	Effects	Reference
Pb acetate	Administered Pb acetate (12.5 mg/kg) i.p. Animals studied 24 h after injection.	Male B6 Mice	None	Pb acetate induced TNF-alpha in glial and neuronal cells in the cerebral cortex and subcortical white matter and on Purkinje cells in the cerebellum, but did not induced apoptosis in these areas	Cheng et al. (2002)
Pb nitrate	Liver initiation induced by the resistant hepatocyte model Initiation followed by i.v. injection of Pb nitrate (100 μM/kg) or partial hepatectomy Studied DNA synthesis (30 h after injection) and preneoplastic nodule formation (5 wks after injection)	Male Wistar Rats—4 per group	Partial Hepatectomy	Pb nitrate stimulated DNA synthesis and liver cell proliferation Pb nitrate did not induce preneoplastic nodule. Partial hepatectomy did.	Columbano et al. (1987)
Pb nitrate	Liver initiation induced by the resistant hepatocyte model (diethylnitrosamine followed by 2-acetylaminofluorene plus carbon tetrachloride) Initiation followed by i.v. injection of 4 doses of Pb nitrate (100 μM/kg) given once every 20 days or partial hepatectomy, ethylene dibromide, or nafenopine Animal were evaluated for preneoplastic foci at 75 or 155 days after initiation.	Male Wistar Rats—4 per group	Diethylnitrosamine	Pb nitrate, partial hepatectomy, ethylene dibromide, or nafenopine all stimulated DNA synthesis and liver cell proliferation Pb nitrate, ethylene dibromide, or nafenopine did not induce preneoplastic nodule. Partial hepatectomy did.	Columbano et al. (1990)
Pb nitrate	Liver initiation induced by the orotic acid model (diethylnitrosamine plus orotic acid) Initiation followed by i.v. injection of Pb nitrate (100 μM/kg) or partial hepatectomy, or by gavage: ethylene dibromide, or cyproterone DNA synthesis was examined at various time intervals (24 h–5 days) after injection.	Male Wistar Rats—4 per group	Diethylnitrosamine	Pb nitrate, partial hepatectomy, ethylene dibromide, or cyproterone all stimulated DNA synthesis within 30 min. Pb nitrate induced DNA synthesis for 5 days.	Coni et al. (1992)

Table AX5-6.18 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Mitogenesis—Animal

Compound	Exposure Regimen	Species	Co-exposure	Effects	Reference
Pb nitrate	Liver initiation induced by the resistant hepatocyte model (diethylnitrosamine followed by 2-acetylaminofluorene plus carbon tetrachloride) or the phenobarbital model (diethylnitrosamine plus orotic acid), or the orotic acid model (diethylnitrosamine plus orotic acid) Initiation followed by i.v. injection of Pb nitrate (100 μM/kg) or partial hepatectomy, or carbon tetrachloride by gavage Animals were studied 6 wks after initiation.	Male Wistar rats—4 per group	Partial Hepatectomy, carbon tetrachloride	Pb nitrate, partial hepatectomy, carbon tetrachloride all stimulated DNA synthesis and liver cell proliferation Pb nitrate, did not induce preneoplastic nodules. Partial hepatectomy and carbon tetrachloride did.	Ledda-Columbano et al. (1992)
Pb nitrate	Liver initiation induced by the resistant hepatocyte model (diethylnitrosamine followed by 2-acetylaminofluorene plus carbon tetrachloride) Initiation followed by i.v. injection of Pb nitrate (100 μM/kg) or partial hepatectomy, or by gavage: ethylene dibromide, or cyproterone, or nafenopine Also tried either 1 or 2 additional i.v. injections of Pb over 3-day intervals. Animals were studied at various intervals (1–6 days) after injection	Male Wistar rats—4 per group	Diethylnitrosamine, 2-AAF	This study aimed to determine if mitogens induce nodules at different time points. Pb nitrate, ethylene dibromide, cyproterone, or nafenopine did not induce preneoplastic nodules at all. Partial hepatectomy did within 3 days. Multiple injections of Pb nitrate did not induce preneoplastic lesions.	Coni et al. (1993)
Pb nitrate	Administered as i.v. injection of Pb nitrate (100 μM/kg) or partial hepatectomy, or by gavage: carbon tetrachloride, or ethylene dibromide, or cyproterone, or nafenopine Animals were studied at various time intervals (0.25–24 h) after injection.	Male Wistar rats—4 per group	Partial Hepatectomy, carbon tetrachloride	Pb nitrate, ethylene dibromide, cyproterone, or nafenopine induced c-jun and c-myc but did not induce c-fos. Partial hepatectomy and carbon tetrachloride induced c-jun, c-fos, and c-myc.	Coni et al. (1993)
Pb nitrate	Administered as i.v. injection of Pb nitrate (100 μM/kg) or partial hepatectomy, or nafenopine by gavage. Animals were studied at various time intervals (24–96 h) after injection.	Male Wistar rats—4 per group, 8 wks old	None	Pb nitrate induced a high incidence of polyploidy and binucleated cells. These changes were irreversible after 2 wks. Many of these cells were the newly synthesized cells. Partial hepatectomy and carbon tetrachloride induced tetraploid and octaploid mononucleated cells.	Melchiorri et al. (1993)
Pb nitrate	Administered as i.v. injection of Pb nitrate (10 μM/100 g) Studies for apoptosis at 12, 24, 36, 48, 72, 96, 120, 168, 336 h after injection	Male Wistar rats—4 rats per group	None	Liver weight increased until day 5 then returned to control levels. DNA synthesis peaked at 36 h Apoptosis peaked at day 4 and then decreased gradually.	Nakajima et al. (1995)

Table AX5-6.18 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Mitogenesis—Animal

Compound	Exposure Regimen	Species	Co-exposure	Effects	Reference
Pb nitrate	Administered as i.v. injection of Pb nitrate (100 μM/kg) or TNF-alpha. Animals were studied at various time intervals (12–48 h) after injection.	Male Wistar Rats—4 per group, 5–6 wks old	None	Pb nitrate and TNF-alpha induced similar proliferative responses.	Shinozuka et al. (1996)
Pb nitrate	Administered after diethylnitrosamine (200 mg/kg given i.p) as i.v. injection of Pb nitrate (100 μM/kg) or instead carbon tetrachloride by gavage Animals were studied at various time intervals (3–21 days) after injection.	Male Wistar Rats—4 per group	Carbon tetrachloride	Pb nitrate induced apoptosis affects both newly synthesized cells and non-replicative cells. Pb nitrate decreased the number and had no effect on the size of placental glutathione-S-transferase lesions. Carbon tetrachloride substantially increased these lesions both in number and in size.	Columbano et al. (1996)
Pb nitrate	Administered as i.v. injection of Pb nitrate (100 μM/kg) or partial hepatectomy, or by gavage: carbon tetrachloride, or cyproterone, or nafenopine Animals were studied at various time intervals (0.5–24 h) after injection.	Male Wistar Rats—8 wks old	Partial Hepatectomy, ethylene dibromide, nafenopine, or cyproterone	Pb nitrate induced NF-kB, TNF-alpha and iNOS, but not AP-1. Carbon tetrachloride induced and activated NF-kB, TNF-alpha iNOS, and AP-1. Nafenopine and cyproteone did not induce or activate NF-kB,TNF-alpha iNOS, or AP-1.	Menegazzi et al. (1997)

Table AX5-6.19. Genotoxic/Carcinogenic Effects of Lead—Mitogenesis Human and Animal Cell Culture Studies

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	Cell Proliferation (0.1–100 μM for 2–6 days) DNA synthesis (1–100 μM for 72 h) Tyrosine aminotransferase expression and activity (0.3–10 μM for 24– 48 h)	H4-II-C3—human hepatoma cells in DMEM + 2.5% FCS	Dexamethasone (0.1 μM for 16 h)	Pb acetate inhibited cell growth in a time- and dose-dependent manner. Pb acetate inhibited DNA synthesis in a dose-dependent manner. Pb acetate alone did not inhibit tyrosine aminotransferase. Pb acetate inhibited glucocorticoid–induction of tyrosine aminotransferase in a time- and dose-dependent manner.	Heiman and Tonner (1995)
Pb acetate	Cell proliferation (10 μM–1mM for 24 h–7 days)	REL cells—Rat Epithelial cells in Ham's F10 medium + 10% FBS	None	Pb acetate inhibited cell growth at all concentrations for 24 h–7 days. Pb acetate did not affect gap junction capacity, which is often inhibited by tumor promoters.	Apostoli et al. (2000)
Pb acetate	Cell growth (0.01–10 μM for 12-72 h) Expression of genes in cytokine pathways (0.01–10 μM for 24 h)	U-373MG—human glioma cell line in DMEM + 10 or 20% FBS	None	Pb acetate did not inhibit or enhance cell growth. Pb acetate enhanced the expression of TNF-alpha, but decreased interleukin-1 beta, interleukin-6, gamma-aminobutyric acid transaminase, and glutamine synthetase under 10% FBS. Pb acetate further enhanced the expression of TNF-alpha under 20% serum, but had no effect at all on expression of the other genes.	Liu et al. (2000)
Pb acetate	Cell proliferation (0.078–320 μM for 48 h) Apoptosis (1.25–80 μM) Cell cycle analysis	Rat-1 fibroblasts in EMEM +10% FBS	None	Pb acetate inhibited cell growth at 0.635–320 μM. Pb acetate induced apoptosis from 2.5–10 μM. Pb acetate caused GS/M and S-phase arrest.	Iavicoli et al., (2001)
Pb acetate	DNA synthesis (1–50 μM for 24 h) Expression of genes in mitogen activated pathways (1–50 μM for 5 min–4 h)	1321N1–human astrocytoma cells in DMEM + 0.1% BSA	None	Pb acetate induced DNA synthesis. Pb acetate induced activation of MAPK, ERK1. ERK2, MEK1 , MEK2, PKC, and $p90^{RSK}$. Pb acetate did not activate PI3K or $p70^{s6k}$.	Lu et al. (2002)
Pb acetate	Cell proliferation (1 μM for 24 h) Cell differentiation (1 μM for 48 h) PKC activation (1 μM for 24 h)	Primary oligodendrocyte progenitor cells–in DMEM + 1% FBS	None	Pb acetate inhibited basal and growth factor stimulated growth. Pb acetate inhibited cell differentiation in a PHC-dependent manner. Pb acetate redistributes PKC from the cytosol to the membrane, but did not increase PKC activity.	Deng and Poretz (2002)

Table AX5-6.19 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Mitogenesis Human and Animal Cell Culture Studies

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	Expression of TNF-alpha (0.1–10 μM for 24 h)	U-373MG—human glioma cell line in DMEM + 20% FBS	None	Pb acetate did not induce apoptosis. Pb acetate increased the expression of TNF-alpha in a dose-dependent manner. TNF-alpha was not involved in Pb-induced apoptosis.	Cheng et al. (2002)
Pb chloride	Cell proliferation (10 μM–1mM for 24–48 h)	REL cells—Rat Epithelial cells in Ham's F10 medium + 10% FBS	None	Pb chloride inhibited cell growth at all concentrations for 24–48 h. Pb chloride did not affect gap junction capacity, which is often inhibited by tumor promoters.	Apostoli et al. (2000)
Pb oxide	Cell proliferation (10 μM–1mM for 24 h–7 days)	REL cells—Rat Epithelial cells in Ham's F10 medium + 10% FBS	None	Pb oxide inhibited cell growth at all concentrations for 24 h–7 days. Pb oxide did not affect gap junction capacity, which is often inhibited by tumor promoters.	Apostoli et al. (2000)
Pb sulfate	Cell proliferation (10 μM–1mM for 24–48 h)	REL cells—Rat Epithelial cells in Ham's F10 medium + 10% FBS	None	Pb sulfate inhibited cell growth at all concentrations for 24–48 h. Pb sulfate did not affect gap junction capacity, which is often inhibited by tumor promoters.	Apostoli et al. (2000)
Pb chromate	Apoptosis (350 μM for 24 h)	Chinese Hamster Ovary AA8 cells in AMEM + 10% FBS	None	Pb chromate induced apoptosis. This study was focused on chromate.	Blankenship et al. (1997)
Pb chromate	Apoptosis (0.4–2 μg/cm^2 for 24 h)	Primary Human Small Airway Cells in Clonetics growth medium	None	Pb chromate induced apoptosis in a concentration-dependent manner.	Singh et al. (1999)
Pb chromate	Growth Curve (0.5–5 μg/cm^2 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 10% CCS	None	Pb chromate inhibited cell growth.	Holmes et al. (2005)
Pb glutamate	Growth Curve (250–1,000 μM for 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 10% CCS	None	Pb glutamate had no effect on growth.	Wise et al. (2005)
Pb glutamate	Mitotic Index (250–2,000 μM for 24 h) Growth Curve (250–2,000 μM for 24 h) Cell cycle Analysis (250–2,000 μM for 24 h)	WTHBF-6—human lung cells with hTERT in DMEM/F12 + 10% CCS	None	Pb glutamate induced a concentration-dependent increase in intracellular Pb ions. Pb glutamate increased the mitotic index, but either had no effect or inhibited growth and induced mitotic arrest.	Wise et al. (2005)

Table AX5-6.19 (cont'd). Genotoxic/Carcinogenic Effects of Lead—Mitogenesis Human and Animal Cell Culture Studies

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb nitrate	Mitotic Index (3–30 μM for 2h +16 h recovery)	CHO cells in EMEM + 10% FBS	None	Lower concentrations (1 and 3 μM) of Pb nitrate significantly increased the mitotic index. Higher concentrations (10 and 30 μM) had no effect.	Lin et al. (1994)
Pb nitrate	Mitotic Index (0.05–1 μM for 3–12 h)	CHO AA8 in DMEM +10% NCS	Crown ethers to modify effect through chelation and uptake	Pb nitrate dramatically reduced the mitotic index at 1 μM though this was not statistically analyzed. There was no effect on mitotic index at lower concentrations. Crown ethers had no modifying effect.	Cai and Arenaz (1998)
Pb nitrate	Apoptosis (15–240 μM for 3 h)	Rat Alveolar Macrophages in DMEM + 10% FBS	None	Pb nitrate induced apoptosis in a dose-dependent manner.	Shabani and Rabbani (2000)

Abbreviations

G12–CHV79 are derived from V79;
V79 are a Chinese Hamster Lung Cell Line;
hTERT is the catalytic subunit of human telomerase

Medium and Components

AMEM—Alpha Minimal Essential Medium;
DMEM—Dulbecco's Minimal Essential Medium;
DMEM/F12—Dulbecco's Minimal Essential Medium/Ham's F12;
EMEM—Eagle's Minimal Essential Medium;
BSA—Bovine Serum Albumin
CCS—Cosmic Calf Serum
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum
NCS—Newborn Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

Table AX5-6.20. Genotoxic/Carcinogenic Effects of Lead—Mitogenesis Other

Compound	Assay (Concentration and Exposure Time)	Cell Type and Culture Medium	Co-exposure	Effects	Reference
Pb acetate	Production of reactive oxygen species (1 mM for 180 min) Glutathione levels (1 mM for 0–180 min)	SH-SY5Y—Human neuroblastoma cells in DMEM + 7% FCS	Glutamate (1 mM) or PKC inhibitor (1 μM)	Pb acetate alone did not produce reactive oxygen species. Glutamate alone did. Pb acetate plus glutamate increase glutamate induced increases in reactive oxygen species. Pb acetate alone did not deplete glutathione. Glutamate alone did. Pb acetate plus glutamate decreased glumate-induced decrease in glutathione.	Naarala et al. (1995)
Pb acetate	Catalase Activity (500–2,000 μM for 24 h)	Human Foreskin Fibroblasts (Chinese) in DMEM +10% FCS	3-aminotriazole (3-AT) (80 mM to inhibit catalase)	Pb acetate had no effect on catalase activity.	Hwua and Yang (1998)
Pb acetate	Thiol Levels (100 μM for 30 min–4 h)	HeLa in HEPES/glucose buffer	Buthionine sulfoximine (BSO) to deplete cells of thiols	Pb acetate only lowered thiols marginally	Snyder and Lachmann (1989)
Pb chloride	Oxidative Metabolism (0.1–100 μM for 20 h) Phagocytosis (0.1–100 μM for 20 h)	Macrophages from NMRI mice in EMEM (serum not given)	Zymosan and latex particles as substrates for phagocytosis	Pb inhibited oxidative metabolism. Pb inhibited phagocytosis, but only significantly at the highest dose.	Hilbertz et al. (1986)
Pb chloride	Oxidative Enzyme Levels (0.1–1 μM for 1 h)	AS52-CHO-gpt, lack hprt in HBSS followed by Ham's F12 + 5% FBS	Allopurinol (50 μM) to inhibit xanthine oxidase	Pb chloride at low concentrations produced H_2O_2 at 1 h and not at 24 h. Pb chloride at high concentrations produced no change at 1 h and increased H_2O_2 at 24 h. Allopurinol inhibited H_2O_2 formation at high Pb concentrations. Pb chloride had no effect on catalase, glutathione peroxidase, glutathione reductase. Pb chloride inhibited glutathione-S-transferase, CuZn-superoxide dismutase, and xanthine oxidase.	Ariza et al. (1998)

Abbreviations
AS52 are derived from CHO;
CHO are a Chinese Hamster Ovary Cell Line;

Medium and Components
DMEM—Dulbecco's Minimal Essential Medium;
EMEM—Eagle's Minimal Essential Medium;
HBSS—Hank's Balanced Salt Solution
FBS—Fetal Bovine Serum
FCS—Fetal Calf Serum

Differences between the serum types are unclear as insufficient details are provided by authors to distinguish.

ANNEX TABLES AX5-7

Table AX5-7.1. Light Microscopic, Ultrastructural, and Functional Changes

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Khalil-Manesh et al. (1992a)	Sprague-Dawley rat	0.5% Pb acetate in drinking water for 12 mo	Max 125.4 µg/dL Mean 55 µg/dL	Hyperfiltration at 3 mo. Decreased filtration at 12 mo. NAG and GST elevated. Nuclear inclusion bodies at all times. Tubulointerstitial scarring from 6 mo. No arterial or arteriolar pathology.
Khalil-Manesh et al. (1992b)	Sprague-Dawley rat	0.5% Pb discontinued after 6 mo 0.01% Pb discontinued after 6 mo DMSA 0.5% used in 1/2	Hi Pb @12 mo Disc 30.4 µg/dL Disc + DMSA 19.1 µg/dL Ctrl 3.1 µg/dL Lo Pb@12mo Disc 6.9 µg/dL DMSA5.5 µg/dL	High Pb: Nuclear inclusion bodies prominent. Tubulointerstitial disease severe but less than 12 mo continuous DMSA caused reduction in nuclear inclusion bodies and tubuloint decrease, and an increase in GFR. Low Pb: Neg pathology and increase in GFR with DMSA
Khalil-Manesh et al. (1993a)	Sprague-Dawley rat	0.01% Pb acetate for 12 mo	Max 29.4 µg/dL Range 9–34 µg/dL	GFR increased at 1 and 3 mo. NAG increased but GST normal. Pathology neg except at 12 mo—mild tubular atrophy and interstitial fibrosis seen.
Sanchez-Fructuoso et al. (2002a)	Wistar rat	500 ppm (0.05%) Pb acetate for 2 mo, then EDTA	Max 52.9 µg/dL Day 90: 33.2 Day 137: 22.8 Ctrl: 5.90 µg/dL	Rats given Pb to day 90, then treated with EDTA or untreated to day 137. Marked decrease in kidney, liver, and brain Pb with EDTA but no change in femur Pb
Sanchez-Fructuoso et al. (2002b)	Wistar rat	500 ppm (0.05%) Pb acetate for 2 mo, then EDTA	Max 52.9 µg/dL Day 90: 33.2 Day 137: 22.8 Ctrl: 5.90 µg/dL	Hypertrophy and vacuolization of medium and small arteries, mucoid edema and muscular hypertrophy of arterioles, include bodies and fibrosis. EDTA slowed progression.
Papaioannou et al. (1998)	Dogs	12 mg Pb acetate i.p. × 10	—	Pb includes bodies intracytoplasmically in mesothelial and giant cells of peritoneum and in interstitial connective tissue cells of kidney. None in prox tubules of kidney.

Table AX5-7.1 (cont'd). Light Microscopic, Ultrastructural, and Functional Changes

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Vyskocil et al. (1989)	Wistar rat	0.5%, 1%, and 2% Pb acetate for 2–3 mo	0.5%–105 µg/dL 1%–196 µg/dL 2%–320 µg/dL	0.5%—no morphologic or functional changes. 1%—Incr in β-2 microglobulin excretion. 2%—Incr in β2micr, glucose, protein, lysozyme, and LDH. Hyperplasia and include bodies of prox tubules seen in both 1% and 2%.
Vyskocil et al. (1995)	Wistar rat	1% or 0.1% Pb acetate for 2–4 mo	1%–173 µg/dL 0.1%–37.6 µg/dL	1% caused increase in β-2 microglobulin excretion and injury to proximal tubule. 0.1% caused no changes.
Vyskocil and Cizkova (1996)	Wistar rats	Unleaded petrol vapor (4mg/m^3) 8 hrs/day for 60 days	—	B-2 microglobulin excretion increased at 60 days.
Sanchez et al. (2001)	Sprague-Dawley rat	0.06% Pb acetate for 4 mo	13.9 µg/dL vs. <0.5 µg/dL in ctrl	Decrease in expression of laminin-1 and increase in expression of fibronectin in kidneys.
Herak-Kramberger et al. (2001)	Rat brush border membranes	500 µM Pb	—	58% loss of sealed brush border membrane vesicles. Lower loss of sealed basolateral membrane vesicles.
Fujiwara et al. (1995), Kaji et al. (1995b)	Bovine cultured vascular smooth muscle and endothelial cells	0.5–10 µM Pb nitrate	—	Stimulated proliferation in smooth muscle cells. Reduced proliferation in endothelial cells No leakage of LDH.

Table AX5-7.2. Lead and Free Radicals

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Pereira et al. (1992)	Rats	ALA-treated (40 mg/kg every 2 days for 15 days)	—	Fatigued earlier than controls. Increase of CuZn SOD in brain, muscle and liver.
Somashekaraiah et al. (1992)	Chick embryos	1.25 and 2.5 momol/kg of Pb acetate	—	Lipoperoxides maximal at 9 hrs and returned to normal at 72 hrs. GSH depleted. GST, SOD and catalase increased in liver, brain and heart at 72 hrs.
Bondy and Guo (1996)	Sprague-Dawley rat cerebral synaptosomes	0.5 mM Pb acetate	—	Generation of ROS not increased by Pb alone but increased when 50 µM iron sulfate added.
Blazka et al. (1994)	Mouse brain microvascular endothelial cell culture	10, 100, and 1,000 nM Pb acetate	—	Constitutive production of nitrite, but not inducible, decreased by Pb. Extracellular calcium abolishes this effect.
Quinn and Harris (1995)	Rat cerebellum homogenates	17–80 nM Pb nitrate	—	Constitutive NOS activity inhibited 50% by 17 nM Pb and 100% by 80 nM Pb. Reversed by increasing Ca concentration.
Ercal et al. (1996)	C57BL/6 mice	1300 ppm Pb acetate for 5 wks, Nac, 5.5 mmol/kg, or DMSA, 1 mmol/kg, given in 6th week.	36.5 µg/dL in Pb-treated; 13.7 µg/dL in Pb + DMSA-treated	Liver and brain GSH depleted by Pb and MDA increased. Both were restored by either DMSA or NAC. However, DMSA reduced blood, liver, and brain Pb levels while NAC did not.
Vaziri and co-workers (1997–2004)	Sprague-Dawley rats	See Section 5.5 for details	Variable	See Section 5.5 for details.
Farmand et al. (2005)	Sprague-Dawley rats	100 ppm Pb acetate for 3 mo	—	CuZnSOD activity increased in kidney. CuZnSOD activity increased in aorta whereas protein abundance unchanged. Guanylate cyclase protein abundance in aorta decreased.
Gurer et al. (1999)	Fischer 344 rats	1100 ppm Pb acetate for 5 wks, Captopril for 6th wk	24.6µg/dL in Pb-treated. 23.8 µg/dL in Pb + Captopril-treated	MDA in liver, brain, and kidney increased by Pb. GSH decreased. Captopril reversed these findings.

Table AX5-7.2 (cont'd). Lead and Free Radicals

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Acharya and Acharya (1997)	Swiss mice	200 mg/kg Pb acetate i.p. × 1	—	MDA-TBA increased × 4 in liver, brain, kidney, and testis by end of 1st wk and persisted for 4 wks.
Upasani et al. (2001)	Rats	100 ppm Pb acetate for 30 days, Groups given vit C, vit E, or algae	—	MDA, conj dienes, and H_2O_2 increased in liver, lung, and kidney by Pb. Treatment with vit C, vit E, or Blue Green algae reversed these findings.
Pande et al. (2001)	Wistar rats	Pb nitrate 50 mg/kg i.p. × 5 Pb + DMSA,MiADMSA,NAC, DMSA + NAC,DMSA + MiADMSA	—	DMSA most effective in blocking inhib of ALAD, elev of ZPP, and inhib of GSH. Combined DMSA+NAC most effective when given during or post-exposure.
Pande and Flora (2002)	Wistar rats	2000 ppm Pb acetate × 4 wks, DMSA,MiADMSA, DMSA + LA,MiADMSA + LA × 5 days	—	Pb caused decrease in ALAD, GSH, and increase ZPP. Lipoic acid (LA) did not chelate Pb in contrast to DMSA, but both agents increased ALAD and GSH.
Flora et al. (2003)	Wistar rats	1000 ppm Pb acetate × 3 mo, DMSA or MiADMSA + vit C or vit E × 5 days	13.3 µg/dL Pb Rx 3 µg/dL DMSA Rx <1µg/dL DMSA+ vit E	Both thiol chelators and 2 vitamins increased ALAD. GSH increase only after thiol chelators. Vitamin E or C with thiol chelators reduced blood Pb further.
Saxena and Flora (2004)	Wistar rats	2000 ppm Pb acetate × 6 wks, $CaNa_2EDTA$ + DMPS or MiADMSA × 5 days	15.1µg/dL Pb Rx 9.8 µg/dL EDTA Rx 6 µg/dL EDTA + MiADMS	Pb caused inhib of ALAD and GSH and depl of ALAD in kidney, ALAS in liver, GSH in brain, increase in brain TBARS and GST. Combined Rx with CaNa2EDTA and MiADMSA most effective in reducing oxidative stress and tissue Pb burden.
Tandon et al. (2002)	Rats	2000 ppm Pb acetate × 9 wks, DMSA, MiADMSA, or NAC or combo × 6 days	—	Pb raised MDA, inhibited ALAD, increased catalase, and depleted GSH. DMSA plus NAC was most effective in reversing these changes.

Table AX5-7.2 (cont'd). Lead and Free Radicals

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Sivaprasad et al. (2002)	Wistar rats	2000 ppm Pb acetate × 5 wks LA and DMSA during 6th week.	—	Pb caused red in kidney GGT and NAG, decline in GSH, catalase, SOD, GPx and Glut reductase, and increased MDA. Lipoic acid +DMSA restored these changes.
Senapati et al. (2000)	Rats	1% sol of 5 mg/kg Pb acetate × 43 days Thiamine 25 mg/kg	—	Thiamine reduced Pb content and MDA levels of both liver and kidney and improved pathology.
Patra et al. (2001)	IVRI 2CQ rats	1 mg/kg Pb acetate for 4 wks Vit E, vit C or methionine in 5th wk. Vit E + EDTA.	6.8 µg/dL Pb-Rx 6.3 µg/dL Pb, vit E +EDTA	Pb in liver, kidney and brain reduced by vit E + EDTA treatment. MDA increased by Pb in all 3 organs but decreased by vit E + EDTA.
McGowan and Donaldson (1987)	Chicks	2000 ppm Pb acetate × 3 wks	—	GSH, non-protein SH, lysine and methionine increased in liver and non-prot SH, glycine, cysteine and cystathionine in kidney. Cysteine reduced in plasma.

Table AX5-7.3. Chelation with DMSA

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Cory-Slechta (1988)	Rats	50 ppm Pb acetate for 3–4 mo	20 µg/dL-Pb 1 µg/dL-Pb+25 mg/kg DMSA	DMSA 25–50 mg/kg i.p. for 1–5 days mobilized Pb from blood, brain, kidney and liver, but not femur.
Pappas et al. (1995)	Sprague-Dawley rats	550–1100 ppm Pb acetate for 35 days	52 µg/dL @ 550 ppm Pb 65 µg/dL @ 1100 ppm Pb	DMSA @16–240 mg/kg/d p.o. for 21 days given with and without concurrent Pb exposure. Rats showed dose-related reduction in Pb content of blood, brain, femur, kidney, and liver with or without concur Pb.
Smith and Flegal (1992)	Wistar rats	^{206}Pb 210 ng/mL for 1.5 days DMSA 20 mg/kg i.p.	5.1 ng/g-ctrl 3.0 ng/g-DMSA	Rats on low Pb diet given DMSA decreased soft tissue but not skeletal Pb. Pb redistributed to skeleton.
Varnai et al. (2001)	Wistar rats (suckling)	2 mg/kg/d for 8 days DMSA 0.5 mmol/kg 6x/d on d1-3 and 6–8	—	DMSA reduced Pb concentration in carcass, liver, kidneys, and brain by ~50%.

Table AX5-7.4. Effect of Chelator Combinations

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Flora et al. (2004)	Wistar rats	1000 ppm Pb acetate for 4 mo	46 µg/dL-Pb 12.8 µg/dL-combined Rx	5 days Rx with DMSA. $CaNa_2EDTA$, or DMSA + $CaNa_2EDTA$. Comb Rx resulted in increased ALAD and decreased Pb in blood, liver, brain, and femur.
Jones et al. (1994)	Mice	10 i.p. injections of Pb acetate, 5.0 mg/kg	—	Mice Rx'ed with DMSA, $CaNa_2EDTA$, $ZnNa_2EDTA$, or $ZnNa_3DTPA$ 1.0 mmol/kg/d 4–8 days. $CaNa_2EDTA$ most effective in removing brain Pb; DMSA in removing kidney and bone Pb.
Kostial et al. (1999)	Wistar rats (suckling)	5 mg Pb/kg i.p. × 1 Chel agents days 2 and 3	—	EDTA, DMSA, racemic DMSA, EDTA + DMSA, EDTA + rac DMSA given. EDTA reduced Zn in carcass and liver; rac DMSA reduced Zn in kidneys. DMSA reduced Pb w/o affecting Zn.
Flora et al. (2004)	Wistar rats	1000 ppm Pb acetate × 2 mo	—	DMSA, taurine or DMSA + taurine given for 5 days. Both taurine and DMSA restored GSH. Comb of DMSA + taurine increased RBC SOD and decreased TBARS, while most effectively depleting blood, liver, and brain Pb.
Sivaprasad et al. (2004)	Wistar rats	2000 ppm Pb acetate × 5 wks	—	DMSA, lipoic acid or combination given during 6th week. Renal enzymes, kidney Pb and renal ALAD restored by combined Rx.
Malvezzi et al. (2001)	Wistar rats	750 ppm Pb acetate × 70 days DMSA, arginine, DMSA + arg or H_2O × 30 days	67.8 µg/dL to 11.2 µg/dL in H_2O Rx'ed to 6.1 µg/dL in DMSA + arg	Pb increased BP and Pb levels in blood, liver, femur, kidney, and aorta. DMSA + L-arginine most effective in lowering BP and mobilizing Pb from tissues.
Tandon et al. (1997)	Rats	1000 ppm Pb acetate for 7 wks. Dithiocarbamate × 4 days	105.3 µg/dL in Pb 86 µg/dL in dithiocarbamate.	Two dithiocarbamates were compared: N-benzyl-D-glucamine and N-(4-methoxybenzyl)-D-glucamine. They were only partially effective in restoring ALAD, reducing liver and kidney, but not brain Pb. They depleted Zn, Cu, and Ca.

Table AX5-7.5. Effect of Other Metals on Lead

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Maldonado-Vega et al. (1996)	Wistar rats (pregnant and nonpregnant)	100 ppm Pb acetate for 144–158 days	5.2 (ctrl) to 27.3 µg/dL in Pb-exposed 8 (non-preg) to 17 µg/dL in rats exposed only during lactation	Pb administered to period before lactation (144 days) or to mid-lactation (158 days).Pb in blood, kidney, liver, and bone increased. ALAD decreased and FEP incr. Lactation increased. Blood Pb from 24.7 to 31.2 µg/dL and decreased bone Pb from 83.4 to 65.2 nmol/g.
Olivi et al. (2002)	MDCK canine kidney cells	1 µM	—	In response to agonists ADP or bradykinin levels of intracellular Ca increased 3-fold and 2-fold. Pb inhibited the response.
Bogden et al. (1991)	Wistar rats	0,1,100 ppm Pb for 31 wks 0.2% or 4.0% Ca diet	1.9 to 39.1 µg/dL on low Ca diet and 2.0 to 53.3 µg/dL on high Ca diet	At 100 ppm Pb high Ca diet produced higher BP and more renal cancers than low Ca diet and higher levels of Pb in brain, liver, bone, heart, and testis but lower levels in kidney. Serum Ca on high Ca diet was 13.2 mg/dL.
Skoczyńska et al. (1994)	Buffalo rats	Pb 70 mg/kg 2x/wk for 7 wks Cd 20 mg/kg 1x/wk for 7 wks. All intragastric.	5.1 to 29.6 µg/dL in Pb-exposed. 37.4 µg/dL in Pb + Cd	Simultaneous Pb and Cd administration increased blood Pb but decreased Pb in liver and kidneys as compared to Pb administration alone.
Othman and El-Missiry (1998)	Albino rats	Pb acetate 100 momol/kg I.M. × 1 Se 10 momol/kg I.M. 2 hrs before Pb	—	Sodium selenite (Se is a well-known anti-oxidant) prevented lipid peroxidation (TBARS) and reduction in GSH caused by Pb. SOD and glut reductase also normalized.
Tandon et al. (1992)	Albino rats	Pb acetate 10 mg/kg/d p.o. × 6 wks. EDTA or DTPA given for 5 days w/ or w/o Se	17 to 138 µg/dL after Pb 58 µg/dL after EDTA. 50 µg/dL after EDTA + Se	Selenium had no additional benefit over chelators except for higher ALAD and lower ZPP in blood, lower Pb in liver and kidney.
Flora et al. (1989)	Albino rats	Pb acetate 10 mg/kg/d p.o. × 6 wks Thiamine, Zn or thiamine + Zn × 6 wks	6.2 to 120.9 µg/dL after Pb 44.1 µg/dL after thiamine + Zn	Thiamine given as 25 mg/kg/d and Zn sulfate as 25 mg/kg/d. ALAD restored by combined Rx. Liver and kidney Pb affected to a minor degree but brain Pb not affected.
Flora et al. (1994)	Wistar albino rats	Pb acetate 10 mg/kg/d × 56 days p.o. EDTA or EDTA + Zn × 5 days p.o.	4.6 to 43.0 µg/dL in Pb. 22.5 µg/dL in EDTA 16.5 µg/dL in EDTA + Zn.	CaNa2 EDTA given as 0.3 mmol/kg/d i.p. and Zn sulfate as 10 or 50 mg/kg/d. ALAD partially restored after EDTA + Zn but not after EDTA. EDTA reduced Pb in bone, kidney, and liver but not in brain. Zn conc increased in blood, kidney, and brain by 50 mg Zn dosage.

Table AX5-7.5 (cont'd). Effect of Other Metals on Lead

Author	Animal Species	Lead Dosage	Blood Lead	Findings
Satija and Vij (1995)	Albino rats	Pb acetate 20 mg/kg/d i.p. × 3 days Zn acetate 5 mg/kg/d i.p. × 3 days	—	Pb caused a decrease in Hgb, ALAD, and uroporphyrinogen I synthetase, partially restored by Zn. Total SH and non-protein SH reduced by Pb, partially restored by Zn.
Munoz et al. (1993)	Wistar rats	Pb acetate 60 ppm × 90 days, Zn or methionine given simultaneously	<60 µg/dL-Pb SAM reduces to average of 7.3 µg/dL	S-adenosyl-l-methionine (SAM) reduces blood Pb and uroporphyrinogen I synthetase. RBC ALAD reduced by Pb and 2 Rx. Liver ALAD decreased by Pb, increased by SAM.
Tandon et al. (1997)	Albino rats	Pb acetate 10 mg/kg/d × 8 wks p.o. Ethanol, Zn and lysine × 8 wks	1.8 to 47.2 µg/dL w Pb. Decreased to 34.2 µg/dL w Zn + lysine.	Ethanol reduced blood but not liver GSH beyond Pb alone. Zn + lysine partially restored ALAD, increased GSH, and reduced Pb in kidney.
Hashmi et al. (1989)	Rats	Pb acetate 1000 ppm × 6 wks Fe-deficient or norm diet	—	Fe deficiency increased Pb in liver, kidney, spleen but increased femur Pb at 3 wks and decreased femur Pb at 6 wks.
Tandon et al. (1993)	Rats	Pb acetate 400 momol/kg i.p. × 1 Fe deficient and Fe-sufficient diets × 6 wk	—	Pb induced hepatic metallothionein (MT). Fe deficient diet + Pb restored kidney and intestinal MT from low levels caused by Fe def. Pb in liver and kidney enhanced by Fe def
Crowe and Morgan (1996)	Wistar rat pups	Pb acetate 2000 ppm × 15, 21, and 63 days Fe def and Fe suff diets	At 63 days Fe def-410 µg/dL Fe suff rats 170 µg/dL	Fe deficiency increased blood and kidney Pb but did not affect brain or liver Pb. Fe levels in brain and kidney were unaffected by Pb intoxication.
Singh et al. (1991)	Pregnant female albino rats	Pb acetate 250–2000 ppm from 15–20 days of gestation.	At 2000 ppm Pb, Fe def 220 µg/dL Fe suff 160 µg/dL	Fe def and Fe suff diets given to dams for 30 days. Fetuses removed on 21st day. At 2000 ppm, Pb in maternal blood, placenta, and fetus higher in Fe def. Max pathol changes in fetal kidney.
Shakoor et al. (2000)	Albino rats	Pb acetate 125 mg/kg × 90 days Al chloride 50–100 mg/kg × 90 days	—	Plasma creat 1.88 mg/dL in Pb-Rx'ed; 1.34 mg/dL in Pb + Al-Rx'ed Kidney Pb increased from 5.4 in ctrl to 220 µg/g in Pb-Rx'ed, decreased to 98.9 µg/g in Pb + Al.

ANNEX TABLES AX5-8

Table AX5-8.1. Bone Growth in Lead-exposed Animals

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 41.7 mg Pb/l 83.3 mg Pb/l 166.6 mg Pb/l 12 to 16 wks Drinking water	Rat	Pb level in bone of control animals Wk 0 = 1.3 ± 0.83 µg Pb/g; Wk 4 = 1.2 ± 0.99 µg Pb/g; Wk 8 = 1.3 ± 1.08 µg Pb/g; Wk 12 = 0.8 ± 0.13 µg Pb/g; Wk 16 = 1.3 ± 0.95 µg Pb/g Pb level in bone of animals receiving 41.7 mg Pb/l Wk 0 = 1.0 ± 0.50 µg Pb/g; Wk 4 = 5.9* ± 1.76 µg Pb/g; Wk 8 = 2.9* ± 1.15 µg Pb/g; Wk 12 = 6.2* ± 1.01 µg Pb/g; Wk 16 = 6.0* ± 0.75 µg Pb/g Pb level in bone of animals receiving 83.3 mg Pb/l Wk 0 = 2.0 ± 0.97 µg Pb/g; Wk 4 = 11.7* ± 3.56 µg Pb/g; Wk 8 = 8.8* ± 3.37 µg Pb/g; Wk 12 = 14.3* ± 4.29 µg Pb/g Pb level in bone of animals receiving 166.6 mg Pb/l Wk 0 = 0.9 ± 0.23 µg Pb/g; Wk 4 = 17.0* ± 3.89 µg Pb/g; Wk 8 = 35.7* ± 3.64 µg Pb/g; Wk 12 = 21.7* ± 5.11 µg Pb/g; *significantly higher than control animals at corresponding time point	Not given	Hać and Krechniak (1996)
Pb aerosol 77, 249, or 1546 µg/m^3 for 50 to 70 days Inhalation	Rat	16.9 ± 6.6 µg Pb/g bone taken up in animals exposed to 77 µg/m^3 for 70 days versus 0.2 ± 0.2 µg Pb/g in control animals; 15.9 ± 4.3 µg Pb/g bone in rats exposed to 249 µg/m^3 for 50 days; 158 ± 21 µg Pb/g bone in rats exposed to 1546 µg/m^3 for 50 days	Control: 2.6 µg/dL 77 µg/m^3: 11.5 µg/dL 249 µg/m^3: 24.1 µg/dL 1546 µg/m^3: 61.2 µg/dL	Grobler et al. (1991)
Pb acetate 250 ppm or 1000 ppm 7 wks to females prior to mating, continuing through gestation and lactation Drinking water	Rat	Offspring body weight was depressed relative to controls during suckling (Day 11) and after weaning (Day 24) in high dose and continuously Pb-exposed groups. Continuous Pb exposure caused a greater decrease in offspring body weight than Pb exposure only prior to or after parturition. Decreased tail length growth suggested possible effects of Pb on tail vertebral bone growth.	Dams prior to mating: Control = 2.7 ± 0.6 µg/dL 250 ppm = 39.9 ± 3.5 µg/dL 1000 ppm = 73.5 ± 9.3 µg/dL	Hamilton and O'Flaherty (1994)

Table AX5-8.1 (cont'd). Bone Growth in Lead-exposed Animals

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate Hi Pb animals 5000 ppm for 6 mo, reduced to 1000 ppm; Lo Pb animals 100 ppm Drinking Water	Rat	In male rats exposed to 100 ppm Pb in drinking water and a low calcium diet for up to one yr, bone density was significantly decreased after 12 mo, while rats exposed to 5000 ppm Pb had significantly decreased bone density after 3 mo. Pb content of femurs was significantly elevated over the content of control rats at all time points (1, 3, 6, 9, 12 mo). Trabecular bone from the low dose animals was significantly decreased from 3 mo forward.	Low Pb (µg%): 1 mo Control = 2 ± 1; Exp = 19 ± 10* 3 mo Control = 2 ± 1; Exp = 29 ± 4* 6 mo Control = 3 ± 1; Exp = 18 ± 2* 9 mo Control = 1 ± 1; Exp = 17 ± 3* 12 mo Control = 3 ± 1; Exp = 21 ± 3* Hi Pb (µg%): 1 mo Control = 3 ± 1; Exp = 45 ± 13* 3 mo Control = 3 ± 1; Exp = 90 ± 15* 6 mo Control = 4 ± 1; Exp = 126 ± 10* 9 mo Control = 4 ± 1; Exp = 80 ± 39* 12 mo Control = 3 ± 1; Exp = 59 ± 18* *p < 0.001	Gruber et al. (1997)
Pb acetate 17 mg per kg of feed 50 days In diet	Rat	No differences in the length of the femurs, but the mean length of the 5th lumbar vertebra was significantly decreased. The mean length of the femur growth plate cartilage was also significantly decreased in Pb-exposed animals.	Not given	González-Riola et al. (1997)
Pb acetate 17 mg per kg of feed 50 days In diet	Rat	No differences in the length of the femurs, but the mean length of the 5th lumbar vertebra was significantly decreased. The mean length of the femur growth plate cartilage was also significantly decreased in Pb-exposed animals.	Not given	Escribano et al. (1997)

Table AX5-8.1 (cont'd). Bone Growth in Lead-exposed Animals

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 0.6% GD 5 to Adulthood (various) In drinking water	Rat	Early bone growth was significantly depressed in a dose-dependent fashion in pups of Pb-exposed pups, with growth suppression in male offspring considerably greater than females. Significant decreases in plasma insulin-like growth factor and plasma sex steroids and increased pituitary growth hormone were also observed. Groups: DDW = Dams and pups received distilled deionized water entire study Ac/Ac = Dams and pups received acetic acid solution entire study Preg = Dams received 0.6% Pb water from GD 5 to parturition Lact = Dams received 0.6% Pb water during lactation only P + L = Dams received 0.6% Pb water from GD 5 through lactation Postnatal = Dams and pups received 0.6% Pb water from parturition through adulthood Pb/Pb = Dams and pups received 0.6% Pb water from GD 5 through adulthood	Whole blood Pb (µg/dL) in male/female offspring at age Day 85: DDW = 5.5 ± 2.0/6.8 ± 1.5; Ac/Ac = 1.9 ± 0.2/1.4 ± 0.3; Preg = 9.1 ± 0.7*/11.6 ± 4.6*; Lact = 3.3 ± 0.4/3.4 ± 0.8; P + L = 16.1 ± 2.3*/10.4 ± 1.8*; Postnatal = 226.0 ± 29.0*/292.0 ± 53.0*; Pb/Pb = 316.0 ±53.0*/264.0 ± 21.0* *p < 0.05 compared to Ac/Ac group.	Ronis et al. (1998a)
Pb acetate 0.05% to 0.45% GD 5 through sacrifice of pups at 21, 35, 55, and 85 days In drinking water	Rat	Early bone growth was significantly depressed in a dose-dependent fashion in pups of all Pb-exposed groups, with growth suppression in male offspring considerably greater than females. Significant decreases in plasma insulin-like growth factor and plasma sex steroids and increased pituitary growth hormone were also observed. Between age 57 and 85 days growth rates were similar in control and Pb-exposed pups, suggesting exposure at critical growth periods such as puberty and gender may account for differences in growth reported by various investigators.	Offspring: 0.05% Pb = 49 ± 6 µg/dL; 0.15% Pb = 126 ± 16 µg/dL; 0.45% Pb = 263 ± 28 µg/dL	Ronis et al. (1998b)
Pb nitrate 0.02% (125 ppm) GD5 to 1 day before sacrifice In drinking water	Rat	Exposure to 0.02% Pb nitrate (125 ppm Pb) did not significantly affect growth, though males weighed significantly less than females.	Rat Pups 5 days old: 43.3 ± 2.7 µg/dL 49 days old: 18.9 ± 0.7 µg/dL (females: 19.94 ± 0.8 µg/dL; males: 17.00 ± 1.1 µg/dL)	Camoratto et al. (1993)

Table AX5-8.1 (cont'd). Bone Growth in Lead-exposed Animals

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 0.15% or 0.45% GD 4 until Day 55 In drinking water	Rat	A dose-dependent decrease in load to failure in tibia from Pb-exposed (0.15% and 0.45% Pb acetate in drinking water) male pups only. Hormone treatments (L-dopa, testosterone or dihydrotestosterone in males, or estradiol in females) failed to attenuate Pb deficits during the pubertal period. Distraction osteogenesis experiments performed after stabilization of endocrine parameters (at 100 days of age) found decreased new endosteal bone formation and gap x-ray density in the distraction gaps of Pb-exposed animals.	Offspring: 0.15% Pb = 67–192 µg/dL; 0.45% Pb = 120–388 µg/dL	Ronis et al. (2001)
Pb acetate 1000 ppm 22–26 days In drinking water	Rat	Pb disrupted mineralization during growth in demineralized bone matrix implanted subcutaneously into male rats. In the matrix that contained 200 micrograms Pb/g of plaque tissue, alkaline phosphatase activity and cartilage mineralization were absent, though calcium deposition was enhanced. Separate experiments found enhanced calcification and decreased alkaline phosphatase activity in rats implanted with a control (no Pb) matrix and given 1000 ppm Pb in drinking water for 26 days.	Blood Pb (µg/dL) Control: Implantation Day 0 = 1.3 ± 0.6; Day 8 = 2.2 ± 0.9; Day 12 = 2.1 ± 0.7. Pb added to matrix: Implantation Day 0 = 1.5 ± 0.8; Day 8 = 5.7 ± 0.8[a,b]; Day 12 = 9.5 ± 0.5[a,b]. Pb in drinking water: Implantation Day 0 = 129.8 ± 6.7[a]; Day 8 = 100.6 ± 6.8[a,b] Day 12 = 96.4 ± 5.3[a,b]. [a] Significant ($p \leq 0.05$) difference from control. [b] Significance ($p \leq 0.05$) difference from corresponding value at implantation (Day 0).	Hamilton and O'Flaherty (1995)

Abbreviations

Mg—milligram
µg—microgram
ppm—parts per million
GD—gestational day
Pb—lead
g—gram
µg%—microgram percent
l—liter
m^3—cubic meter
Exp—experimental group
wk—week
dL—deciliter
%—percent

Table AX5-8.2. Regulation of Bone Cell Function in Animals—Systemic Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 30 mg/kg Single i.v. injection	Rat	Groups of male rats were killed 0.5, 5, 15, and 30 min and 1, 2, 6, and 12 h after the single Pb injection. Serum calcium and phosphorus levels both initially increased after Pb injection with serum phosphorus reaching a maximum value (13.5 mg%) after 30 min and calcium (17 mg%) after 1 h. Calcium and phosphorus levels decreased after 1 h and returned to baseline levels after 12 h.	Not given	Kato et al. (1977)
Pb acetate 0.82% 1 wk In diet	Rat	Ingestion of 0.82% Pb in male rats fed either a low phosphorus or low calcium diet reduced plasma levels of 1,25-$(OH)_2$CC, while Pb had no effect in rats fed either a high calcium diet or a normal phosphorus diet.		Smith et al. (1981)
		Effect of Pb on serum 1,25-$(OH)_2$CC levels in rats fed low P or normal P diet		
		Dietary Phosphorus / Supplement / Serum 1,25-$(OH)_2$CC	µg/100mL	
		0.1% / Control / <10 pg/mL	3 ± 1	
		0.1% / Cholecalciferol / 248 ± 7 pg/mL	9 ± 8	
		0.1% / 0.82% Pb+Cholecalciferol / 94 ± 13 pg/mL	352 ± 40	
		0.3% / Control / <10 pg/mL	<3	
		0.3% / Cholecalciferol / 285 ± 44 pg/mL	<3	
		0.3% / 0.82% Pb+Cholecalciferol / 245 ± 46 pg/mL	284 ± 36	
		Effect of Pb on serum 1,25-$(OH)_2$CC levels in rats fed low Ca or high Ca diet		
		Dietary Calcium / Supplement / Serum 1,25-$(OH)_2$CC	µg/100mL	
		0.02% / Control / <10 pg/mL		
		0.02% / Cholecalciferol (50ng/day) / 754 ± 18 pg/mL		
		0.02% / 0.82% Pb+Cholecalciferol / 443 ± 79 pg/mL		
		1.2% / Control / <10 pg/mL	<3	
		1.2% / Cholecalciferol (50ng/day) / 285 ± 44 pg/mL	<3	
		1.2% / 0.82% Pb+Cholecalciferol / 245 ± 46 pg/mL	284 ± 36	
Pb acetate 0.15% or 0.45% GD 4 until Day 55 In drinking water	Rat	No effects of Pb on plasma concentrations of vitamin D metabolites, 25-OH D_3 or 1,25-$(OH_2)D_3$, in pubertal male rats exposed to either 0.15% or 0.45% Pb acetate in drinking water and maintained on an adequate diet.	Offspring: 0.15% Pb = 67–192 µg/dL; 0.45% Pb = 120–388 µg/dL	Ronis et al. (2001)

Table AX5-8.2 (cont'd). Regulation of Bone Cell Function in Animals—Systemic Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
$PbCl_2$ 0, 0.2, or 0.8% 1 or 2 wks In diet	Chicks	Compared with control animals, Pb exposure significantly increased intestinal calbindin protein and mRNA levels in addition to plasma 1,25-dihydroxyvitamin D concentration. The effect was present after 1 wk of exposure and continued through the second week. In calcium-deficient animals increased plasma 1,25-dihydroxyvitamin D and calbindin protein and mRNA were significantly ($p < 0.05$) inhibited by Pb exposure in a dose dependent fashion over the 2 wk experimental period.	None given	Fullmer (1995)
$PbCl_2$ 0, 0.2, or 0.8% 1 or 2 wks In diet	Chicks	Dose dependent increases in serum 1,25-$(OH_2)D_3$ levels (and Calbindin-D protein and mRNA) with increasing dietary Pb exposure (0.1% to 0.8%) in experiments performed on Leghorn cockerel chicks fed an adequate calcium diet.	None given	Fullmer et al. (1996)
Pb acetate 1% for 10 wks or 0.001–1% for 24 wks In drinking water	Rat	Short term administration of 1% Pb resulted in significant increases in bone Pb. Total serum calcium and ionized serum calcium were significantly decreased, as compared to controls. Circulating levels of 1,25-$(OH_2)D_3$ were also decreased, though the rats were maintained on a normal calcium diet (0.95%). In the long term study, a dose-dependent increase in parathyroid weight occurred with increasing exposure to Pb in drinking water.	Short term (10 wk) study: Control: < 0.02 µg/l Pb-exposed: > 5µg/l	Szabo et al. (1991)

Short term (10 wks) exposure	Controls	Pb-exposed
Serum Calcium (mM) Ionized Calcium	2.42 ± 0.03	2.32 ± 0.02*
(mM) 1,25$(OH)_2D_3$ (pM)	1.25 ± 0.03	1.15 ± 0.03*
Parathyroid Weight (µg/gland)	232 ± 18.9	177 ± 10.8*
*p < 0.01	96 ± 34	178 ± 25*

Long term (24 wks) exposure Pb in water	Normalized Parathyroid Weight (µg/g body wt)	1,25$(OH)_2D_3$ (pM)
0%	0.50 ± 0.06	241 ± 32
0.001%	0.72 ± 0.25	188 ± 27
0.01%	0.81 ± 0.28	163 ± 17
0.1%	0.94 ± 0.27	206 ± 24
1.0%	0.81 ± 0.29*	144 ± 33*
p < 0.01		

Table AX5-8.2 (cont'd). Regulation of Bone Cell Function in Animals—Systemic Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb nitrate 0.02% (125 ppm) GD5 to 1 day before sacrifice In drinking water	Rat	Basal release of growth hormone from control and Pb-exposed pups at age 49 days was not significantly different. Growth hormone releasing factor-stimulated release of growth hormone from pituitaries of Pb-exposed pups was smaller than the stimulated release of growth hormone from pituitaries of control animals (75% increase over baseline vs. 171% increase, respectively), but the difference did not achieve significance (P = 0.08). Growth hormone content of the pituitary glands was also not influenced by Pb exposure.	Rat Pups 5 days old: 43.3 ± 2.7 µg/dL 49 days old: 18.9 ± 0.7 µg/dL (females: 19.94 ± 0.8 µg/dL; males: 17.00 ± 1.1 µg/dL)	Camoratto et al. (1993)
Pb acetate 0.05% to 0.45% GD 5 through sacrifice of pups at 21, 35, 55, and 85 days In drinking water	Rat	Pituitary GH content (µg/mg) at postnatal day 55: Control Male Pups = 56.6 ± 8.0; Female Pups = 85.6 ± 9.3 0.05% Pb Male Pups = 107.2 ± 10.5*; Female Pups = 116.2 ± 9.1 0.15% Pb Male Pups = 96.8 ± 5.0*; Female Pups = 105.1 ± 7.3 0.45% Pb Male Pups = 106.0 ± 9.8*; Female Pups = 157.0 ± 9.9* *significantly different from control, $p < 0.05$	Offspring: 0.05% Pb = 49 ± 6 µg/dL; 0.15% Pb = 126 ± 16 µg/dL; 0.45% Pb = 263 ± 28 µg/dL	Ronis et al. (1998b)

Abbreviations

mg—milligram
h—hour
1,25-$(OH)_2$CC—1,25-dihydroxycholecalcigerol
µg—microgram
25-OH D_3—25-hydroxycholecalciferol
$PbCl_2$—lead chloride
1,25-$(OH)_2$ D_3—vitamin D_3
kg—kilogram
mg%—milligram percent
pg—picogram
GD—gestational day
mM—millimolar
Pb—lead
pM—picomolar
i.v.—intravenous
%—percent
mL—milliliter
dL—deciliter
mRNA—messenger ribonucleic acid
ppm—parts per million
GH—growth hormone
min—minute

Table AX5-8.3. Bone Cell Cultures Utilized to Test Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Stable "Pb" 5 mg/mL in drinking water given during gestation. On GD 18, 50 µCi ^{210}Pb given i.v. to pregnant dams	Rat (fetal bone organ culture)	PTH (3885 IU/mg bone) enhanced cell-mediated release of ^{210}Pb from bone. Release of ^{210}Pb was accompanied by proportional loss of stable Pb and calcium from treated bones. Time: Release of ^{210}Pb (EM/CM ratio) 0 min 1.00 10 min 0.82 ± 0.05 2 hr 1.12 ± 0.04 6 hr 1.59 ± 0.08* 24 hr 3.69 ± 0.15* 48 hr 3.75 ± 0.09* 48 hr 0.78 ± 0.14* (in presence of 30 mU/mL salmon calcitonin) *Different from 1.00, $p < 0.01$.	Not given/not applicable	Rosen and Wexler (1977)
^{210}Pb nitrate 6.5 to 65 µM 5 min to 2 h In medium	Mice (bone cell isolation from calvaria)	Uptake of ^{210}Pb by OC cells rapid. OC cells have greater avidity for Pb compared to OB cells. OC cell uptake of Pb almost linear vs. little increase in Pb uptake by OB cells with increasing Pb concentrations in media. 15–30% release of ^{210}Pb label occurred in OC cells over 2 h time period. Physiological concentrations of PTH resulted in marked increase in ^{210}Pb and ^{45}Ca uptake by OC cells. ^{210}Pb uptake linear over PTH concentrations of 50 to 250 ng/mL). Media concentrations of Pb ≥26 µM enhanced calcium uptake by cells.	Not applicable	Rosen (1983)
^{210}Pb nitrate 5 µM 20 hours In medium	Mice (osteoclastic bone cell isolation from calvaria)	Three readily exchangeable kinetic pools of intracellular Pb identified, with the majority (~78%) associated with the mitochondrial complex.	Not applicable	Pounds and Rosen (1986)
Pb acetate 0 to 50 µM 20 h In medium	Mice (osteoclastic bone cell isolation from calvaria)	Cultures were labeled with ^{45}Ca (25 µCi/mL) for 2 or 24 h and kinetic parameters were examined by analysis of ^{45}Ca washout curves. In kinetic analysis using dual-label (1–2 µCi/mL ^{210}Pb and 25 µCi/mL ^{45}Ca) wash out curves, the Ca:Pb ratios of the rate constants were ~1:1, suggesting similar cellular metabolism.	Not applicable	Rosen and Pounds (1988)

Table AX5-8.3 (cont'd). Bone Cell Cultures Utilized to Test Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate and ^{210}Pb label 0–100 μM 20 hr In medium	Mice (osteoclastic bone cell isolation from calvaria) and Rat Osteosarcoma Cells (ROS 17/2.8)	Concentrations as high as 100 μM did not cause toxicity in either cell culture. There was a slight decrease in growth of ROS cells at 5 μM Pb concentration and a 50% decrease in growth at 25 μM Pb at day 9. ^{210}Pb washout experiments with both cell cultures indicated similar steady-state Pb kinetics and intracellular Pb metabolism. Both cell cultures exhibited one large, slowly exchanging pool of Pb, indicative of the mitochondrial pool.	Not applicable	Long et al. (1990)
Pb acetate 5 or 25 μM Up to 5 hr In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Used ^{19}F NMR in combination with 1,2-bis(2-amino-5-fluorophenoxy)ethane-N,N,N',N'-tetraacetic acid (5F-BAPTA) to distinguish and measure concentrations of Pb^{2+} and Ca^{2+} in aqueous solution. Basal concentration of $[Ca^{2+}]_i$ was 128 ± 24 nM. Treatment of cells with 5 and 25 μM Pb^{2+} produced sustained 50% and 120% increases in $[Ca^{2+}]_i$, respectively, over a 5 hour exposure period. At a medium concentration of 25 μM Pb^{2+} a measurable entry of Pb^{2+}into the cells ($[Pb^{2+}]_i$ of 29 ± 8 pM) was noted.	Not applicable	Schanne et al. (1989)
Pb nitrate 5 μM 20 min In medium	Rat (osteoblastic bone cell isolation from calvaria)	Pb (5 μM) linearly raised the emission ratio of FURA-2 loaded cells 2-fold within 20 min of application, most likely due to increase in $[Pb^{2+}]_i$ rather than increase in $[Ca^{2+}]_i$. Intracellular calcium increased even in the absence of extracellular calcium.	Not applicable	Schirrmacher et al. (1998)
Pb^{2+} 5 or 12.5 μM Up to 100 min In medium	Rat (osteoblastic bone cell isolation from calvaria)	5 or 12.5 μM Pb^{2+} applied simultaneously with re-added calcium reduced immediate CRAC to 70% or 37% of control value, respectively. During CRAC a large influx of Pb^{2+} occurred, leading to a 2.7-fold faster increase in the FURA-2 excitation ratio. These effects were exclusive of any inhibitory action of Pb^{2+}on calcium ATPase activity.	Not applicable	Wiemann et al. (1999)

Table AX5-8.3 (cont'd). Bone Cell Cultures Utilized to Test Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb nitrate 0–150 μM Up to 72 hr In medium	Mice (bone cell isolation from parietal bones)	Pb^{2+} concentrations of 50 μM and above stimulated release of hydroxyproline and previously incorporated ^{45}Ca from organ culture. This did not occur in bone inactivated by freezing and thawing. Eel calcitonin, bafilomycin A_1, and scopadulcic acid B significantly inhibited Pb mediated ^{45}Ca release. There was a high correlation between ^{45}Ca and PGE_2 release ($p < 0.001$), inferring Pb-induced bone resorption mediated by PGE_2. This was further supported by the significant depression of Pb-stimulated ^{45}Ca release that occurred with concurrent exposure to 10 μM of either indomethacin or flurbiprofen, both inhibitors of cyclooxygenase.	Not applicable	Miyahara et al. (1995)
Pb acetate 0–25 μM 48 hr In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Osteocalcin production in cells treated with 100 pg 1,25-dihydroxyvitamin D_3/mL of medium and 0 μM Pb^{2+} for 16, 24, or 36 h was 20.1 ± 2.1, 23.5 ± 3.4, 26.1 ± 2.5 in cell digests, and 87.2 ± 3.3, 91.6 ± 6.7, 95.1 ± 5.2 in the medium, respectively. The presence of 25 μM Pb^{2+}in the medium, reduced osteocalcin levels to as low as 30% of control levels. Cells treated with 0, 5, 10, or 25 μM Pb acetate for 24 h, followed by an additional 24 h exposure to 0 or 100 pg of 1,25-dihydroxyvitamin D_3 and continued Pb^{2+} exposure, resulted in a concentration-dependent reduction of 1,25-dihydroxyvitamin D_3-stimulated osteocalcin secretion. 10 μM Pb resulted in medium osteocalcin levels similar to control levels, however, 25 μM Pb resulted in about a 30% decrease. Cellular osteocalcin levels were unaffected.	Not applicable	Long et al. (1990)
Pb glutamate 4.5×10^{-5} to 4.5×10^{-7} M 2, 4, or 6 days In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	In the presence of serum in the cultures, concentrations of Pb^{2+} less than 4.5×10^{-5} M had no effect on cell proliferation. In the absence of serum, 4.5×10^{-7} M Pb^{2+} increased proliferation at Day 4 and 4.5×10^{-6} M Pb^{2+} inhibited proliferation at Day 6. Pb exposure for 48 h (4.5×10^{-6} M) significantly ($p < 0.01$) increased total protein production in cells and media of cultures labeled with [^{3}H] proline, but did not increase collagen production. Protein synthesis and osteonectin were enhanced in cells following Pb^{2+} exposure.	Not applicable	Sauk et al. (1992)
Pb glutamate 4.5×10^{-5}M–10^{-7}M 1,3, or 5 days incubation In medium	Human Dental Pulp Cells	All concentrations significantly increased cell proliferation on Day 1, 3, and 5 of exposure in serum free conditions. Pb exposure resulted in dose-dependent decrease in intracellular protein and procollagen I production over 5 days. In presence of serum only, 4.5×10^{-5}M Pb^{2+} significantly increased protein production, however, at that same concentration Pb significantly decreased osteocalcin production (i.e., reduced the level of osteocalcin by 55% at 12 hr).	Not applicable	Thaweboon et al. (2002)

Table AX5-8.3 (cont'd). Bone Cell Cultures Utilized to Test Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb glutamate 5–20 μM 48 hr In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Cells treated with 0, 5, 10, or 20 μM Pb acetate for 24 h, followed by an additional 24 h exposure to 0 or 100 pg of 1,25-dihydroxyvitamin D_3 and continued Pb^{2+} exposure, resulted in a significant ($p < 0.05$ or less) reduction of osteocalcin secretion, both in the presence and absence of 1,25-dihydroxyvitamin D_3 at all Pb^{2+} concentrations. This effect is not mediated by PKC.	Not applicable	Guity et al. (2002)
Pb 0.5 to 5 μM 40 min In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	1 and 5 μM Pb^{2+} significantly increased $[Ca^{2+}]_i$ in the absence of 1,25-dihydroxyvitamin D_3 and significantly reduced the peak elevation in $[Ca^{2+}]_i$ induced by 1,25-dihydroxyvitamin D_3. Simultaneous treatment of previously unexposed cells to $Pb^{2+}$and 1,25-dihydroxyvitamin D_3 produced little reduction in the 1,25-dihydroxyvitamin D_3-induced ^{45}Ca uptake, while 40 min of treatment with Pb^{2+} before addition of 1,25-dihydroxyvitamin D_3 significantly reduced the 1,25-dihydroxyvitamin D_3-induced increase in ^{45}Ca influx.	Not applicable	Schanne et al. (1992)
Pb nitrate 5×10^{-4} to 5×10^{-15} M 24 h In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Osteocalcin secretion significantly reduced below control values by culture with 1 μM Pb^{2+} in the presence or absence of added 1,25-dihydroxyvitamin D_3 or 1,25-dihydroxyvitamin D_3 and IGF-I. Inhibition of osteocalcin secretion was almost complete in either hormone-stimulated or basal cultures with the addition of 100 μM Pb^{2+}. Cellular alkaline phosphatase activity paralleled those of osteocalcin, though there was no response to IGF-I alone or in combination with 1,25-dihydroxyvitamin D_3. Pb^{2+}at 10^{-15}, 10^{-12}, and 10^{-9} to 10^{-7} M did not influence DNA contents of cell cultures, but 1 μM significantly ($p < 0.05$) inhibited basal cultures and those with IGF-I + D3. Cell cultures exposed to 1,25-dihydroxyvitamin D_3 and Pb^{2+} were inhibited at 10 μM Pb^{2+}.	Not applicable	Angle et al. (1990)
Pb acetate 2 to 200 μM 72 h In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Pb (2 to 200 μM) had no effect on cell number or DNA and protein synthesis. Alkaline phosphatase activity was significantly reduced ($p < 0.001$) by Pb in a dose- and time-dependent manner. Pb Concentration. Alkaline Phosphatase Inhibition 2 μM. 10.0 ± 1.1% 20 μM. 22.0 ± 6.4% 200 μM. 57.8 ± 8.8% Reductions in alkaline phosphatase mRNA levels mirrored Pb^{2+} -induced inhibition of enzyme activity.	Not applicable	Klein and Wiren (1993)

Table AX5-8.3 (cont'd). Bone Cell Cultures Utilized to Test Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Unidentified Pb^{2+} Various incubation times Not applicable	Bovine (Bovine-derived osteocalcin)	Binding studies of Ca^{2+} to osteocalcin suggested a single binding site with a dissociation constant (Kd) of 7 ± 2 µM for Ca-osteocalcin. Competitive displacement experiments by addition of Pb^{2+} indicated the Kd for Pb-osteocalcin is 1.6 ± 0.42 nM, ~3 orders of magnitude higher.	Not applicable	Dowd et al. (1994)
Unidentified Pb^{2+} Various incubation times Not applicable	Bovine (Bovine-derived osteocalcin)	Circular dichroism indicated Pb^{2+} binding induced a structural change in osteocalcin similar to that found in Ca^{2+} binding, but at 2 orders of magnitude lower concentration. Pb^{2+} has 4 orders of magnitude tighter binding to osteocalcin (Kd = 0.085 µM) than Ca^{2+} (Kd = 1.25 mM). Hydroxyapatite binding assays showed similar increased adsorption of Pb^{2+} and Ca^{2+} to hydroxyapatite, but Pb^{2+} adsorption occurred at a concentration 2–3 orders lower than Ca^{2+}.	Not applicable	Dowd et al. (2001)
Pb acetate 10 µM 2 h In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Pb^{2+} treatment reduced the unidirectional rate of ATP synthesis (P_i to ATP) by a factor of 6 or more ($\Delta M/M_o$: Control = 0.18 ± 0.04, Pb^{2+} < 0.03). Intracellular free Mg^{2+} concentration decreased 21% after 2 h of 10 µM Pb^{2+} treatment (0.29 ± 0.02 mM prior to Pb^{2+} treatment and 0.23 ± 0.02 mM after 2 h of Pb^{2+} treatment, $p < 0.05$).	Not applicable	Dowd et al. (1990)
Pb acetate 5 or 25 µM Up to 24 h In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	5 µM Pb^{2+} significantly altered effect of EGF on intracellular calcium metabolism. In cells treated with 5 µM Pb^{2+} and 50 ng/mL EGF, there was a 50% increase in total cell calcium over cells treated with 50 ng/mL EGF alone.	Not applicable	Long and Rosen (1992)
Pb acetate 5 or 25 µM 20 h In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Treatment with 400 ng/mL culture medium for 1 h or with 25 µM Pb^{2+} for 20 h increased total cell calcium: Treatment — Cell Calcium Control — 7.56 ± 1.05 nmol/mg protein PTH (400 ng/mL) — 23.28 ± 1.40* nmol/mg protein Pb (25 µM) — 11.37 ± 0.57* nmol/mg protein PTH + Pb — 37.88 ± 4.21* nmol/mg protein * $p \leq 0.05$ from control	Not applicable	Long et al. (1992)

Table AX5-8.3 (cont'd). Bone Cell Cultures Utilized to Test Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 10^{-11} to 10^{-7} M 3 min In medium	Rat Osteosarcoma Cells (ROS 17/2.8)	Treatment of ROS cells with Pb at 1 or 5 μM concentrations produced a rise in $[Ca^{2+}]_i$ to 170 nM and 230 nM, respectively, over the basal level of 125 nM. An elevation in $[Ca^{2+}]_i$ to 210 nM occurred during treatment with an activator of PKC, phorbol 12-myristate 13-acetate (10 μM). Pretreatment with a selective inhibitor of PKC, calphostin C, did not change basal $[Ca^{2+}]_i$, but prevented the Pb-induced rise in $[Ca^{2+}]_i$. Free Pb^{2+}activated PKC in a range from 10^{-11} to 10^{-7} M, with a Kcat (activation constant) of 1.1×10^{-10} M and a maximum velocity (Vmax) of 1.08 nmol/mg/min compared with Ca activation of PKC over a range of 10^{-8} to 10^{-3} M, with a Kcat of 3.6×10^{-7} M, and a Vmax of 1.12 nmol/mg/min.	Not applicable	Schanne et al. (1997)
Pb acetate 0.5 to 60 μM 24 to 48 h In medium	Human Osteosarcoma Cells (HOS TE 85) and Rat Osteosarcoma Cells (ROS 17/2.8)	HOS TE 85 Cells Inhibition of proliferation (IC_{50}) = 4 μM Pb Cytotoxicity = 20 μM Pb ROS 17/2.8 Cells Inhibition of proliferation (IC_{50}) = 6 μM Pb Cytotoxicity = 20 μM Pb Highest Pb concentration in both cell types found in mitochondrial fraction.	Not applicable	Angle et al. (1993)
Pb acetate or Pb chloride 0.1 to 200 μM 24 h to 6 days In medium	Chick growth plate chondrocytes	Growth plate chondrocytes were exposed to 3 or 30 μM for up to 6 days. Maximal inhibition of cell proliferation as measured by thymidine incorporation occurred after a 3-day exposure to Pb. A similar 40% inhibition was found at both concentrations. Higher concentrations (up to 100 μM) did not produce further inhibition. In cultures treated for 24 h, Pb produced a dose-dependent inhibition of alkaline phosphatase, with 10 μM producing maximal inhibition (40–50% inhibition). Effects of Pb on proteoglycan synthesis were not found until after 48 h of exposure, with maximal effect after 72 h of exposure (twofold, 30 μM). Pb exposure (10 to 200 μM) for 24 h produced a dose-dependent inhibition of both type II and type X collagen synthesis.	Not applicable	Hicks et al. (1996)

Table AX5-8.3 (cont'd). Bone Cell Cultures Utilized to Test Effects of Lead

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 0.1 to 30 μM 24 h In medium	Chicken growth plate and sternal chondrocytes	A dose-dependent inhibition of thymidine incorporation into growth plate chondrocytes was found with exposure to 1–30 μM Pb for 24 h. A maximal 60% reduction occurred at 30 μM. Pb blunted the stimulatory effects on thymidine incorporation produced by TGF-β1 (24% reduction) and PTHrP (19% reduction), however, this effect was less than with Pb alone. Pb (1 and 10 μM) increased type X collagen in growth plate chondrocytes ~5.0-fold and 6.0-fold in TGF-β1 treated cultures and 4.2-fold and 5.1-fold in PTHrP treated cultures when compared with controls, respectively. Pb exposure alone reduced type X collagen expression by 70–80%.	Not applicable	Zuscik et al. (2002)

Abbreviations

Pb—lead
μCi—microCurie
IU—international units
hr—hour
OB—osteoblast
5F-BAPTA—1,2-bis(2-amino-5-fluorophenoxy)ethane-N,N,N',N'-tetraacetic acid
$[Pb^{2+}]_i$—free intracellular lead
FURA-2—1-[6-Amino-2-(5-carboxy-2-oxazolyl)-5-benzofuranyloxy]-2-(2-amino-5-methylphenoxy) ethane-N,N,N',N'-tetraacetic acid
M—molar
DNA—deoxyribonucleic acid
ΔM—decrease in magnetization of intracellular P_i upon prolonged saturation of gamma-phosphate of ATP
mM—millimolar
Kcat—activation constant
IC_{50}—inhibitory concentration 50%
mg—milligram
^{210}Pb—lead-210 radionuclide
EM—experimental medium
mU—milliunits
^{45}Ca—calcium-45 radionuclide
CRAC—calcium release activated calcium reflux
pg—picogram
mRNA—messenger ribonucleic acid
ng—nanogram
Vmax—maximum velocity
TGF-β1—transforming growth factor-beta 1
mL—milliliter
i.v.—intravenous
CM—control medium
μM—micromolar
ng—nanogram
$[Ca^{2+}]_i$—free intracellular calcium
PGE_2–prostaglandin E_2
PKC—protein kinase C
Kd—dissociation constant
nmol—nanomole
HOS TE 85 cells—human osteosarcoma cells
PTHrP—parathyroid hormone-related protein
GD—gestational day
PTH—parathyroid hormone
min—minute
OC—osteoclast
ROS 17/2.8—rat osteosarcoma cells
nM—nanomolar
h—hour
IGF-I—insulin growth factor I
ATP—adenosine triphosphate
EGF—epidermal growth factor

Table AX5-8.4. Bone Lead as a Potential Source of Toxicity in Altered Metabolic Conditions

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 200 µg/mL 105 days prior to mating or 105 days prior to mating and during gestation and lactation (160 days) In drinking water	Mice	Results suggested very little Pb was transferred from mother to fetus during gestation, however, Pb transferred in milk and retained by the pups accounted for 3% of the maternal body burden of those mice exposed to Pb prior to mating only. The amount of Pb retained in these pups exceeded that retained in the mothers, suggesting lactation effectively transfers Pb burden from mother to suckling offspring. Transfer of Pb from mothers was significantly higher when Pb was supplied continuously in drinking water, rather than terminated prior to mating.	Not given	Keller and Doherty (1980)
Pb acetate 12 mM 8 wks prior to mating and during gestation In drinking water	Rat	Considerably higher lactational transfer of Pb from rat dams compared to placental transfer was reported. Continuous exposure of rat dams to Pb until day 15 of lactation resulted in milk Pb levels 2.5 times higher than in whole blood, while termination of maternal Pb exposure at parturition yielded equivalent blood and milk levels of Pb, principally from Pb mobilized from maternal bone.	Concentration (µg/l) in whole blood at day 15 of lactation: Controls = 14 ± 4; Pb-exposed until parturition = 320 ± 55; Pb-exposed until day 15 of lactation = 1260 ± 171* *$p < 0.001$ compared with dams at parturition.	Palminger Hallén et al. (1996)
Pb acetate 100 ppm (A) Exposure for 158 ± 2 days from 21 days of age to midlactation; (B) Exposure 144 ± 2 days from day 21 up to delivery; (C) Exposure only during lactation; (D, E, and F) groups of nonpregnant rats exposed for periods equivalent to groups A, B and C, respectively. In drinking water	Rat	In rats exposed to Pb 144 days prior to lactation (B), the process of lactation itself elevated blood Pb and decreased bone Pb, indicating mobilization of Pb from bone as there was no external source of Pb during the lactation process. Rats exposed to Pb for 158 days (A)(144 days prior to lactation and 14 days during lactation) also experienced elevated blood Pb levels and loss of Pb from bone. Pb exposure only during the 14 days of lactation was found to significantly increase intestinal absorption and deposition (17 fold increase) of Pb into bone compared to nonpregnant rats, suggesting enhanced absorption of Pb takes place during lactation. The highest concentration of Pb in bone was found in nonpregnant, nonlactating control animals, with significantly decreased bone Pb in lactating rats secondary to bone mobilization and transfer via milk to suckling offspring.	Concentration (µg/dL) in whole blood at day 14 of lactation or equivalent: Group A = 31.2 ± 1.1; Group B = 28.0 ± 1.7; Group D = 27.3 ± 2.2; Group E = 24.7 ± 1.2	Maldonado-Vega et al. (1996)

Table AX5-8.4 (cont'd). Bone Lead as a Potential Source of Toxicity in Altered Metabolic Conditions

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 100 ppm (A) Exposure for 158 ± 2 days from 21 days through 14 days of lactation; (B) Nonpregnant control Group A; (C) Exposure 144 ± 2 days from day 21 up to delivery; (D) Nonpregnant control Group C; (E) Lactating rats not exposed to Pb; (F) Nonpregnant rats not exposed to Pb. In drinking water	Rat	When dietary calcium was reduced from the normal 1 to 0.05%, bone calcium concentration decreased by 15% and bone Pb concentration decreased by 30% during the first 14 days of lactation. In nonlactating rats on the 0.05% calcium diet, there were also decreases in bone calcium, but no incremental bone resorption nor Pb efflux from bone, suggesting the efflux from bone during lactation was related to bone resorption. Enhancement of calcium (2.5%) in the diet of lactating rats increased calcium concentration in bone by 21%, but did not decrease bone resorption, resulting in a 28% decrease in bone Pb concentration and concomitant rise in systemic toxicity.	Concentration (µg/dL) in whole blood at day 14 of lactation or equivalent: Group B = 26.1 ± 2.1, Group A = 32.2 ± 2.7*; Group D = 23.8 ± 2.1, Group C = 28.2 ± 2.2*; Groups E and F = 5.1 ± 0.4. * $p < 0.01$, compared to appropriate control	Maldonado-Vega et al. (2002)
Pb acetate 250 mg/mL Beginning at 5 wks of age, rats exposed to Pb for 5 wks, followed by no additional exposure. In drinking water	Rat	Demonstrated adverse effects in rat offspring born to females whose exposure to Pb ended well before pregnancy. Five wk-old-female rats given Pb acetate in drinking water (250 mg/mL) for five wks, followed by a one mo period without Pb exposure before mating. To test the influence of dietary calcium on Pb absorption and accumulation, some pregnant rats were fed diets deficient in calcium (0.1%) while others were maintained on a normal calcium (0.5%) diet. All Pb-exposed dams and pups had elevated blood Pb levels; however, pups born to dams fed the diet deficient in calcium during pregnancy had higher blood and organ Pb concentrations compared to pups from dams fed the normal diet. Pups born to Pb-exposed dams had lower mean birth weights and birth lengths than pups born to non-Pb-exposed control dams ($p < 0.0001$), even after confounders such as litter size, pup sex, and dam weight gain were taken into account.	Blood Pb concentration of pups (µM): Low calcium/no Pb = 0.137 ± 0.030^{C}; Low calcium/Pb = 1.160 ± 0.053^{A}; Normal calcium/No Pb = 0.032 ± 0.003^{C}; Normal calcium/Pb = 0.771 ± 0.056^{B}. Values that are not marked by the same letter are significantly different ($p < 0.05$).	Han et al. (2000)

Table AX5-8.4 (cont'd). Bone Lead as a Potential Source of Toxicity in Altered Metabolic Conditions

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 1500 µg/Common Pb/kg/d ~10 yrs, replaced by a ^{204}Pb-enriched dose (50 days), then ^{206}Pb-enriched dose (50 days), and finally a ^{207}Pb-enriched dose (50 days, with reduced concentration) Orally, in gelatin capsule	Nonhuman Primate	Sequential doses of Pb mixes enriched in stable isotopes (^{204}Pb, ^{206}Pb, and ^{207}Pb) were administered to a female cynomolgus monkey (*Macaca fascicularis*) that had been chronically administered a common Pb isotope mix. The stable isotope mixes served as a marker of recent, exogenous Pb exposure, while the chronically administered common Pb served as a marker of endogenous (principally bone) Pb. From thermal ionization mass spectrometry analysis of the Pb isotopic ratios of blood and bone biopsies collected at each isotope change, and using end-member unmixing equations, it was determined that administration of the first isotope label allowed measurement of the contribution of historic bone stores to blood Pb. Exposure to subsequent isotopic labels allowed measurements of the contribution from historic bone Pb stores and the recently administered enriched isotopes that incorporated into bone. In general the contribution from the historic bone Pb (common Pb) to blood Pb level was constant (~20%), accentuated with spikes in total blood Pb due to the current administration of the stable isotopes. After cessation of each sequential administration, the concentration of the signature dose rapidly decreased.	Total blood Pb range: 31.2 to 62.3 µg/100g.	Inskip et al. (1996)
Pb acetate 1300 to 1500 µg/Common Pb/kg/d ~10 yrs, replaced by a ^{204}Pb-enriched dose (47 or 281 days), then ^{206}Pb-enriched dose (50 or 105 days), and finally a ^{207}Pb-enriched dose (50 days, with 650 µg concentration in only one primate) Orally, in gelatin capsule	Nonhuman Primate	Initial attempts to apply a single bone physiologically based model of Pb kinetics were unsuccessful until adequate explanation of these rapid drops in stable isotopes in the blood were incorporated. Revisions were added to account for rapid turnover of the trabecular bone compartment and slower turnover rates of cortical bone compartment, an acceptable model evolved. From this model it was reported that historic bone Pb from 11 yrs of continuous exposure contributes ~17% of the blood Pb concentration at Pb concentration over 50 µg/dL, reinforcing the concept that the length of Pb exposure and the rates of past and current Pb exposures help determine the fractional contribution of bone Pb to total blood Pb levels. The turnover rate for cortical (~88% of total bone by volume) bone in the adult cynomolgus monkey was estimated by the model to be ~4.5% per yr, while the turnover rate for trabecular bone was estimated to be 33% per yr.	Various	O'Flaherty et al. (1998)

Table AX5-8.4 (cont'd). Bone Lead as a Potential Source of Toxicity in Altered Metabolic Conditions

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 1100 to 1300 µg/Common Pb/kg/d ~14 yrs, replaced by a ^{204}Pb-enriched dose, ^{206}Pb-enriched dose, and/or finally a ^{207}Pb-enriched dose of varied durations and concentrations. Orally, in gelatin capsule	Nonhuman primate	Using the method of sequential stable isotope administration examined flux of Pb from maternal bone during pregnancy of 5 female cynomolgus monkeys. Blood Pb levels in maternal blood attributable to Pb from mobilized bone were reported to drop 29 to 56% below prepregnancy baseline levels during the first trimester of pregnancy. This was ascribed to the known increase in maternal fluid volume, specific organ enlargement (e.g., mammary glands, uterus, placenta), and increased metabolic activity that occurs during pregnancy. During the second and third trimesters, when there is a rapid growth in the fetal skeleton and compensatory demand for calcium from the maternal blood, the Pb levels increased up to 44% over pre-pregnancy levels. With the exception of one monkey, blood Pb concentrations in the fetus corresponded to those found in the mothers, both in total Pb concentration and proportion of Pb attributable to each isotopic signature dose (common = 22.1% vs. 23.7%, ^{204}Pb = 6.9% vs. 7.4%, and ^{206}Pb = 71.0% vs. 68.9%, respectively). Between 7 and 25% of Pb found in fetal bone originated from maternal bone, with the balance derived from oral dosing of the mothers with isotope during pregnancy. In offspring from a low Pb exposure control monkey (blood Pb <5 µg/100 g) ~39% of Pb found in fetal bone was of maternal origin, suggesting enhanced transfer and retention of Pb under low Pb conditions	Various, with total blood Pb as high as ~65 µg/100 g	Franklin et al. (1997)
Pb acetate 250 mg/L Exposure began either at 5, 10, or 15 wks of age and continued for a total of 5 wks. Drinking water	Rat	Exposed rats for 5 wks to 250 mg/l Pb as acetate in drinking water beginning at 5 wks of age (young child), 10 wks of age (mid-adolescence), or 15 wks of age (young adult), followed by a 4 wk period of without Pb exposure. An additional group of rats were exposed to Pb beginning at 5 wks, but examined following an 8 or 20 wk period after cessation of Pb. Significantly lower blood and bone Pb concentrations were associated with greater age at the start of Pb exposure and increased interval since the end of exposure. Young rats beginning exposure to Pb at 5 wks and examined 20 wks after cessation of exposure still, however, had bone Pb concentrations higher than those found in older rats only 4 wks after cessation of exposure.	Pb concentration (µM) 4 wks after cessation of Pb exposure: Exposure started at 5 wks of age = 1.39 ± 0.09; Exposure started at 10 wks of age = 1.18 ± 0.12; Exposure started at 15 wks of age = 0.82 ± 0.05.	Han et al. (1997)

Table AX5-8.4 (cont'd). Bone Lead as a Potential Source of Toxicity in Altered Metabolic Conditions

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 50 ppm 11 mo Drinking water	Rat	Studied differences in tissue distribution of Pb in adult and old rats. Adult (8 mo old) and old (16 mo old) rats were exposed to 50 ppm Pb acetate in drinking water for 11 mo at which time the experiment was completed. Bone (femur) Pb levels in older rats were found to be less than those in younger rats, however, blood Pb levels were higher in the older rats. Brain Pb concentration in the older rats exposed to Pb were significantly higher, and brain weight significantly less than the brain Pb concentration and weights of unexposed older control rats or adult rats exposed to Pb, suggesting a potential detrimental effect. Authors suggested that a possibility for the observed differences in tissue concentrations of Pb was due to changes in the capacity of bone to store Pb with advanced age.	Approximate median values after 6 mo of exposure: Adult rats : 23 µg/dL Old rats: 31 µg/dL After 11 mo of exposure: Adult rats: 16 µg/dL Old rats: 31 µg/dL	Cory-Slechta et al. (1989)
Pb acetate 0, 2, or 10 mg/kg/d 9.5 mo Drinking water	Rat	Examined kinetic and biochemical responses of young (21 days old), adult (8 mo old), and old (16 mo old) rats exposed to Pb at 0, 2, or 10 mg Pb acetate/kg/d over a 9.5 mo experimental period. Results suggested older rats may have increased vulnerability to Pb due to increased exposure of tissues to Pb and greater sensitivity of the tissues to the effects of Pb.	Various from ~1 µg/dL up to 45 µg/dL	Cory-Slechta (1990b)
Pb acetate 7 yrs total Drinking water	Nonhuman primate	In studies of bone Pb metabolism in a geriatric, female nonhuman primates exposed to Pb ~10 yrs previously, there were no significant changes in bone Pb level over a 10 mo observation period as measured by ^{109}CD K X-ray fluorescence. The mean half-life of Pb in bone of these animals was found to be 3.0 ± 1.0 yrs, consistent with data found in humans, while the endogenous exposure level due to mobilized Pb was 0.09 ± 0.02 µg/dL blood.	Historic concentrations during exposure: 44 to 89 µg/100 mL.	McNeill et al. (1997)
Pb (type unidentified) occurring naturally in diet (0.258 ng/mg dry wt) and water (5.45 ppb). Exposure from age 1 mo up to 958 days. Drinking water and diet	Mice	The Pb content of femurs increased by 83% (values ranged from 0.192 to 1.78 ng Pb/mg dry wt), no significant relationship was found between Pb and bone density, bone collagen, or loss of calcium from bone. The results suggest against low levels of bone Pb contributing to the osteopenia observed normally in C57BL/6J mice.	None given	Massie and Aiello (1992)

Table AX5-8.4. (cont'd). Bone Lead as a Potential Source of Toxicity in Altered Metabolic Conditions

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 250 mg/l Exposure for 5 wks Drinking water	Rat	Rats were exposed to Pb for 5 wks, followed by a 4 wk washout period without Pb to allow primarily accumulation in the skeleton. Rats were then randomly assigned to a weight maintenance group (WM), a moderate weight loss (MWL) group (70% of maintenance diet), or a substantial weight loss (SWL) group (40% of maintenance diet) for a 4 wk period. At the end of this experimental period the blood and bone levels of Pb did not differ between groups, however, the amount and concentration of Pb in the liver increased significantly. Femur: WM 826 ± 70; MWL 735 ± 53; SWL 935 ± 84 Spinal Column Bone: WM 702 ± 67; MWL 643 ± 59; SWL 796 ± 59	WM = 1.25 ± 0.10 µM; MWL = 1.16 ± 0.10 µM; WM = 1.32 ± 0.10 µM;	Han et al. (1996)
Pb acetate 250 µg/l 14 days Drinking water	Rat	Study was undertaken to determine the effect of weight loss and exercise on the distribution of Pb. Weight loss secondary to dietary restriction was a critical factor elevating organ Pb levels and, contrary to prior study (Han et al. (1996)), elevated blood levels of Pb. No significant difference in organ or blood Pb concentrations were reported between the exercise vs. no exercise groups.	Graphs indicate concentrations ranging from 0.20 to 2.00 µM.	Han et al. (1999)

Abbreviations

µg—microgram
mL—milliliter
%—percent
mM—millimolar
l—liter
ppm—parts per million
dL—deciliter
mg—milligram
µM—micromolar
Pb—lead
kg—kilogram
g—gram
^{204}Pb, ^{206}Pb, ^{207}Pb—Stable isotopes of lead 204, 206, 207, respectively
wt—weight
ppb—parts per billion

Table AX5-8.5. Uptake of Lead by Teeth

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 1 µg/kg body weight Single IP injection	Rat	Uptake of Pb label into incisors of suckling rats: 0.7% of injected dose in 4 incisors of suckling rat after 24 h, 1.43% after 192 h. 0.6% of injected dose in 4 incisors of adult after 24 h, 0.88% after 192 h.	Mean percent of dose after time: Suckling: 3.04% after 24 h 1.71% after 72 h 1.52% after 144 h 1.18% after 192 h Adult: 6.40% after 24 h 3.41% after 24 h 1.92% after 24 h 1.04% after 72 h 0.72% after 144 h 0.48% after 192 h	Momčilović and Kostial (1974)
Pb aerosol 77, 249, or 1546 µg/m^3 for 50 to 70 days Inhalation	Rat	11 micrograms Pb/g incisor taken up in animals exposed to 77 µg/m^3 for 70 days vs. 0.8 µg Pb/g in control animals 13.8 µg Pb/g incisor in rats exposed to 249 µg/m^3 for 50 days 153 µg Pb/g incisor in rats exposed to 1546 µg/m^3 for 50 days	Control: 2.6 µg/dL 77 µg/m^3: 11.5 µg/dL 249 µg/m^3: 24.1 µg/dL 1546 µg/m^3: 61.2 µg/dL	Grobler et al. (1991)
Pb acetate 0, 3, or10 ppm During pregnancy and 21 days of lactation Drinking water	Rat	Pb concentration in teeth of offspring: 0 ppm group–Incisors (1.3 ppm), 1st molars (0.3 ppm) 3 ppm group–Incisors (1.4 ppm), 1st molars (2.7 ppm) 10 ppm group–Incisors (13.3 ppm), 1st molars (11.4 ppm)	Not given	Grobler et al. (1985)

Abbreviations

µg—microgram
kg—kilogram
IP—intraperitoneal
%—percent
h—hour
m^3—cubic meter
Pb—lead
g—gram
ppm—parts per million

Table AX5-8.6. Effects of Lead on Enamel and Dentin Formation

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb "salt" 0.075 mM/100 g , 0.15 mM/100 g or 1.5 mM/100 g Single, SC injection	Rat	0.075 mM dose, no disruption of dentin and enamel. 0.15 mM dose, mild mineralization disruption of dentin and enamel. 1.5 mM dose, mild to moderate disruption of dentin and enamel.	Not given	Eisenmann and Yaeger (1969)
Pb acetate 30 mg/kg Single, i.v. injection	Rat	Rapid rise in serum calcium and phosphorus after injection. Formation of a "Pb line" in growing dentin within 6 hr after injection.	Not given	Appleton (1991)
Pb acetate 3 mg/kg Single, i.v. injection	Rat	Production of a hypomineralized band in dentin.	Not given	Appleton (1992)
Pb acetate 0 mg/l, 34 mg/l, or 170 mg/l 70 days Drinking water	Rat	Increased in relative amount of protein in enamel matrix. Significant ($p < 0.05$) decrease in microhardness values of groups exposed to Pb in regions of maturation enamel, but not fully mature enamel. Delay in enamel mineralization in animals exposed to Pb.	0 mg/l group: 0 ppm 34 mg/l group: 18.1 ppm 170 mg/l group: 113.3 ppm	Gerlach et al. (2002)
Pb acetate 40 mg/kg Single, IP injection	Rat	Significantly ($p < 0.05$) reduced eruption rates at various time points (days 8, 14, 16, 22, 24, 28) under hypofunctional conditions.	Days after injection 0 days: 48 µg/dL 10 days: 37 µg/dL 20 days: 28 µg/dL 30 days: 16 µg/dL (Values estimated from graph)	Gerlach et al. (2000b)

Abbreviations

Pb—lead
mM—millimolar
g—gram
SC—subcutaneous
mg—milligram
kg—kilogram
i.v.—intravenous
l—liter
ppm—parts per million
IP—intraperitoneal
µg—microgram
dL—deciliter

Table AX5-8.7. Effects of Lead on Dental Pulp Cells

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb glutamate 4.5×10^{-5}M–10^{-7}M 1,3, or 5 days incubation	Human Dental Pulp Cells	All concentrations significantly increased cell proliferation on Day 1, 3 and 5 of exposure in serum free conditions. Pb exposure resulted in dose-dependent decrease in intracellular protein and procollagen I production over 5 days. In presence of serum only 4.5×10^{-5}M significantly increased protein production. Pb significantly decreased osteocalcin production.	Not applicable	Thaweboon et al. (2002)

Abbreviations

Pb—lead
M—molar

Table AX5-8.8. Effects of Lead on Teeth—Dental Caries

Compound Dose/Concentration Duration Exposure Route	Species	Effects	Blood Level	Reference
Pb acetate 0.5 mEq 84 days males 98 days females Drinking water	Hamster	Significant increase in dental caries in male hamsters only (85 mean molar caries score control vs. 118 for Pb exposed). No significant difference in dental caries in female hamsters (68 mean molar caries score control vs. 85 for Pb exposed).	Not given	Wisotzky and Hein (1958)
Pb acetate 34 ppm Pre- and perinatal Drinking water	Rat	Pb exposure resulted in an almost 40% increase in the prevalence of caries and nearly 30% decrease in stimulated parotid salivary gland function.	Control: <5 µg/dL 34 ppm Pb: 48 ± 13 µg/dL	Watson et al. (1997)
Pb acetate 10 or 25 ppm Pb 3 wks Drinking water	Rat	When 15 ppm fluoride was concurrently given in diet, Pb did not increase prevalence of caries.	Not given	Tabchoury et al. (1999)

Abbreviations

mEq—milliequivalents
d—days
ppm—parts per million
%—percent
µg—microgram
dL—deciliter

ANNEX TABLES AX5-9

Table AX5-9.1. Studies on Lead Exposure and Immune Effects in Humans

Nature of Exposure	Dose or Blood Lead Levels (BLLs)	Sample Population	Reported Effects	Reference
Environmental	10.1–48.2 µg/L (BLL)	2nd grade children living near industrial waste incinerator or other industries causing pollution	Increased blood Pb concentration associated w/ increased IgE, especially above 28 µg/dL. Also decreased T-cells, cytotoxic T-cells, and B-cells (non-linear relation).	Karmaus et al. (2005)
Occupational	22 µg/dL: <30 yrs old 23.0 µg/dL: 30–39 yrs old 24.1 µg/dL: ≥40 yrs old	Employees of Pb storage battery factories in Korea 554 Men 52 Women	Serum IgE higher when BLL >30 µg/dL—Correlation of BLL with serum IgE. For employees less than 30 yrs old, IL-4 was lower when BLL >30 µg/dL.	Heo et al. (2004)
Environmental	3.47–49.19 µg/dL	Children 6–11 yrs of age 30 girls 35 boys Proximity to smelter	Indirect (PHA) macrophage activation. NO production negatively associated with BLL. With proximity closest to smelter monocytes had increased superoxide anion production by indirect and direct activation (positive correlation with BLL–stronger for boys than girls).	Pineda-Zavaleta et al. (2004)
Environmental	2.56–43.69 µg/dL (mean 9.52 µg/dL)	38 preschool children (3–6 yrs of age); 35 controls	Percent of $CD4^+$ and $CD4^+CD+$ cells decreased while $CD8^+$ increased.	Zhao et al. (2004)
Occupational	Range of 10.0–400.9 µg/dL Mean = 88.3 µg/dL Controls all below 10 µg/dL	Male Pb-exposed workers	PHA-mitogen response decreased; and IFN-gamma production increased. No effect on NK cytotox.	Mishra et al. (2003)
Environmental	2.56–43.69 µg/dL (BLL mean of 9.52 µg/dL)	96 females 121 males (3–6 yrs old)	IgG and IgM lower in high BLL group (≥9.52 µg/dL). IgE greater in high BLL group ($P < 0.10$). No difference among males but females exposed to higher Pb had significant decreases in IgG and IgM and increased in IgE. Correlation of BLL and serum IgE $r = 0.48$; $P = 0.002$.	Sun et al. (2003)
Occupational	10–20 yr exposure (original BLL mean 60 µg/dL; at time of study BLL mean = 30 µg/dL)	30 Pb workers from battery manufacturing plant (43 males and 21 females)	Increased percentage of monocytes while percentage of B-cells, numbers of lymphocytes, monocytes, and granulocytes decreased.	Sun et al .(2003)
Occupational	74.8 ± 17.8 µg/dL vs. 16.7 ± 5.0 µg/dL for controls	25 male storage battery workers exposed >6 mo; age 33 ± 8.5 yrs	Decreased blood hemoglobin, $TCD4^+$ cells, IgG, IgM, C3 and C4 compliment proteins. Increased zinc protoporphyrin. Impaired neutrophil chemotaxis and random migration.	Basaran and Undeger (2000)

Table AX5-9.1 (cont'd). Studies on Lead Exposure and Immune Effects in Humans

Nature of Exposure	Dose or Blood Lead Levels (BLLs)	Sample Population	Reported Effects	Reference
Environmental	1.7–16.1 µg/dL (Range in <3 yr old group)	1561 children and adults in high Pb community 480 controls	6–35 mo: increased IgA, IgG, IgM, number and proportion of B lymphocytes decreased proportion of T-lymphocytes especially true when BLL > 15 µg/dL >3 yrs of age–no differences.	Sarasua et al. (2000)
Epidemiological study	Blood Pbs from 1–45 µg/dL	Urban Children population in Missouri; 56% male 279 children 9 mo–6 yr of age	Correlation of blood Pb levels and serum IgE levels in Missouri children.	Lutz, et al. (1999)
Occupational	BLL=39 Range 15–55 µg/dL	145 Pb exposed workers 84 controls	No major effects; only subtle effects. Elev. B cells elevated CD4+/CD45RA+ cells. Decr. Serum IgG.	Pinkerton et al. (1998)
Occupational	Pb workers with BLL between 7–50 µg/dL; mean 19 µg/dL	71 male chemical plant workers vs. 29 controls	T cell populations, Naïve T cells correlated positively with blood PB levels. Memory T cells reduced with Pb.	Sata et al. (1998)
Occupational	Exposed—Range of 38–100 µg/dL mean = 74.8 µg/dL; Controls 11–30 µg/dL mean = 16.7 µg/dL (high controls!)	25 Male battery plant workers vs. 25 controls	Absolute and relative numbers of CD4+ T cells reduced in exposed group. IgG, IgM C3 and C4 serum levels all lower in workers.	Undeger et al. (1996)
Occupational	BLL 12–80.0 µg/dL	33 male workers in a storage battery plant	No changes in serum Igs of PHA response of PBMC.	Queiroz et al. (1994)
Occupational	Males high BLL ≥25 µg/dL lower BLL <25 µg/dL control BLL ≤10 µg/dL	51 Firearms instructors (high and lower) vs. controls	T cell phenotypes and response—Pb reduced relative CD3+ cells and relative and absolute CD4+ cells also reduced PHA (high Pb)and PWM mitogen responses, reduced MLR also(high Pb).	Fischbein et al. (1993)
Occupational	>60 µg/dL for group showing best IgE effect	2 groups of male workers occupationally exposed	IgE positively correlated with BLL.	Horiguchi et al. (1992)
Occupational	BLL 14.8–91.4 µg/dL	39 male workers of storage battery plant (4 yr mean exposure)	Impaired neutrophil migration. Impaired nitroblue tetrazolium positive neutrophils. Greater for those exposed up to 1 yr than those with longer exposure "safe" levels of Pb can still cause immunosuppression.	Queiroz et al. (1993)
In vitro	207–1035 µg/L	Human lymphocytes from adults 25–44 yrs of age	Pb associated with greater IgG production after stimulation with PWM–not dose dependent.	Borella and Giardino (1991)

Table AX5-9.1 (cont'd). Studies on Lead Exposure and Immune Effects in Humans

Nature of Exposure	Dose or Blood Lead Levels (BLLs)	Sample Population	Reported Effects	Reference
Occupational	33.2 µg/dL in Pb-exposed group 2.7 µg/dL in controls	10 Male workers in scrap metal refinery vs. 10 controls	PMN chemotaxis reduced to 2 different chemoattractants.	Valentino et al. (1991)
Occupational	10 Pb exposure workers vs. controls Worker BLLs of 41–50 µg/dL No controls >19 µg/dL		ConA-generated suppressor cell production—increased. Some other cellular parameters unchanged.	Cohen et al. (1989)
Occupational	Blood Pbs 64 µg/dL Range 21–90	39 male workers in Pb exposed group	PHA response of lymphocytes from workers decreased.	Alomran and Shleamoon (1988)
Occupational	Comparison of workers with 25–53 µg/dL vs. controls with 8–17 µg/dL	Workers exposure to Pb	No change in serum Ig levels PHA response of cells or NK activity.	Kimber et al. (1986)
Environmental	Near smelter BLLs varied seasonally 25–45 µg/dL Control area BLLs varied seasonally 10–22 µg/dL	Boys and girls ~11.5 yrs old living near Pb smelting plant	Higher BLL associated with: decreased Δ-amino levulinic acid dehydrogetase. Decreased IgM and secretory IgA. Inversely related to IgG.	Wagnerova et al. (1986)
Occupational	Workers (18–85.85.2 µg/dL BLL) controls (6.6–20.8 µg/dL BLL)	73 workers vs. 53 controls	Negative correlation of BLL and serum IgG and C3. Positive correlation of BLL and saliva IgA.	Ewers et al. (1982)
Environmental	12 Afr.- American children BLLs 41–51µg/dL; 7 controls BLLs 14–30 µg/dL	12 African American preschool children vs. 7 controls	No difference in anti-tetanus antibody levels or in complement levels.	Reigart and Graber (1976)

Table AX5-9.2. Effect of Lead on Antibody Forming Cells (In Vitro Stimulation)

Species	Strain/Gender	Age	Effect	In Vivo/ Ex Vivo	Lead Dose/ Concentration	Duration of Exposure	Reference
Mouse	Various	Adult	↑AFC	No	10 µM	5 days	McCabe and Lawrence (1991)
Mouse	Various	Adult	AFC No change	Yes	10 mM in water	8 wks	Mudziuski et al. (1986)
Mouse	CBA/J females	Adult	↑AFC primary response	No	100 µM	5 days	Warner and Lawrence (1986)
Mouse	BDF_1 females	Adult	↑AFC—T dependent antigen AFC—T independent antigen, no change		50 µg Pb acetate in water	3 wks	Blakley and Archer (1981)
Mouse	CBA/J females	Adult	↑AFC	Yes	0.08 mM and 0.4 mM	4 wks	Lawrence (1981a)
Mouse	CBA/J	Adult	↑AFC	No	10^{-5} M	5 days	Lawrence (1981b)
Mouse	CBA/J females	Adult	↑AFC	No	10^{-4} M	1 hr preincubation	Lawrence (1981c)
Mouse	Swiss males	Adult	↓AFC	Yes	0.5 ppm tetraethyl Pb	3 wks	Blakley et al. (1980)
Mouse	Swiss	Adult	↓AFC	Yes	1300 ppm	10 wks	Koller and Roan (1980)
Rat	SD	Neonate–Juvenile	↓AFC (IgM)	Yes	25 ppm and 50 ppm	3 wks prenatal and 6 wks postnatal	Luster et al (1978)
Mouse	Swiss	Adult	↑AFC–IgM ↓AFC–IgG	Yes	4 mg i.p. or oral	Single dose	Koller et al. (1976)
Mouse	Swiss	Adult	↓AFC–IgM ↓AFC–IgG	Yes	13.75 ppm–1,375 ppm	8 wks	Koller and Kovacic (1974)

Table AX5-9.3. Studies Reporting Lead-induced Suppression of Delayed Type Hypersensitivity and Related Responses

Species	Age	Strain/Gender	Route	Lowest Effective Dose	Duration of Exposure	Reference
Rat	Embryo	SD females	Oral to Dam	250 ppm (BLL at 4 wk = 6.75 µg/dL)	5 wks	Chen et al. (2004)
Chicken	Embryo	Cornell K females	*in ovo*	200 µg	Single injection E12	Lee et al. (2002)
Rat	Fetal	CD females	Oral to Dam	500 ppm	6 days	Bunn et al. (2001c)
Rat	Embryo–fetal	F344 and CD females	Oral to Dam	250 ppm	3 wks	Bunn et al. (2001b)
Rat	Embryo–fetal	F344 females	Oral to Dam	250 ppm (BLL = 34.8µg/dL at birth)	3 wks	Bunn et al. (2001a)
Chicken	Embryo	Cornell K females	*in ovo*	200 µg (BLL = 11 µg/dL)	Single injection E12	Lee et al. (2001)
Mouse	Adult	BALB/c females	Oral	512 ppm (BLL = 87 µg/dL)	3 wks	McCabe et al. (1999)
Rat	Embryo-fetal	F344 females	Oral to Dam	250 ppm Pb acetate	5 wks (2 before, 3 during gestation)	Chen et al. (1999)
Rat	Embryo-fetal	F344 females	Oral to Dam	250 ppm Pb acetate	5 wks (2 before, 3 during gestation)	Miller et al. (1998)
Goat	Adult	Females	Gastric intubation	50 mg/kg Pb acetate	6 wks	Haneef et al. (1995)
Rat	Adult	Wistar males	Oral	6.3 m mol kg^{-1}	8 wks	Kumar et al. (1994)
Mouse	Adult	Swiss	s.c.	0.5 mg/kg/d	Shortest = 3 days just prior to challenge	Laschi-Loquerie et al. (1984)
Rat	Neonatal/ Juvenile	CD females	Oral	25 ppm Pb acetate (BLL= 29.3 µg/dL)	6 wks	Faith et al. (1979)
Mouse	Adult	BALB/c	i.p.	0.025 mg Pb acetate	30 days	Muller et al. (1977)

Table AX5-9.4. Effect of Lead on Allogeneic and Syngeneic Mixed Lymphocyte Responses

Species	Strain/Gender	Age	Proliferation Effects	In Vivo/ Ex Vivo	Lead Dose/Concentration	Duration of Exposure	References
Mouse	C57Bl/6 and BALB/c	Adult	↑Allo-MLR	No	0.1 µM	4 days	McCabe et al. (2001)
Rat	Lewis males	Adult	↑Allo-MLR ↑Syngeneic-MLR	No	50 ppm Pb acetate	4 days	Razani-Boroujerdi et al. (1999)
Mouse	CBA/J females	Adult	↑Allo-MLR	No	10^{-6}–10^{-4} M	5 days	Lawrence (1981b)
Mouse	CBA/J females	Adult	↑Allo-MLR	Yes	0.08 mM and 0.4 mM	4 wks	Lawrence (1981a)
Mouse	DBA/2J males	Adult	Allo-MLR no significant change	Yes	13, 130 and 1300 ppm	10 wks	Koller and Roan (1980)

Table AX5-9.5. Effect of Lead on Mitogen-induced Lymphoid Proliferation

Species	Strain/ Gender	Age	Proliferation Effects	In Vivo/ Ex Vivo	Lead Dose/ Concentration	Duration of Exposure	References
Human	—	Adult	↓PHA	Yes	Not available	Occupational	Mishra et al. (2003)
Mouse	TO males	Adult	↓ConA ↓LPS	Yes	1 mg/kg daily	2 wks	Fernandez–Carbezudo et al. (2003)
Mouse	Several	Adult	PHA stimulation No change	No	25 μM	3 days	McCabe et al. (2001)
Rat	Lewis and F344 males	Adult	↑ConA ↑LPS	No	25 ppm	3 days	Razani–Boroujerdi et al. (1999)
Mouse	CBA/J	Adult	LPS No change	No	10 μM	3 days	McCabe and Lawrence (1990)
Rat	AP strain males	Adult	PHA No change	Yes	100 ppm and 1,000 ppm	2–20 wks	Kimber et al. (1986)
Mouse	CBA/J females	Adult	ConA LPS No change	No	10^{-4} M	2 days	Warner and Lawrence (1986)
Mouse	BDF1 females	Adult	↑ConA ↑PHA ↑Staph A enterotoxin LPS no change	Yes	0–1,000 ppm	3 wks	Blakley and Archer (1982)
Rat	SD males	Adult	↑ConA ↑PHA ↑LPS	Yes	1% Pb acetate in diet	2 wks	Bendich et al. (1981)
Mouse	CBA/J females	Adult	PHA no change ↓LPS (high doses only)	Yes	10 mM	4 wks	Lawrence (1981a)
Mouse	CBA/J females	Adult	ConA, PHA no change ↑LPS	No	10^{-6}–10^{-4} M	2.5 days	Lawrence (1981b)
Mouse	CBA/J females	Adult	ConA, PHA no change ↑LPS	No	10^{-6}–10^{-4} M	2–5 days	Lawrence (1981c)

Table AX5-9.5 (cont'd). Effect of Lead on Mitogen-induced Lymphoid Proliferation

Species	Strain/ Gender	Age	Proliferation Effects	In Vivo/ Ex Vivo	Lead Dose/ Concentration	Duration of Exposure	References
Mouse	C57 Bl/6 males	Adult	↓PHA ↓ConA LPS No change	Yes	1,300 ppm	8 wks	Neilan et al. (1980)
Rat	SD females	Neonatal–Juveniles	↓PHA ↓ConA	Yes	25 ppm	6 wks	Faith et al. (1979)
Mouse	BALB/c	Adult	↑LPS	No	10^{-5}–10^{-3} M	3 days	Gallagher et al. (1979)
Mouse	Swiss males	Adult	↓PHA ↓PWM	Yes	2,000 ppm	30 days	Gaworski and Sharma (1978)
Mouse	Swiss males	Adult	↑PHA ↑PWM	No	0.1 mM–1.0 mM	2–3 days	Gaworski and Sharma (1978)
Mouse	CBA/J	Adult	↑LPS	Yes	13 ppm	18 mo	Koller et al. (1977)
Mouse	BALB/c	Adult	↑LPS	No	10^{-5}–10^{-3} M	2–3 days	Shenker et al. (1977)

Table AX5.9.6. Pattern of Lead-induced Macrophage Immunotoxicity

Species	Strain/ Gender	Age	Function	In Vivo/ Ex Vivo	Lowest Effective Dose	Duration of Exposure	References
Nitric Oxide							
Human	Both genders	Juvenile	↓NO	Yes	NK		Pineda-Zavaleta et al. (2004)
Rat	CD males	Embryo	↓NO	Yes	500 ppm	6 days	Bunn et al. (2001c)
Chicken	Cornell K strain females	Embryo	↓NO	Yes	10 µg	One injection (E5)	Lee et al. (2001)
Mouse	BALB/c females	Adult	↓NO	No	20 µg/mL one lower dose ↑NO	2 hrs	Krocova et al. (2000)
Chicken	HD-11 cell line	-	↓NO	No	4.5 µg	18 hrs	Chen et al. (1997b)
Mouse	CBA/J females	Adult	↓NO	No	1.0 µg	4 days	Tian and Lawrence (1996)
Mouse	CBA/J females	Adult	↓NO	No	0.625 µM	4 days	Tian and Lawrence (1995)
Reactive Oxygen Intermediates							
Human	Associated in males	Juvenile	↑ROI	Yes	NK	NK	Pineda-Zavaleta et al. (2004)
Rat	Not indicated	NK	↑ROI	No	240 µM	3 hrs	Shabani and Rabbani (2000)
Mouse	BALB/c females	Adult	↑ROI	Yes	1.5 mg/kg diet	30 days	Baykov et al. (1996)
Rabbit	New Zealand white males	Adult	↑ROI	Yes	31 µg/m^3 inhaled	3 days	Zelikoff et al. (1993)

ANNEX TABLES AX5-10

Table AX5-10.1. Hepatic Drug Metabolism

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Triethyl Pb chloride, 0–3.0 mg/kg b. wt. In vitro, 0.0–3.0 mM triethyl Pb	2 days	In vitro, rat microsomes	—	Triethyl Pb increased microsomal N-oxygenation in vivo and decreased microsomal C oxygenation by in vitro treatment. Either treatment thus gave rise to an increase in the N-oxygenation/C-oxygenation ratio, which may lead to tumor potentiation.	Odenbro and Arhenius (1984)
	Not specified	In vivo, rat microsomes	—		
5 or 10 µmol/100g b. wt. Pb nitrate; i.v.	36 h	Male Fischer 344 rats	—	Pb decreases phase I components (liver microsomal cyt.P-450), and increases Phase II components (GST, DT diaphorase etc). Liver cytosol in treated animals had a polypeptide that cross-reacted with GSTP.	Roomi et al. (1986)
5, 10, 50 mg Pb acetate kg^{-1} b. wt.	Multiple durations (15 days, 2 and 3 mo)	Female albino rats	—	Over all induction of cyt-p—450 and b5 in liver, long-term increase in liver GST and GSH.	Nehru and Kaushal (1992)
100 µmol/kg; i.v. Pb acetate	24 h	Male Fischer 344 rats	—	Decrease in total CYP amount, selective inhibition of CYP1A2 and decrease in the expression at m-RNA and protein level, induction of placental form of glutathione s-transferase (GST-P).	Degawa et al. (1994)
100 µmol/kg Pb nitrate; i.v.	9 h before or 6 h after 2-methoxy-4-aminoazobenzene (2-Meo-AAB)	Male Fischer 344 rats	—	Male fisher rats treated with different metal ions ─Pb nitrate, nickel chloride, cobalt chloride or cadmium chloride exhibited decreased total CYP amount in liver microsomes. However, only Pb reduced the levels of the mRNA and protein of CYP 1A2 induced with 2-methoxy-4-aminoazobenzene (2-Meo-AAB) and decreased the microsomal activity (Per CYP), Pb also induced placental form of Glutathione, a marker enzyme for preneoplastic lesion.	Degawa et al. (1995)
100 µmol/kg; i.v. Pb acetate	24 h	Male F 344 rats	—	Inhibition of CYP1A mRNA(s) by Pb nitrate is by aromatic amines, not by aryl hydrocarbons.	Degawa et al. (1996)
100 µmoles /kg; i.v.	Multiple durations (3, 6, 12, 24, and 36 h)	Male Wistar rats	—	Stimulation of TNFα preceding hepatocyte DNA synthesis indicates a role for it in liver cell proliferation. Pb nitrate enhances sensitivity to bacterial LPS, in hepatocytes.	Shinozuka et al. (1994)

Table AX5-10.1 (cont'd). Hepatic Drug Metabolism

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Single 0.33 mg/kg-1 Pb nitrate	Multiple durations	Male Wistar rats	—	Pb confers protection against the CCL4 induced hepatotoxicity as evident by marked reduction in serum Alanine aminotransferase (AST) and aspartate aminotransferase (AST) and this protection is not associated with the mitotic response of Pb.	Calabrese et al. (1995)
Pb acetate, 75 mg of Pb^{2+}/kg, intraperitonial	Multiple analyses up to 30 h	C57BL/6 male mice	—	The decrease in P-450 as a result of Pb poisoning occurs at two levels. (1) A mechanism unrelated to heme, where Pb interferes with P-450 in 2 ways. (2) A mechanism dependent on heme, in which Pb inhibits heme synthesis.	Jover (1996)
0–10^{-6} M Pb nitrate	3 days	Fish hepatoma cell line PLHC-1	—	Effect of heavy metals Cu(II), Cd(II), Co(II), Ni(II), Pb(II), and Zn(II), on Cytochrome induction (CYP1A) induction response and Ethoxy resorufin-o-deethylase (EROD) activity. All metals had a more pronounced effect on EROD activity than Cyp1 A protein. The rank order of the metal inhibition on EROD is Cd(II) > Ni(II) > Cu(II) > Co(II) = Zn(II), Pb(II), Cd(II) and (Cu). May affect Cyp1 A system of the fish liver at low concentrations through the direct inhibition of CYP 1A enzyme activity.	Bruschweiler et al. (1996)
DT Diaphorase activity 0–125 mg/kg Pb acetate, Pb nitrate Time course experiments 100 mg/kg Pb acetate, i.p.	24 h–120 h	Male Wistar rats	—	Pb acetate and nitrate induce DT diaphorase activity which is inhibited significantly by Dil a calcium antagonist, showing that these changes are mediated by intracellular calcium changes. Pb acetate induces DT diaphorase activity with out thymus atrophy and hence was suggested to be a monofunctional inducer as against the Methyl cholanthrene induced DT diaphorase activity.	Arizono et al. (1996)
Cell viability assays 0–30 μM, for all other As , Pb, Hg, 5 μM, Cd, 1 μM	24 h in general and for EROD assays by PAHs 24–72 h	Primary human hepatocytes	—	The effect of metals on PAH induced CYP1A and 1A2 as probed by Ethoxy resorufin o- deethylase activity has demonstrated, metals -Arsenic, Pb, mercury and cadmium decreased CYP1A1/ A2 expression by polycyclic aromatic hydrocarbons depending on the dose, metal and the PAH. Arsenic was most effective, followed by Pb, cadmium, and mercury. Cell viability was decreased by 20–28% by metals.	Vakharia (2001)

Table AX5-10.1 (cont'd). Hepatic Drug Metabolism

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
10–100 µM, in vitro	24 h	Murine hepatoma cell line	—	Effect of heavy metals on Aryl hydrocarbon regulated genes—metals alone did not induce a significant change in the cyp1a1 activity and protein levels but increased its m-RNA expression. AHR ligand-mediated induction of cyp1a1 activity and protein was observed by all the metals. Pre and post translational modulation in this regulation have been implicated. These results demonstrate that the heavy metals differentially modulate the constitutive and the inducible expression of AHR regulated genes.	Korashy and El-Kadi (2004)
5 and 10 µmoles/100 g of b.wt, single i.p	—	Wistar Rat	—	Pb nitrate induced the expression of Placental form of Glutathione transferase along with liver cell proliferation. The biochemical lesions induced by Pb under these conditions were similar to that of hepatic nodules.	Roomi et al. (1987)
100 µmoles/100 g b. wt. Pb nitrate, single injection, i.v.	Animals were sacrificed at 1, 2, 3, 4, and 15 days	Wistar rats	—	Acute Pb treatment results in induced activity of Gamma-glutamyl transpeptidase, induced GSTP, a typical marker of pre neoplastic lesion in most hepatocytes. Pb also inhibited liver adenylate cyclase activity 24 h postexposure.	Columbano et al. (1988)
100 mg/kg i.p., single exposure	Multiple analyses 0–96 h	Male DDY strain mice	—	Pb decreased Glutathione content and decreased Glutathione s-transferase activity that is independent of Glutathione levels.	Nakagawa et al. (1991)
100 µmol/kg body wt, i.v	70 h	Male Sprague Dawley rats	—	Acute Pb nitrate treatment caused a significant increase of GST activity in liver and kidney. While in liver the activity increase is mainly due to isozyme GST 7-7, in kidney it is through the induction of all the isozymes.	Planas-Bhone and Elizalde (1992)
100 µmol/kg b. wt., intra cardiac	Multiple time point analyses starting 6 days to 5 mo	Male and female Wistar rats	—	Intracardiac administration of Pb acetate results in elevation of glutathione transferase (GST) in Kupffer cells, the early response to GST.Yp was observed in sinusoidal cells and had a later patchy response in the expression of GST.Yp Yp in hepatocytes	Boyce and Mantel (1993)
10 µmol/100g b. wt., Pb nitrate, i.v. single dose	Analyses at multiple time points 0–10 days	Male Fischer 344 young adult rats	—	Glutathione transferase P1-1 is induced significantly by a single intravenous dose of Pb nitrate through increased transcription and modulations at post transcription and translational levels.	Koo et al. (1994)

Table AX5-10.1 (cont'd). Hepatic Drug Metabolism

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Pb nitrate, 100 μm/kg i.p, 3 times every 24 h Pb acetate 100 μM/kg.	48 h 0.5–24 h	Transgenic rats with 5 different constructs having GST-P and/or chloromphenical acetyl transferase coding sequence.	— —	GSTP (placental GST), is regulated by Pb at transcriptional level. GST-P enhancer (GPEI), is an essential cis-element required for the activation of the GST-P gene by Pb and is involved in the activation regardless of the trans-activators involved. GPEI element consists of two AP-1 binding sites. Activation of GST-P gene by Pb is mediated in major part by enhancer GPEI, which may involve AP-1 activation partially.	Suzuki et al. (1996)
10 nM Pb nitrate	24 h before transfection with ECAT deletion mutant, every 24 h there after till 48 h after transfection	NRK Kidney fibroblasts	—	Pb induces GST-P in NRK normal rat kidney fibroblast cell line.	
10 mg Triethyl Pb, i.p. single dose	Analyses at multiple durations (3, 4, 7, 10, or 14 days)	Fischer 344 rats	—	Decreased liver Glutathione s-transferase (GST) activity and lower levels of several hepatic GST. Increase in quinone reductase activity by day 14 in liver.	Daggett et al. (1997)
114 mg Pb acetate/kg b. wt. i.p	Single (0.5–12 h group) or multiple (72 h and 7 days group) exposure	Sprague Dawley	—	Pb exposure resulted in hepatic Glutathione (GSH) depletion and increased malondialdehyde (MDA) production.	Daggett et al. (1998)
A. 1.5–3.0 mg/kg wt Triethyl Pb (TEL) i.p.	2 exposures for 48 h	Female Wistar	—	Pretreatment of rats did not affect the liver microsomal Oestradiol-17β metabolism or the content of cytochrome P-450 and cytochrome b5.	Odenbro and Rafter (1988)
B. 0.05–0.5, TEL to liver microsomal fractions	30 min incubations	Liver microsomes from female Wistar rats	—	TEL at 0.05 mM significantly reduced 17β-hydroxy steroid oxidation and at concentration of 0.05 mM decreased 16α-hydroxylation.	

Table AX5-10.1 (cont'd). Hepatic Drug Metabolism

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
50 mg/kg, intragastric	8 wks	Male Albino Wistar rats	—	Accentuation of liver membrane lipid peroxidation. significant inhibition of liver antioxidant enzymes. Reduced ratio of reduced glutathione(GSH) to oxidized glutathione (GSSG),	Sandhir and Gill (1995)

Abbreviations

b. wt.—body weight
[a]CYP—Cytochrome P-450
GSH—Glutathione
GSSG—Oxidized glutathione
TEL—Triethyl lead
CCL—Carbon tetrachloride
GSTP—Placental glutathione transferase
MDA—Malondialdehyde
Cu—Copper
Cd—Cadmium
Al—Aluminum
Zn—Zinc
Pb—Lead
Ni—Nickel
TNFα—Tumor necrosis factor
ALA—Alanine aminotransferase
PAH—Polycyclic aromatic hydrocarbons
LPS—Lipopolysaccharides

Table AX5-10.2. Biochemical and Molecular Perturbations in Lead-induced Liver Tissue

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Pb-diethyl dithiocarbomate complex, Pb (DTC) 2, or Pb acetate 0.033–10 μM	0.5–20 h	Primary hepatocytes	—	Effect of interactions between Pb and diethyl dithiocarbomate (DTC) on the enzyme δ amino levulinic acid dehydratase in primary hepatocytes. Lipophilic Pb (DTC)2 caused a more rapid and stronger inhibition of ALAD activity than Pb acetate. Pb uptake is higher and more rapid with Pb (DTC) 2 than Pb acetate. This increased inhibition of ALAD activity by Pb (DTC) 2 might be due to facilitated cellular transport in the complexed form resulting in higher cellular concentrations of Pb.	Oskarsson and Hellström-Lindahl (1989)
—	—	Primary rat hepatocytes	—	DTC decreases cellular effects of Pb and Cd despite unchanged/ even slightly increased concentrations of the metals. Hepatic ALAD was significantly inhibited in cells treated with Pb Ac and Pb (DTC)2.	Hellström-Lindahl and Oskarsson (1990)
—	—	DBA and C57 mice	—	DBA mice(with a duplication of the ALAD gene accumulated twice the amount of Pb in their blood and had higher Pb levels in liver and kidney than mice with the single copy of the gene (C57), exposed to the same oral doses of the Pb during adult hood. Blood Zinc protoporphyrin (ZPP) increased with Pb exposure in C57 mice and were not affected in DBA mice.	Claudio et al. (1997)
100 μmol/kg b. wt. i.v. single dose	Single dose, analyses performed 12, 24, 48, 72, 96 and 168 h	Male Wistar Albino Rats	—	First in vivo report showing association between Pb induced liver hyperplasia, Glucose-6-phosphate levels, and cholesterol synthesis. Pb treatment increased hepatic de novo synthesis of cholesterol as evident by increased cholesterol esters and increase of G-6-PD to possibly supply the reduced equivalents for de novo synthesis of cholesterol. Changes in these biochemical parameters were accompanied by liver hyperplasia.	Dessi et al. (1984)
Pb nitrate, Single dose 100 μmol/kg b. wt.	0–168 h	Male Wistar rats	—	Pb nitrate induces hepatic cell proliferation followed by reabsorption of excess tissue with in 10–14 days. The proliferation was correlated with hepatic denovo synthesis of cholesterol, stimulation of hexose monophosphate shunt pathway and alterations in serum lipo proteins.	Pani et al. (1984)
Pb nitrate	—	Wistar rats	—	Pb nitrate induces multiple molecular forms of Glucose-6- phosphate dehydrogenase with an increase of band 3 and a concomitant increase of band 1, shifting from the pattern induced by fasting with an increase in band 1.	Batetta et al. (1990)

Table AX5-10.2 (cont'd). Biochemical and Molecular Perturbations in Lead-induced Liver Tissue

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Pb nitrate, single i.v. 10 µM/100 g b. wt.	Multiple time points 24–72 h and 20 days	Male Wistar rats	—	Pb nitrate exposure results in complete loss of liver glycogen between 24 and 48 h, which was replenished and was found in excess in treated liver hepatocytes by 20 days. Glycogen synthase and glycogen phosphorylase activities were diminished by 24 h and return to normal values by day 20. The pentose phosphate enzymes were upregulated, which coincided highly with the increase in mitotic rate. Overall Pb nitrate induces drastic alterations in hepatic carbohydrate metabolism along with increased hepatic cell proliferation.	Hacker et al. (1990)
—	—	Rats	—	Pb acetate induced mitotic response much more effectively in renal epithelial cells than liver cells (675 fold less).	Calabrese and Baldwin et al. (1992)
10 or 20 mg/kg as Pb acetate, subcutaneous	Once a wk for 5 wks	Occupationally exposed workers Rats	Pb-exposed workers: 0.24–30 nM/mL Control rats: 0.18 nM/mL 10 mg Pb/kg: 2.42 nM/mL: 20 mg Pb/kg: 3.82 nM/mL	Pb induces lipid peroxidation in serum of manual workers, while blood superoxide dismutase (SOD) activity decreased. Similar phenomenon was observed with rats that were subcutaneously injected with Pb acetate. At higher than 20 µM concentration, Pb in untreated microsomes increased NADPH dependent lipid peroxidation.	Ito et al. (1985)
100 µM/kg b. wt Pb nitrate, i.v	36 h postexposure	Male Wistar Albino rats	—	Endogenous source of newly synthesized cholesterol together with increase of HMP shunt enzyme activities is essential for hepatic cell proliferation by Pb nitrate.	Dessi et al. (1990)
2000 ppm Pb acetate in diet.	3 wks	Arbor Acres male chicks	—	Liver non protein sulphahydryl (NPSH) and glutathione (GSH) were increased upon Pb exposure. The concentrations of liver glutamate, glycine, and methionine were also elevated upon Pb exposure.	Mc Gowan and Donaldson et al. (1987)
0–4000 ppm Pb acetate, oral	21 days	Arbor Acre broiler chicks	—	Pb increases tissue peroxidation via a relative increase of 20:4 fatty acids. Decrease in the hepatic ratio of 18:2/20:4 might be specific to Pb toxicity.	Donald and Leeming (1984)

Table AX5-10.2 (cont'd). Biochemical and Molecular Perturbations in Lead-induced Liver Tissue

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Sodium vanadate, 30 mg/kg subcutaneous in mice 30 mg/kg b.wt, i.p. in rats 0.5 mM	Acute studies, 24 h	Male Swiss-Webster mice Male Sprague Dawley Rat	—	Sodium orthovandate increases lipid peroxidation in kidneys of mice and rats. Malondialdehyde (MDA) formation increased 100%, with in 1 h after injection. In both rat and mice, no significant increase in lipid peroxidation was observed in brain, heart, lung, and spleen. Chronic exposure to vanadium, through maternal milk and drinking water for 10 wks increased MDA formation and lipid peroxidation in kidneys.	Donaldson et al. (1985)
Vanadium sulphate in drinking water for chronic treatment	Chronic studies 10 wks		—		
250–2000 ppm Pb acetate in diet	19 days	Arbor Acre broiler chicks	—	Dietary Pb consistently increased liver arachidonic acid, the arachidonate/linoleate ratio and hepatic non-protein sulfhydryl concentration. Hepatic microsomal fatty acid elongation activity was decreased by Pb over all. These results demonstrate that changes in the precursors and mechanisms involved with eicosanoid metabolism are not always reflected in tissue concentrations of leukotriens and prostaglandin.	Knowles and Donaldson et al. (1990)
1.25–20.00 mg/L Pb nitrate, oral	30 days	Fresh water fish	—	Pb accumulation in the liver and other tissue increased in a dose dependent manner up to 5mg/L, exposure to sublethal concentration (5 ppm) of Pb reduced the total lipids, phospholipids, and cholesterol levels in the liver and ovary. Pb nitrate may affect the fecundity of fish by altered lipid metabolism.	Tulasi et al. (1992)
250 mg/L of Pb as Pb acetate, oral	5 wks of exposure followed by 4 wks of recovery	Weanling female SD rats	—	Effect of weight loss on body burden of Pb: weight loss increases the quantity and concentration of Pb in the liver even in the absence of continued exposure.	Han et al. (1996)
35–70 mg, Pb intra gastric	One or two times a wk/7 wks	Male Buffalo rats	Control: 4.6 µg/dL Pb 35 mg/kg: 16.8 µg/dL Pb 70 mg/kg: 32.4 µg/dL	Decrease in plasma cholesterol, and HDL fraction, increase in serum triglyceride, atrophy of the elastic fibers in the aorta.	Skoczynska et al. (1993)

Abbreviations

[a]CYP—Cytochrome P-450
ALAD—Aminolevulinic acid dehydratas
GSH—Reduced Glutathione
ZPP—Zinc protoporphyrin
HMP—Hexose monophosphate shunt pathway
b. wt.—body weight

Table AX5-10.3. Effect of Lead Exposure on Hepatic Cholesterol Metabolism

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
100 μmol/kg body wt, i.v. Pb nitrate	Multiple durations 0, 3, 6, 12, 24, and 48 h	Male Sprague Dwaley (SD) rats	—	Pb nitrate, activates the expression of the SREBP-2 and CYP 51 gene with out decreasing the serum cholesterol level.	Kojima et al. (2002)
100 μmol/kg body wt, i.v. Pb nitrate	Multiple durations 0, 1, 3, 6, 12, 18, 24, 48, and 72 h	Male Sprague Dawley (SD) rats	—	Pb nitrate effects on hepatic enzymes involved in cholesterol homeostasis. Demonstrated for the first time sterol independent gene regulation of cholesterol synthesis in Pb nitrate treatment.	Kojima et al. (2004)
0.05 mg/kg body wt/d. Pb acetate, subcutaneous, with or without cadmium acetate 0.025 mg Pb acetate/kg body wt/d	Preexposure for 5–7 days, gestation through lactation	Female Charles Foster rats	—	Pb and cadmium accumulated in the livers of metal treated pregnant and lactating rats. Hepatic steroid metabolizing enzyme 17-β-hydroxy steroid oxidoreductase and UDP glucaronyl transferase were decreased and the hepatic Cytochrome P-450 content was reduced by the metal exposure. Pb and cadmium alter liver biochemical parameters, however, combined exposure had no intensifying effect on liver parameters. When administered together on similar concentration basis, the major effects are mediated by cadmium.	Pillai and Gupta (2004)
300 mg/L Pb acetate, oral	Gestation through lactation analyses done at day 12 and day 21 postnatal	Female Wistar rats	Control: 1.13 μg/dL Pb-exposed 12 days PN: 22.01 μg/dL 21d PN: 22.77 μg/dL	In neonates, decrease in liver Hb, iron, alkaline and acid phosphatase levels. Protein, DNA and lipid total amounts were reduced and hepatic glycogen content was reduced. Pb intoxication of mothers in gestation and lactation results in alterations in the hepatic system in neonates and pups.	Corpas et al. (2002b)

[a] CYP—Cytochrome P-450
[b] wt.—body weight

Table AX5-10.4. Lead, Oxidative Stress, and Chelation Therapy

Concentration and Compound	Duration	Species	Blood Lead	Effects	Reference
Pb acetate, 50 mg/kg b.wt, intragastric	8 wks	Male Albino Wistar rats	—	Pb induces accentuation of membrane lipid peroxidation in liver by the changes (decrease) in the activities of several antioxidant enzymes such as SOD, Catalase, GPx and Glutathione reductase. Pb exposure also caused a reduction in GSH/GSSG ratio (reduced to oxidized Glutathione).	Sandir and Gill (1995)
2,000 ppm, Pb acetate, Diet	5 wks	Male Fisher 344 rats, young and old	Young control: <1 µg/dL Young Pb-exposed: 38.8 µg/dL Old control: <1 µg/dL Old Pb-exposed: 21.7 µg/dL	Effect of Pb on lipid peroxidation in young vs. adult rats– Liver GSSG and malondialdehydehyde levels were significantly higher in young rats than adult rats. Blood Pb levels were higher in young exposed animals as compared to adults. In young, Pb exposed animals, Pb induced oxidative stress was more pronounced particularly in liver tissue.	Aykin-Burns et al. (2003)
0.1–1.0 µM		Rat liver hepatocytes. Normal and LAN loaded	—	Lipid peroxidation as indicated by Malondialdehyde accumulation upon exposure to various redox-sensitive metals in cultured rat hepatocytes and hepatocytes loaded with α-linolenic acid indicated that Al, Cr and Manganese, Ni, Pb and tin did not effectively induce lipid peroxidation in these cells. – The induction was the highest in ferrous iron treated cells compared to other metals (Cu, Cd, V, Ni).	Furono et al. (1996)
$FeSO^4$, VCl_3, $CuSO^4$, $CdCl_2$, $CoCl_2$, $AlCl_3$, $CrCl_3$, $MnCl_2$, $NiSO^4$, $Pb(NO_3)_2$, $SnCl_2$, culture medium	9 h		—		
LAN—bovine serum complex 0.8 mM in culture medium	Additional 12 h incubation		—	With any metal, the induction was higher in α-linolenic acid treated cells. Iron and V induced cell injury in LAN loaded cells was prevented by addition of DPPD. Cd was a weak inducer of lipid peroxidation under these conditions.	
5 mg kg−1, Pb acetate, i.p., single dose followed by therapy with chelating agents	Analyses after 6 days of treatment DMSA, Mi-ADMSA at multiple times (0.5, 24 hr, 4th and 5th day after Pb treat	Wistar 6 days old suckling rats	—	Treatment with DMSA and Mi- ADMSA showed Mi-ADMSA to be more effective in reducing the skeletal, kidney and brain content of Pb. However there was no difference in reducing the liver Pb content between the two compounds.	Blanusa et al. (1995)

Table AX5-10.4 (cont'd). Lead, Oxidative Stress, and Chelation Therapy

Concentration and Compound	Duration	Species	Blood Lead	Effects	Reference
550 ppm Pb acetate, oral DMSA treatment.	(A) Pb for 35 + 21 days (B) Pb 35 days and Pb and DMSA for 21 days (C) Pb 35 days and DMSA for 21 days (D) Acedified Di H_2O for 35 days and Di water for 21 days	6–7 Wk old male Sprague-Dawley rats	Pb-exposed: 50 µg/dL Pb 35 days: Ranged from 5–20 µg/dL + DMSA from 0–240 µg/kg/d	DMSA reversed the hematological effects of Pb, decreased the blood, brain , bone, kidney and liver concentration and produced marked Pb diuresis, even when challenged with ongoing Pb exposure.	Pappas et al. (1995)
Pb acetate Dose to achieve blood Pb levels of 35–40 µg/dL. Biweekly dose adjustments, oral followed by treatment with chelator.	1 yr, chelator for two successive 19 day period following Pb exposure.	Infant rhesus monkeys	Pb-exposed: 35–40 µg/dL	Specific emphasis on the beneficial effects of succimer treatment to cessation of Pb exposure. These data demonstrated that succimer efficiently reduces blood Pb levels which does not persist beyond the completion of treatment. They also demonstrate the relative benefit of eliminating Pb exposures , which serves to underscore the importance of primary prevention of Pb exposure. Neither DMSA treatment nor the cessation of Pb exposure were beneficial in reducing skeletal Pb levels.	Smith et al. (2000)
5 mg Pb kg−1, i.p Pb acetate followed by chelators for various time points.	Analyses at Day 5	Suckling Wistar rats	—	Meso—DMSA is the treatment of choice for acute Pb poisoning in infants compared to EDTA and Rac-DMSA.	Kostial et al. (1999)
50 mg/kg Pb as Pb nitrate, i.p, two injections, 16h apart 50% Ethanol, 0.5 mL, two injections, 16 h apart	24 h	Male Albino rats	—	S-Adenosyl methionine confers protection against alterations in several parameters (ALAD, GSH, MDA) indicative of lipid peroxidation in blood, liver and brain in Pb and acute Pb and ethanol exposed animals as well as the organ concentration of Pb.	Flora and Seth (1999)
0.1% Pb acetate in drinking water with and without Sodium Molybdate, i.p	4 wks	Male Albino rats	Pb-exposed: 39 µg/dL Pb + chelators: 4.6–13.1 µg/dL	Sodium molybdate significantly protected the uptake of Pb in blood, liver and kidney. The treatment with molybdate also restored the Pb induced inhibited activity of blood δ-aminolevulinic acid dehydratase and the elevation of blood Zn protoporphyrin , hepatic lipid peroxidation and serum ceruloplasmin.	Flora et al. (1993)

Table AX5-10.4 (cont'd). Lead, Oxidative Stress, and Chelation Therapy

Concentration and Compound	Duration	Species	Blood Lead	Effects	Reference
20 mg/kg Pb acetate, i.p.	3 days treatment	Male Albino rats	—	Significant Pb induced inhibition of hepatic heme synthesis associated with decline of mixed function oxidases, depletion in anti oxidants such as vitamin C. Oral supplementation with vitamin C confers protection against toxic insult by reversing these parameters.	Vij et al. (1998)
1.5 mg/per bird /d	30 days	Broiler chicken	—	Pb-induced inhibition of 5' mono deiodinase (5'- D) activity in chickens appeared to be mediated through the lipid peroxidative process.	Chaurasia et al. (1998)
1. Pb acetate 10 mg/mL/kg (a) 2. Ethanol 1 g/ 4 mL/kg (b) 3. a + b = (c) 4 a + zinc 10 mg/ 4 mL/kg + lysine 25 mg/4 mL/kg (d) 5. b + 2n + lysine as in days, oral 6. a + b + Zn + lysine as in days	5 days/wk/8 wk	Male Albino rats	Control: 1.75 µg/dL 1. 47.23 µg/dL 2. 2.08 µg/dL 3. 45.37 µg/dL 4. 34.19 µg/dL 5. 1.84 µg/dL 6. 46.69 µg/dL	Influence of lysine and zinc administration on the Pb-sensitive biochemical parameters and the accumulation of Pb during exposure to Pb. (1) Pb exposure inhibited blood ALAD activity. Serum enzymes increased blood and tissue Pb levels. (2) Decreased blood and hepatic glutathione. Some of these effects were enhanced with co-exposure to ethanol. Simultaneous administration of lysine and zinc reduced tissue accumulation of Pb and most of the Pb-induced biochemical alterations irrespective of exposure to Pb alone or Pb and ethanol.	Tandon et al. (1997)
1300 ppm Pb acetate in drinking water	5 wks	C57BL/6 mice	—	Pb treatment resulted in depletion of GSH, increased GSSG and promoted Malondialdehyde (MDA) production in both liver and brain samples. DMSA or N- acetyl cysteine (NAC) treatment resulted in reversion of these observations. DMSA treatment resulted in reduced Pb levels in blood, liver and brain, where as treatment with NAC did not reduce these levels.	Ercal (1996)
2000 ppm of Pb acetate in drinking water	5 wks followed by treatment with succimer DMSA, or thiol agent NAC	Fisher 344 male rats	—	Pb induces oxidative stress in RBC and these biochemical alterations are reversed by both a thiol antioxidant (NAC) as well as a chelating agent DMSA.	Gurer et al. (1998)
500 µM Pb acetate in cells 2000 ppm of Pb acetate in drinking water	Cells—20 h Animals 5 wks followed by treatment with α-lipoic acid	Male fisher rats and Chinese hamster ovary cells	—	Pb induces oxidative stress. α-lipoic acid (LA)treatment significantly increased thiol capacity of cells and animals via increasing glutathione levels and reducing Malondialdehyde levels, increased cell survival. LA was not effective against reducing blood or tissue Pb levels.	Gurer et al. (1999)

Table AX5-10.4 (cont'd). Lead, Oxidative Stress, and Chelation Therapy

Concentration and Compound	Duration	Species	Blood Lead	Effects	Reference
0–500 µM Pb acetate 2000 ppm of Pb acetate in drinking water for 5 wks Taurine 1.1 kg/d	6 h 5 wks 6th wk	CHO cells and Fischer 344 rats	— Controls: 0.43 µg/dL Pb-exposed: 36.4 µg/dL Pb + Taurine: 33.8 µg/dL	Antioxidant Taurine reversed the abnormalities associated with lipid peroxidation parameters such as increased. Malondialdehyde formation and decreased Glutathione and enhanced CHO cell survival. However, was not effective in reducing cell and tissue Pb burden in CHO cells and Pb exposed Fischer rats.	Gurer et al. (2001)
1 mg Pb2+/kg B.wt , i.p. Pb acetate	4 wks, treatment with various antioxidant in the 5th wk	IVRI 2 CQ rats	—	Pb exposure resulted in increased lipid peroxidation, with tissue specific changes in liver. Treatment of exposed rats with ascorbic acid and α-tocopherol lowered the lipid peroxidation.	Patra et al. (2001)
Pb as acetate, 400 mg Pb2+/mL, drinking water 0.5 mg/mL L-methionine	10 days 4 wks post-Pb exposure	Kunming mice	— —	L- methionine has an ameliorative effect on Pb toxicity–Methionine reduced the decrease in Hb content and depressed body growth caused by Pb. Treatment with dietary methione along with Pb decreased the MDA formation as opposed to Pb, moderately reversed the decreased iron content of the organs and decreased organ Pb content.	Xie et al. (2003)
100 µM/kg b.wt. Pb acetate, intramuscular, single	3 and 24 h	Male Albino rats	—	Pb exposure resulted in significant increases in acid and alkaline phosphatases, serum GOT and GPT, elevated liver and kidney lipid peroxidation and decreased antioxidant enzymes at 3 and 24 h after exposure. Selenium administration prior to Pb exposure produced pronounced prophylactic effects against Pb exposure by enhancing endogenous anti oxidant capacity.	Othman and El Missiry (1998)
100 µg/ Pb acetate, intra gastric, oral and intraperitoneal, treated with or with out thiamin (25, 50 mg/kg b.wt) and or Ca EDTA (50 mg/kg B.wt	3 days	CD-1 mice	—	Two times more whole body Pb was retained by intraperitoneal injection as compared to intragastric administration. Thiamin treatment increased the whole body retention of both intragastric and intraperitoneal Pb by about 10%. Calcium EDTA either alone or in combination with thiamin reduced the whole body retention of Pb by about 14% regardless of the route of exposure. Regardless of the route Ca EDTA in the combined treatment reduced the relative retention of Pb in both in liver and kidney. These studies indicate the combination treatment with thiamin and Ca EDTA alters the distribution and retention of Pb in a manner which might have therapeutic application.	Kim et al. (1992)

Table AX5-10.4 (cont'd). Lead, Oxidative Stress, and Chelation Therapy

Concentration and Compound	Duration	Species	Blood Lead	Effects	Reference
2000 ppm Pb acetate, oral I chelators LA, DMSA, MiADMSA LA + DMSA + LA+ MiADMSA	4 wks, 5 days of treatment with antioxidant or chelators	Male Wistar albino rats	Normal: 1.42 µg/dL Pb: 40.93 µg/dL Pb + chelators: 38.5–4.27 µg/dL	Treatment with all the chelators reduced hepatic GSH and reduced GSSG levels. Significant beneficial role of Alpha-lipoic acid (LA), in recovering the altered biochemical parameters, however showed no chelating properties in lessening body Pb burden either from blood, liver, or kidney. Most beneficial effects against Pb poisoning was observed with combined treatment of lipoic acid and either DMSA (meso 2,3-dimercaptosuccinic acid) or MiADMSA (Mono isoamyl DMSA).	Pande and Flora (2002)
0.1% Pb as acetate in drinking water DMSA—50 mg/kg, i.p./d MiADMSA—50 mg/kg, i.p./d	3 mo	Male Wistar rats	—	Single or combined administration of vitamin C, α-tocopherol and the chelators DMSA and Mi ADMSA against the Parameters of Pb induced oxidative stress– thiol chelators and the vitamins could bring the blood ALAD to normal levels, most significantly by combined administration of Mi ADMSA with vitamin C. Vitamin C and E were effective against reducing oxidized glutathione (GSSG), and thibarbituric acid reactive substance(TBARS) and increasing catalase activity. MiADMSA and DMSA with vitamin C were effective in increasing hepatic GSH levels. In summary combined treatment regimens with thiol chelators and vitamins seem very effective in reducing the Pb induced oxidative stress.	Flora et al. (2003)
Vitamin E 5 mg/kg and vitamin C 25 mg/kg/d, i.v. and oral	5 days post-Pb exposure		—		
500 mg/kg Pb acetate daily, oral treatment with chelators	Multiple durations (2, 4, and 6 wks)	Male Albino rats	Control: 0.32 µg/dL Pb-exposed: 0.48–0.56 µg/dL Pb + chelators: 0.32–0.36 µg/dL	Impact of combined administration of vitamin C and Sylimarin on Pb toxicity. Combined treatment of Pb-exposed animals with vitamin C and Silymarin showed marked improvement of the adverse biochemical, molecular and histopathological signs associated with Pb toxicity.	Shalan et al. (2005)
Pb as acetate 0.2% in drinking water LA 25 mg/kg b.wt and DMSA 20 mg/kg b.wt	5 wks followed by a 6th wk administration of LA and or DMSA	Male Albino rats	—	Pb treatment for 5 wks resulted hepatic enzymes alanine transaminase, aspartate transaminase, and alkaline phosphatase, increased lipid peroxidation, and decreased hepatic anti oxidant enzymes. LA or DMSA alone, partially abrogated these effects, however, in combination completely reversed the lipid oxidative damage.	Sivaprasad et al. (2004)

Abbreviations

b. wt.—body weight
[a]CYP—Cytochrome P-450
SOD—Super oxide dismutase
GSH—Glutathione
GSH/GSSG Ratio—Reduced Glutathione/Oxidized Glutathione
MDA—Malondialdehyde
Al—Aluminum
As—Arsenic
MiDMSA—Mi monoisoamyl DMSA
Cr—Cromium
V—Vanadium
Pb—Lead
NAC—N acetyl cysteine
$FeSO^4$—Ferrous sulphate
$AlCl_3$—Aluminum chloride
VCl_3—Vanadium chloride
$CdCl_2$—Cadmium chloride
$CuSO^4$—Copper sulphate
$CrCl_3$—Cromium chloride
$MnCl_2$—Manganese chloride
$NiSO^4$—Nickel sulphate
$CoCl_2$—Cobalt chloride
LAN—α Linolenic acid
DPPD—DPPD,*N-N* Diphenyl –p-phynylene-diamine
LA—Lipoic acid
DMSA—Monoisoamyl DMSA

Table AX5-10.5. Lead-induced Liver Hyperplasia: Mediators and Molecular Mechanisms

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
—	—	Rat	—	Apoptosis plays a major role in the regressive phase of Pb nitrate induced hepatic hyperplasia as detected by the apoptotic bodies by in situ end labeling and HandE sections of the hepatic tissue. HandE scores mostly cells in apoptosis phase II, ISEL (in situ end labeling) scores for cells in phase I. Combination of these two methods is suggested for the better understanding of the extent and nature of apoptotic process in liver cells treated with chemicals.	Nakajima et al. (1995)
A. Pb nitrate, 100 µM/kg b.wt, intra-gastric B. Diethyl nitrosoamine 200 mg/kg b.wt, i.p.	3 and 15 days	Male Wistar Albino rats	—	Mitogenic stimuli (3 days Pb nitrate treatment) and complete regression (15 days after the treatment), affected the apoptosis differentially. Influence of apoptosis Vs necrosis on the growth of hepatocytes initiated by diethyl nitrosamine followed by Pb nitrate treatment indicated that the regenerative response elicited by a necrogenic dose of CCL4 promoted GSTP (Placental glutathione), a pre-neoplastic marker positive cells as against the Pb nitrate that induced the apoptosis.	Columbano et al. (1996)
0–100 µM Pb sulphate, Pb monoxide, Pb chloride and Pb acetate up to 1 mM, culture media.	Multiple time points ranging from 24 h up to 7 days	REL liver cells	—	Pb compounds showed a dose and time related effect on REL liver cell proliferation with varying potencies specific to the different Pb salts. Pb acetate was the most effective and Pb monoxide, the least effective. On 1 hr treatment none of the compounds tested affected the intracellular communication.	Apostoli et al. (2000)
Choline 1g/kg/d in drinking water	0, 20, and 24 h	Male and female rats , partial hepatectomy	—	PKC isozymes during liver cell regeneration— PKC δ showed a pronounced increase 20h after partial hepatectomy. α, β, and Zeta at 24 h corresponding with S-phase. Sexual dimorphism matching with sexual differences in DNA synthesis was evident. Administration of choline was able to modulate the protein kinase C isozyme pattern in females in relation to DNA synthesis and c-myc expression. Taken together the data positively implicates α, β, and Zeta in growth after partial hepatectomy and δ in negative regulation.	Tessitore et al. (1995)
Pb nitrate, 75 µM/kg b.wt, single i.v.	6 h–4 wks	Adult male Albino rats	—	Pb induced significant increase in liver weight. Increased 3H Thymidine incorporation. Pb induces extensive hypomethylation in treated rat livers. Site-specific effect on methylation was confirmed at Hpa II, Msp I, Hae III.	Kanduc et al. (1991)
75 µmol/kg b. wt. Pb nitrate in adult and 20 µg/mL in the young, i.v.; single dose	Analyses at 72 h	Male Wistar Albino rats	—	Effect of Pb nitrate on the 5- methyl deoxy cytidine (5-mdcyd) content and the HpaII, MSPI, Hae III restriction patterns of hepatic DNA from young, middle aged and senescent rats. The results indicated that the methylation pattern of genomic DNA changed significantly with age and the methylation patterns were differentially affected in all the three populations.	Kanduc and Prisco (1992)

Table AX5-10.5 (cont'd). Lead-induced Liver Hyperplasia: Mediators and Molecular Mechanisms

Concentration	Duration	Species	Blood Level	Effects[a]	Reference
10 µmol/100 g body weight Pb nitrate, i.v.	Multiple analyses up to 40 h	Male Wistar rats, hepatocytes from partial hepatectomy and Pb nitrate treatment.	—	The kinetics of DNA synthesis and expression of Proto oncogenes in partially hepatectamized liver cells and Pb nitrate treated hepatic cells indicated peak DNA synthesis after 24 h in the formal and after 36 h in the later case. Both proliferative stimuli induced c-fos, c-myc and c-Ha Ras expression. Induced c-myc expression persisted for up to 40h during the Pb nitrate- induced liver cell proliferation. Pb induces hepatic hyperplasia through changes in proto-oncogene expression.	Coni et al. (1989)
100 µmol/kg, b. wt. Pb nitrate, i.v.	Analyses at multiple time points, 0.25–24 h	Male Wistar Albino rats	—	Proliferative stimuli by means of Pb nitrate exposure resulted in increased expression of c-jun m-RNA where as compensatory regeneration in partially hepatectamized cells occurred through increased expression of c-fos and c-jun. Different mitogenic stimuli induced differential expression of these protooncogenes, in addition had a different profile than cells from partial hepatectomy despite the cell cycle timings being the same in some cases.	Coni et al. (1993)
100 µmol/kg b. wt.	8 h	Male Sprague Dawley rats	—	In rat liver, in addition to a few hepatocytes four types of non parenchymal cells namely, fibroblasts, macrophages, bile ducts and periductular cells proliferate in response to Pb nitrate treatment. This growth is not related to adaptive response secondary to parenchymal enlargement. However, such growth in parenchymal cells seems dormant and does not play a functional role in adult liver epithelial growth.	Rijhsinghani et al. (1992)
100 µmol/kg b. wt., i.v.	Multiple analyses time points, 1–120 h	Male Wistar rats	—	Both mRNA levels and enzyme activity of DNA polymerase β markedly increased before and/or during DNA synthesis in proliferating hepatocytes in Pb nitrate treated and partially hepatectomized rats. 5 fold increase in the enzyme activity was observed 8 h after Pb nitrate administration. In the regenerative liver cells a 3 fold increase was observed 24–48h after partial hepatectomy.	Menegazzi et al. (1992)
100 µ mol/kg b. wt., i.v. Pb nitrate	Analyses at multiple time points, 8 h to 15 days	Male Wistar rats	—	Pb nitrate induced Poly (ADP-ribose) polymerase mRNA 24 hr after exposure. A 2 fold increase in the mRNA levels of the enzyme occurred 2 days after the exposure. Such changes were also observed in hepatic cells from livers of partial hepatectomy. These changes preceded the increase in DNA synthesis and remained high during the time of extensive DNA synthesis.	Menegazzi et al. (1990)

Table AX5-10.5 (cont'd). Lead-induced Liver Hyperplasia: Mediators and Molecular Mechanisms

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
30 mg/kg b. wt. Pb nitrate	Multiple time points up to 8 days	Adult male and female rats	—	Pb nitrate induced liver hyperplasia exhibited sexual dimorphism where mitogenic action was less effective and was delayed in females as compared with males. Pre administration with choline partially filled these sexual differences.	Tessitore et al. (1994)
30 mg/kg b. wt. Pb nitrate	Multiple time point up to 60 h	Adult male and female rats	—	Pb nitrate induced liver hyperplasia exhibited sexual dimorphism. Pre-administration with choline partially filled these sexual differences. Significant down regulation of PKC β and PKC α activities occurred during Pb induced proliferation.	Tessitore et al. (1994)
100 µmol/kg b. wt. Pb nitrate, i.v., single dose.	Multiple time point analyses ranging from 12–168 h	Male Wistar rats	Serum Pb concentrations peaking to 50–60 µg/dL between 12–24 h and remaining up to 40 µg/dL up to 108 h	Effect of Pb nitrate on protein kinase C (PKC) activity. A single dose of Pb nitrate resulted in enhanced activity of PKC in the purified particulate fraction of the rat liver, reached its peak activity by 24 h which lasted for 48 h. This was accompanied by increased frequency of mitotic cells. These results indicate, Pb nitrate induced PKC activity may play a role in liver cell proliferation.	Liu et al. (1997)
A. Mitosis— Pb nitrate 100 µM/kg, i.v. Ethylene dibromide 100 mg/kg , intra gastric Cyproterone acetate, 60 mg/kg intra gastric. B. Hepatocyte nodules diethyl nitrosamine 200 mg/kg	30'–3 h	Adult male Wistar rats	—	Liver cell proliferation by enhanced DNA synthesis was observed with the mitogens Cyproterone acetate, ethylene dibromide, and Pb nitrate as early as 30 mints after treatment and persisted even after 5 days of treatment by Pb nitrate administration. hepatocytes isolated from pre neoplastic liver nodules have also exhibited enhanced cell proliferation.	Coni et al. (1992)
Pb nitrate, single i.v. 100 µm/kg b.wt LPS—12.5 µg/rat, post Pb nitrate treatment.	Multiple analyses at 3, 6, 12, 24, and 36 h	Male Wistar rats	—	Stimulation of hepatocyte cell proliferation by Pb nitrate was not accompanied by changes in liver levels of Hepatocyte growth factor (HGF), Transforming growth factor-α (TGF-α), or TGF-β1 m-RNA. Pb nitrate treatment resulted in the enhancement of Tumor necrosis factor α at a time preceding the onset of hepatocyte DNA synthesis, indicating its role in Pb induced hepatic cell proliferation. The survival of Pb nitrate treated rats decreased significantly with an after treatment of LPS (lipopolysaccharide).	Shinozuka et al. (1994)

Table AX5-10.5 (cont'd). Lead-induced Liver Hyperplasia: Mediators and Molecular Mechanisms

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
15 mg/kg b. wt. Pb acetate	Pb+ LPS group analyzed after 14 h and the rest after 24 h after Pb administration	Male Sprague Dawley rat	—	Pb augments the lethality of endotoxin lipopolysaccharide (LPS) in rats and enhances liver injury, which is further enhanced by TNF. Pb + LPS treatment increased both serum TNF concentrations and TNF area as compared to LPS alone. simultaneous administration of Pb with either LPS or TNF, serum aspartate transaminase, alanine transaminase, alkaline phosphatase, glutamyl trans peptidase and plasma triglyceride levels were markedly increased.	Honchel et al. (1991)
Pb nitrate 100 µM/kg b. wt. i.v. single dose	Multiple time points of analyses extending up to 48 h after treatment	Male Wistar rats	—	Pb nitrate and ethylene bromide induce liver cell proliferation via induction of TNFα. Dexa methasone, a known TNF inhibitor, decreases TNF expression and liver cell proliferation by these mitogens. These studies support the fact that TNF might mediate hepatic cell proliferation by Pb nitrate and ethylene bromide.	Ledda-Columbano et al. (1994)
100 µmol/kg b. wt Pb nitrate, single, i.v.	Multiple time points of analyses up to 48 h		—	Pb nitrate (LN) treatment resulted in increased Brdu incorporation of hepatocytes and non parenchymal cells at 12 h after treatment and reached the peak index at 36 h. Rats given a single i.v. of recombinant TNFα enhanced proliferation in non parenchymal cells after 24 h, the labeling of hepatocytes at 36 h. NAF, Nafenopin another mitogen which does not induce liver TNFα, increased the number of labeled hepatocytes without increasing the labeling of non parenchymal cells indicating that only Pb nitrate induced proliferation is mediated by TNFα and these mitogens initiate proliferation in different cells based on their capacity to stimulate TNFα production.	Shinozuka et al. (1996)
100 µmol/kg b. wt. single i.v.	Multiple time points of analyses up to 80 h	Male Sprague Dawley rats	—	Pb nitrate induces liver cell proliferation in rats without accompanying liver cell necrosis. This proliferation involves enhanced TNF mRNA and levels but not hepatocyte growth factor. The role of TNF in Pb nitrate induced liver cell proliferation is supported by the inhibition of TNF and reduced hepatocyte proliferation by several TNF inhibitors.	Kubo et al. (1996)
100 µmol/kg b. wt. i.v. single dose	Multiple time points of analyses up to 24 h	Male Wistar rats	—	Pb nitrate induced liver cell proliferation involves TNF α production, enhanced NF-κB activation increased hepatic levels of iNos mRNA as opposed to other mitogens such as Cyproterone acetate or Nafenopine.	Menegazzi et al. (1997)
100 µmol/kg b. wt. i.v., single dose	Multiple time point analyses up to 96 h	Male Sprague Dawley rats	—	The role of neurotrophins, the nerve growth factor (NGF), the brain derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) in Pb nitrate treated liver cells was studied. LN, treatment resulted in increased in the levels of NGF, BDNF and NT-3. The increase in neurotrophin receptors and the gene expression were correlate with liver weights. This study demonstrates that Pb nitrate induced hyperplasia may be mediated by neurotrophins.	Nemoto et al. (2000)

Table AX5-10.5 (cont'd). Lead-induced Liver Hyperplasia: Mediators and Molecular Mechanisms

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Multiple doses 0–50 µM, culture medium	Multiple time points up to 24 h	Hepatocytes from Adult male Swiss-mice, primary	—	Interaction between Pb and cytokines in hepatotoxicity– Pb potentiated cytokine-induced oxidative stress by decreasing GSH and increased efflux of Oxidized glutathione (GSSG). Combined treatment resulted in a decline in intra cellular ATP concentration.	Sieg and Billing (1997)
50 µM Pb acetate, culture medium	24 h	Rat hepatocyte and Kupffer cell and granulocyte co-cultures	—	Pb stimulates intercellular signaling between Kupffer cells and hepatocytes which increased synergistically at low lipopolysaccharide levels. These signals promote proteolytic hepatocyte killing in combination with a direct cellular interaction between the granulocytes and hepatocytes.	Milosevic and Maier (2000)
10 µM/110 g b. wt., single i.v.	Multiple time point analyses up to 5 days	Adult male Wistar rats	—	Pb nitrate induced hepatocyte apoptosis was prevented by pre-treatment with gadolinium chloride, a Kupffer cell toxicant—Role for Kuffer cell in hepatocyte apoptosis.	Pagliara et al. (2003a)
10 µmol/100 g b. wt. single i.v.	Multiple time points up to 9 days	Male Wistar rats	—	Pb nitrate-induced liver hyperplasia in rats results in a significant increase in the expression of aceyl glycoprotein receptor (ASGP-R) during the involutive phase of Pb nitrate induced hyperplasia in rat-liver, which coincided with the massive death by apoptosis of the same cells. A significant rise in the galactose-specific receptors was also observed 3 days after the treatment. These studies demonstrate that carbohydrate receptors regulate Pb nitrate induced liver cell apoptosis.	Dini et al. (1993)
10 mmol/100 g, Pb nitrate, i.v.	Multiple time points	Male Wistar rats	—	Demonstration of the expression of carbohydrate receptors on Kupffer cells. Pb nitrate induced apoptosis in Kupffer cells and internalization of apoptotic cells (Phagocytes) is mediated by both Mannose and Galactose receptors.	Ruzittu et al. (1999)

Table AX5-10.5 (cont'd). Lead-induced Liver Hyperplasia: Mediators and Molecular Mechanisms

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Pb (No3)2, , i.v. 100 μM/110 g .b. wt	1, 3, and 5 days	In vivo Adult male Wistar rats	—	Hepatic apoptosis induced by Pb nitrate in vivo is abolished by gadolium chloride, a Kupffer cell toxicant that suppresses Kupffer cell activity and reduces to half the apoptotic rate. Pb nitrate treatment also deprives the hepatic cells from reduced glutathione and this process is reversed by Gadolium chloride. Pb nitrate induces apoptosis in Kupffer cells, and HepG2 cells in vitro.	Pagliara (2003b)
$GdCl_3$ 0.75 mg/100 g. b. wt, i.v.	2, 4, or 24 h before Pb nitrate injection.		—		
In vitro, 10 mM Pb nitrate	Analyses at multiple time points up to 24 h in Hep G2 cells and at 24 and 48 h in Kupffer cells	Hep G2 cells	—		
Multiple concentrations varying from 300 nM–10 μM, up to 100 μM in certain in vitro expts	1, 2, 4 and 6 days	Hepatoma cell line, H4-II-C3	—	Acute effect of Pb on glucocorticoid regulation of Tyrosine aminotransferase (TAT) in hepatoma cells. Pb treatment does not significantly alter initial glucocorticoid receptor number or ligand binding. Pb may perturb PKC mediated phosphorylations in the glucocorticoid-TAT signal transduction system. Pb also may be increasing the turnover of TAT by actions at transcription, translation and /or post translation.	Heiman and Toner (1995)
0–10 μM Pb acetate in the culture medium	24 and 48 h	H4-IIE—C3 hepatoma cell culture model	—	In HTC cells glucocarticoid signal transduction pathways involve calcium-mediated events and PKC isoforms, Pb exposure interferes with calcium mediated events and aberrant modulation of PKC activities and may contribute to the over all toxicity of Pb.	Tonner and Heiman, (1997)

[a]CYP—Cytochrome P-450
b. wt.—body weight

Table AX5-10.6. Effect of Lead Exposure on Liver Heme Synthesis

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
75 mg Pb/kg b. wt., i.p.	Multiple time point analyses 0–30 h	C57 BL/6 mice	—	Pb poisoning decreases P-450 as a consequence of two different mechanisms, a mechanism unrelated to heme where P-450 transcription is inhibited (reduces the synthesis and activity), and a second mechanism where by inhibition of heme synthesis occurs decreasing the heme saturation of P450 and/or apo-P450 content.	Jover et al. (1996)
10^{-5} ppm Pb nitrate	Multiple analyses up to 24 h	RLC-GA1 Rat liver cell line	—	Pb increases heme synthesis in RLC-GA1 in rat liver cell line, when measured by the amount of ^{59}Fe incorporated into heme fraction. Increased incorporation of ^{59}Fe into the heme fraction of the Pb treated cells was the result of increased uptake of iron ^{59}Fe into the heme fraction of Pb treated cells. Cellular degradation of Pb was not significantly affected by Pb.	Lake and Gerschenson (1978)
A. Triethyl Pb-3.5 and 8.0 mg/kg b.wt. Pb nitrate 3.5, 25, and 100 mg/kg Single Subcutaneous	Multiple analyses up to 28 days	Adult male Fischer rats	Control: 5.2 µg/dL Triethyl Pb 8.0 mg/kg b.wt.: 19.6 µg/dL Pb nitrate 25 mg/kg b.wt.: 19.6 µg/dL Pb nitrate 100 mg/kg b.wt.: 27.2 µg/dL	Triethyl Pb chloride has a similar potency to inorganic Pb nitrate in inhibiting ALAD both in vitro and in vivo. Liver and blood ALAD have similar sensitivities to Pb compounds. Inhibition is reduced in the presence of Zn.	Bondy (1986)
B. In vitro, 10^{-3}–10^{-9} M triethyl Pb or Pb nitrate	30 min		—		
5 µM Pb acetate or Pb diethyldithio-carbomate Pb uptake studies 0.33–10 µM	Multiple analyses from 0–20 h	Rat primary hepatocyte cultures	—	Effect of Pb and diethyl dithiocarbomates on rat primary hepatocytes as studied with Pb acetate and or Pb-diethyldithiocarbomate complex (Pb DTC_{2l}) labeled with ^{203}Pb indicated that (Pb DTC_{2l}) complex caused a more rapid and stronger inhibition of ALAD activity than Pb acetate. Uptake of Pb was rapid and higher with the complex than Pb acetate. The complex also inhibited the ALAD activity in vitro when incubated with purified ALAD enzyme.	Oskarsson and Hellström-Lindahl et al. (1989)
Per OS eqimolar doses (17 µM Me/kg) of $SnCl^2$ or Pb $(CH_3COO)_2$ every day	5 days	Female rabbits	Control: 3.48 µg/100 cm^3 Pb: 17.50 µg/100 cm^3	Pb decreased liver and bone marrow ALAD, but had no change in the Aminolevulinic acid synthetase (ALA-S) and increased erythrocyte free protoporphyrin.	Zareba and Chmielnicka (1992)

Table AX5-10.6 (cont'd). Effect of Lead Exposure on Liver Heme Synthesis

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Pb 500 ppm in drinking water	14 days	Male ddY mice	—	Urinary excretion of β-Aminoisobutyric acid (ABA) and δ-aminolevulinic acid (ALA) increased significantly in mice exposed to Pb in drinking water for 14 days. The degree of increasing excretion for ALA was higher than urinary ABA. Liver and kidney ALA dehydratase was inhibited, while ALA synthatase was not affected.	Tomokuni et al. (1991)
0.5 or 2.4 µM Pb acetate in culture medium	Analyses at multiple time points, 0–28 days	Hepatocyte cultures on 3T3 cells	—	Hepatocyte cultures on 3T3 cells produce and excrete porphyrins for 28 days. Pb exposure for 4 wks alters cell morphology and produces cytotoxic effects that could be monitored by altered porphyrin excretion.	Quintanilla-Vega et al. (1995)
500 ppm Pb in drinking water	Rat exposure 62 days Human occupational exposure 0.3–38 yrs.	A. Male Wistar rats B. Pb smelt workers, males	—	Pb exposure significantly increases the urinary ALA (Aminolevulinic acid) and Coproporphyrins (CP-III>CP-I in rats and exposed workers. Urinary 5-hydroxy indole acetic acid was not influenced by Pb exposure.	Ichiba and Tomokuni (1987)
A. Cu deficient diet: 1 mg/kg Cu in the diet B. Moderately deficient: 2 mg/kg C. High Zn diet: 60 mg/kg b. wt.	4 wks	Weanling Sprague Dawley rats	—	High Zn in the diet reduces plasma copper, but not plasma ceruloplasmin activity or the recovery of plasma copper or ceruloplasmin activity after oral copper sulphate of Cu-deficient rats. High dietary Zn also modifies the response of plasma SOD activity to dietary copper , but does not influence RBC SOD activity.	Panemangalore and Bebe (1996)
1200 mg/kg b. wt. Pb acetate in diet, Sub acute toxic studies 400 mg/Pb	4 wks	Broiler chickens	—	Liver porphyrin levels increased during Pb toxicosis. Concurrent administration of selenium or monensin in the feed further enhances this process.	Khan and Szarek (1994)
0–100 µM Pb acetate in the culture medium	19 h	Primary Rat and chick embryo hepatocyte cultures	—	Formation of Zn protoporphyrins in cultured hepatocytes. Pb did not specifically increase Zinc protoporphyrin accumulation or alter iron availability in cultured hepatocytes.	Jacobs et al. (1998)

Table AX5-10.6 (cont'd). Effect of Lead Exposure on Liver Heme Synthesis

Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
Pb acetate, 160 mg/L, semi liquid diet, oral	8 wks	Male Wistar rats	—	Rats exposed to Pb had a higher blood and liver Pb, increased erythrocytic protoporphyrin. Pb exposure also resulted in hypoactivity of aminolevulinate dehydrase. Rats exposed to ethanol and Pb had altered abnormalities in heme similar to animals exposed to Pb alone. Hepatic levels of Zn decreased significantly only in animals exposed to both. Hepatic GSH, urinary ALA and porphyrin levels were maintained similarly in all the groups. Transferrin bound iron uptake by Pb was also inhibited by Pb at higher concentrations such as 4 μM.	Santos et al. (1999)
Pb acetate, 0.0625 μM–32 μM, in vitro	10 min pre incubation and 20 minute incubation	Rabbit reticulocytes	—	The effect of Pb on ferrous iron transport is similar between Pb chloride, acetate, and nitrate and reversible. Uptake of ferrous iron into all (heme, cytosolic and stromal fractions) was inhibited by low concentrations of Pb. 50% inhibition in the uptake by cytosol occurred at 1 μM Pb.	Qian and Morgan (1990)
1, 5, or 10 mg/kg b. wt. Pb acetate or nitrate, i.p. 10^{-4} M Pb acetate for Hep G2 cells	3 days	A. Transgenic mice carrying chimeric human TF gene	—	These studies present evidence for the modulation of the synthesis of human transferrin by Pb. In transgenic mouse with chimeric human chloromphenical acetyl transferase Pb regulates human Transferrin (TF) transgenes at the m RNA level. Liver catalase (CAT) enzyme activity, CAT protein, and TF-CAT m-RNA levels were all suppressed. Pb did not alter other liver proteins, mouse TF and Albumin.	Adrian et al. (1993)
		B. Hep G2 cells	—	Pb suppressed synthesis of Transferrin protein in cultured human hepatoma Hep G_2 cells.	
10 mg Pb/kg b. wt. as Pb acetate , i.p., single injection 10 and 100 μM Pb acetate	Analyses at multiple time points up to 72 h	Transgenic mice and Hep G 2 cells	—	Pb suppresses human transferrin synthesis by a mechanism different from acute phase response. Common proteins such as C3 and albumin associated with acute phase response were not altered by Pb. Pb acetate suppresses ^{35}S-transferrin protein synthesis and m-RNA levels in Hep G2 cells and transgenic mice, while LPS altered only protein levels.	Barnum-Huckins et al. (1997)

[a]CYP—Cytochrome P-450
b. wt = body weight

Table AX5-10.7. Lead and In Vitro Cytotoxicity in Intestinal Cells

Compound and Concentration	Duration	Species	Blood Lead	Effects[a]	Reference
$HgCl_2$, $CdCl_2$, Ti_2SO_4, $Pb(NO_3)_2$– concentration not given clearly, Butathionine, up to 1 mM Glutathione 1 mM N-Acetyl cysteine, 1 mM	Cell proliferation assays 48 h Glutathione depletion assays 48 h Sulphahydryl repletion studies.	I-407, Intestinal epithelial cell line.	—	Rank order cytotoxicity of various metal salts in I-407 intestinal epithelial cells in terms of LC_{50} values—$HgCl_2$ (32 µM) > $CdCl_2$ (53 µM), $CuCl_2$ (156 µM) > Ti_2SO_4 (377 µM) > $Pb(NO_3)_2$ (1.99 mM) Role of Glutathione, in the cytotoxicity of these metals by the assessment of GSH depletion by Butathionine sulfoxamine pretreatment at non cytotoxic concentration increased the toxicity of $HgCl_2$ (5.7-fold), and $CuCl_2$ (1.44-fold). Administration of glutathione, with either $HgCl_2$ or $CdCl_2$ did not protect the cells against the toxicity. *N*-acetyl cysteine reduced the cytotoxicity of mercury.	Keogh et al. (1994)

[a]CYP—Cytochrome P-450

Table AX5-10.8. Lead and Intestinal Uptake—Effect on Ultrastructure, Motility, Transport, and Miscellaneous

Compound and Concentration	Duration	Species	Blood Lead	Effects[a]	Authors
Pb acetate, 0.1%, in drinking water	Multiple analyses at 2, 30, and 60 days after Pb exposure	Male Wistar rats	—	Small intestinal goblet cells are involved in Pb detoxification. Pb treatment for 30 days produces characteristic goblet cells in the intestine and Pb appears in conjunction with goblet cell membrane. Prolonged exposure to Pb more than 30 days caused silver sulphide deposition (indicative of heavy metal deposition) in the mucus droplets of cytoplasmic goblet cells.	Tomczok et al. (1988)
100 mg/Pb acetate/kg b. wt.	Multiple analyses at 2, 30 and 60 days	Male Wistar rats	—	Pb poisoning changes the ultra structure of intestine. 30 days Pb exposed rat intestinal enterocytes showed numerous, small rough-membraned vesicles and prominent, dilated golgi complexes, in their cytoplasm. By 60th day, Pb-exposed rats had a vacuolated cytoplasm and prominent golgi filled with vacuoles.	Tomczok et al. (1991)
Added Pb concentration in the milk—0–80 µg/mL	—	Adult and Infant rats (16 days) Fresh or frozen rat or Avian milk	—	90% of Pb in rat and bovine milk was found associated with caseine micelles regardless of whether the milk is labeled in vitro or in vivo with ^{203} Pb. Similarly Pb in infant milk formula was also predominantly associated with casein, however, to a much lower extent than rat and bovine milk formulae. Pb tracer studies indicated that in infant rats, as the milk traversed through the intestine, in the collected luminal fluid, Pb was primarily associated with casein curd and remained as a nonprecipitable, nondialyzable fraction as it moved to the small intestine, indicating that Pb remains with protein fraction as it traverses through the stomach and small intestine fraction.	Beach and Henning (1988)
Pb as Pb acetate, for 0.5–10.0 µM, Zn as Zn acetate 0, 5, 10, or 50 µM Temperature variation Expts, 5 µM Pb, and incubated for 10 min at 4, 22, or 37 °C	5, 10, 30 or 60 min, Simultaneously with Pb for 10 min Incubation time 10 min	IEC-6 normal rat intestinal epithelial cells	—	Pb uptake by IEC-6 cells depends on the extracellular Pb concentration. Pb transport in IEC-6 cells is time and temperature dependent, involves sulphahydryl groups, and is decreased by the presence of Zn.	Dekaney et al. (1997)

Table AX5-10.8 (cont'd). Lead and Intestinal Uptake—Effect on Ultrastructure, Motility, Transport, and Miscellaneous

Compound and Concentration	Duration	Species	Blood Lead	Effects[a]	Authors
OECD (Organisation for Economic Co-operation and Development) medium was artificially contaminated at 1, 3, 5, or 10 times the Dutch intervention value of 530 mg/Pb/kg dry wt. Pb containing medium was presented at the apical surface of the cells in 2 mL DMEM/chyme. Neutral red uptake studies had DMEM/chime with low 5 µM and high 50 µM Pb content	Cell viability studies—24 h incubation. Pb transport studies, 1, 3, 5, and 24 h		—	Transport of bioaccessible Pb across the intestinal epithelium—In Coco-2 cells exposed to artificial chime, with in 24 hrs. App. 27% of the Pb was associated with the cells and 3% were transported across the cell monolayer. Pb associated with cells showed a linear relationship with the Pb available in the system. Results indicate that only a fraction of the bioavailable Pb is transported across the intestinal epithelium. On the basis of Pb speciation in chime, It could be attributed that dissociation of labile Pb species, such as Pb phosphate, and Pb bile complexes and subsequent transport of the released free metal ions flow toward the intestinal membrane.	Oomen et al. (2003)
44 mg/kg/d Pb as 53 mmol/L Pb acetate	4 wks	Rat	—	Pb exposure significantly decreases the amplitude of contraction in rat duodenum.	Karmakar and Anand (1989)
2.5 mg/mL Pb acetate in drinking water	55 days	Colonic segments taken from chronically exposed guinea pigs	Exposed: 80 µg/dL	Colonic propulsive activity as measured by the velocity of the displacement of the balloon, from the oral to the aboral end, did not get affected significantly by Pb treatment. In longitudinal muscle-myenteric plexus preparations of distal ileum, addition of Pb nitrate (100 µm) caused slight increase in cholinergic contractions.	Rizzi et al. (1989)
100 µM Pb nitrate, in vitro	Duration not specified	Muscle–myenteric plexus preparations of distal ileum of controlled animals	—	Moderate decrease of electrically induced cholinergic contractions.	

Table AX5-10.8 (cont'd). Lead and Intestinal Uptake—Effect on Ultrastructure, Motility, Transport, and Miscellaneous

Compound and Concentration	Duration	Species	Blood Lead	Effects[a]	Authors
40 µM–240 µM Tri ethyl Pb added in a cumulative manner in vitro to mid-ileal portion.	7.5 sec–2 min	Swiss mice JVI1 ileum	—	1. Peristaltic contractile activity of ileum as measured as a change in period duration and force amplitude indicated that tri ethyl Pb (TEL) concentrations of <40 µM had no obvious effects on these parameters. 2. In the concentration range between 40 µM–120 µM, tri ethyl Pb affected the rhythm of contraction in a concentration dependent manner with elongation in period and reduction in force amplitude. 3. At concentrations above 120 µM, TEL induced irreversible dramatic changes in the ileal contractile activity.	Shraideh (1999)

[a]CYP—Cytochrome P-450

Table AX5-10.9. Lead, Calcium, and Vitamin D Interactions, and Intestinal Enzymes

Compound and Concentration	Duration	Species	Blood Lead	Effects[a]	Authors
Ca—0.5% in diet (low calcium) 1.2% in diet (high calcium) Pb—0.8% in the diet as Pb chloride	10 days	White Leghorn Cockerels	—	Dietary Pb affects intestinal Ca absorption in two different ways depending on the dietary Ca status. A. In chicks fed low Ca diet (0.05%), ingested Pb inhibited intestinal ^{47}Ca absorption, intestinal Calbindin D, and alkaline phosphatase synthesis in a dose dependent fashion. B. In normal calcium diets (1.2%) Pb exposure had no bearing on the intestinal Ca absorption, or Calbindin D, or Alkaline phosphatase synthesis and in fact elevated their levels at higher Pb concentrations. These results indicate that the primary effects of Pb in both cases, occur at or prior to intestinal protein synthesis involving Cholecalciferol endocrine system.	Fullmer and Rosen (1990)
Ca—0.1% or 1.2% in the diet with Pb—0.1–0.8% as Pb chloride in the diet	1 or 2 wks	Leghorn Cockerels	—	—Dietary Ca deficiency, initially (1st week) stimulates Ca absorption and Calbindin D levels regardless of dietary Pb intake. —At 2 wks, this response is reversed by Pb. —Intestinal Pb absorption was enhanced by Ca deficiency initially and was inhibited by prolonged dietary Pb intake. —Intestinal Pb absorption was increased in adequate Ca situation, but only after 2 wks at the lower levels of dietary Pb.	Fullmer (1991)
Ca—0.1–1.2% Pb—0.8%	2 wks	White Leghorn Cockerels	—	Interactions between dietary Pb and Ca-influence on serum vitamin D levels. —Pb ingestion and Ca deficiency alone or in combination generally increased serum 1,25 (OH)2 D levels over the most of the range of dietary Pb and Ca. —In severe Ca deficiency, Pb ingestion resulted in significant decreases in hormone concentration. —Similarities in response profiles for 1,25 (OH)2 D, intestinal Ca absorption and Calbindin- D suggested major interactions between Pb and calcium mediated changes via circulating1,25(OH)2 D concentration.	Fullmer (1997)

Table AX5-10.9 (cont'd). Lead, Calcium, and Vitamin D Interactions, and Intestinal Enzymes

Compound and Concentration	Duration	Species	Blood Lead	Effects[a]	Authors
Pb, Alkaline phosphatase and Ca^{2+} ATPase 2.0–10.0 mM Pb, Sucrase 0.5 mM–6.0 mM Pb, γ-glutamyl transpeptidase1.0–10 mM Pb, Acetyl choline esterase 10.00–35.00 mM	Incubation time not specified	Male Albino rats		Pb inhibited the activity of several intestinal brush border enzymes such as Ca^{2+}- ATPase, Sucrase, γ-glutamyl-transpeptidase and acetyl choline esterase with the exception of alkaline phosphatase. Inhibition of Ca^{2+}-ATPase was competitive and that of the other enzymes is by non-competitive means.	Gupta et al. (1994)
Oral Pb in Similac or apple juice adjusted for attainment of blood Pb levels 35–40 µg/dL. Succimer 30 mg/kg/d ^{204}Pb 24.5 nM followed by ^{206}Pb 352 nM, Single dose	Administered from 8th day post partum, until age 26 wks Two successive 19 days at age 53 wks and 65 wks Administered immediately before chelation	Female infant Rhesus Monkeys	Pb-exposed: 35–40 µg/dL	Effect of oral succimer chelation on the Gastro intestinal absorption and the whole body retention of Pb Radio isotope Pb tracer technique Succimer significantly reduced Gastro intestinal absorption of Pb and increased urinary excretion of Pb The initial decrease in whole body Pb by 10% was over come when majority of administered tracer was retained in the body after 5 days of treatment.	Cremin et al. (2001)

[a]CYP—Cytochrome P-450

ANNEX TABLES AX5-11

Table AX5-11.1. Lead-binding Proteins

Source	Organ	Species	Molecular Weight	Protein Properties	Inducible	Separation Technique
Goyer (1968)	Kidney	Rat		Intranuclear Pb inclusion bodies	Yes	
Goyer et al. (1970a,b)	Kidney	Rat		Pb is concentrated in the intranuclear inclusion body	Yes	
Choie and Richter (1972)	Kidney	Rat		Initial inclusion bodies in cytoplasm	Yes	
Moore et al. (1973)	Kidney	Rat		Protein in inclusion bodies is acidic, with high levels of aspartic a, glutamic a, glycine and cystine	Yes	
Moore and Goyer (1974)	Kidney	Rat	Inclusion body protein is 27.5 kDa		Yes	Acrylamide gel electrophoresis
Shelton and Egle (1982)	Kidney	Rat	Inclusion body is 32 kDa with pI of 6.3	Named p32/6.3	Yes	Two-dimensional gel electrophoresis
Egle and Shelton (1986)	Brain	Rat, mouse, dog, guinea pig, and chicken		p32/6.3 found	No	
Oskarsson et al. (1982)	Kidney cytosol and brain	Rat	11.5 and 63 kDa		No	^{203}Pb binding followed by Sephadex G-75 or G-200 chromatography, then SDS-PAGE
Mistry et al. (1985)	Kidney cytosol	Rat	11.5 kDa, 63 kDa, > 200 kDa	Respective Kd values: 13, 40, 123 nM	No	^{203}Pb binding followed by Sepharose-6B column chromatography
Fowler and DuVal (1991)	Kidney cytosol	Rat		Cleavage product of alpha-2 microglobulin	No	Chromatography followed by reverse phase HPLC, then production of antibodies Kd 10–8 M

Table AX5-11.1 (cont'd). Lead-binding Proteins

Source	Organ	Species	Molecular Weight	Protein Properties	Inducible	Separation Technique
Smith et al. (1998)	Kidney cortex	Human	9 kDa and 5 kDa	ACBP and thymosin B4	No	Sephadex G-75 fractions <30 kDa, Sephadex A-25, then HPLC
Goering et al. (1986)	Brain	Rat	12 kDa		No	Labeled (^{203}Pb) cytosol applied to Sephadex G-75
DuVal and Fowler (1989)	Brain	Rat	23 kDa	Glutamic a, aspartic a, cysteine. Not MT	No	Labeled cytosol applied to Sephadex G-75, DEAE, followed by SDS-PAGE
Fowler et al. (1993)	Kidney and brain	Monkey	Brain Pb-binding protein larger than kidney	aspartic a, glutamic a, glycine, serine	No	Sephadex G-75 and DEAE
Quintanilla-Vega et al. (1995)	Brain	Human	5 kDa and 20 kDa	Thymosin B4 and unidentified protein	No	Sephadex G-75, A-25 DEAE, reversed phase HPLC
Raghavan and Gonick (1977)	RBC	Human Pb-workers	10 kDa		Yes	^{210}Pb binding, Sephadex G-75, followed by SDS-PAGE
Raghavan et al. (1980)	RBC	Human Pb-workers	10 kDa	Pb-binding protein absent in controls, low in symptomatic, high in asymptomatic	Yes	^{210}Pb binding, Sephadex G-75
Raghavan et al. (1981)	RBC	Human Pb workers	10 kDa	Pb in membrane fraction correlates inversely with Na-K-ATPase	Yes	^{210}Pb binding, Sephadex G-75
Gonick et al. (1985)	RBC	Human Pb workers	12 kDa, pI 5.3, and 30 kDa	Glycine, histidine, aspartic a, leucine	Yes	Sephadex G-75, HPLC, isoelectric focusing, SDS-PAGE
Ong and Lee (1980)	RBC	Normal human	67 kDa	Thought to be hemoglobin	Yes	^{203}Pb binding, Sephadex G-75
Lolin and O'Gorman (1988)	RBC	Human Pb workers	Low molecular weight	Pb-binding protein correlates with restored ALAD	Yes	Sephadex G-75, Pb measured by atomic absorption

Table AX5-11.1 (cont'd). Lead-binding Proteins

Source	Organ	Species	Molecular Weight	Protein Properties	Inducible	Separation Technique
Church et al. (1993a)	RBC	Human Pb workers, one asymptomatic and one symptomatic	6–7 kDa	First pt had 67% of RBC Pb bound to protein. Second pt had 22% of RBC Pb in protein	Yes	RBC hemolysate filtered through Amicon YM 30 membrane. Superose 12 column. Pb quantitated by A.A.
Church et al. (1993b)	RBC	Human Pb workers	5, 7 and 12 kDa, pI 4.7–4.9	30 % cysteine Thought to be MT on basis of greater UV abs at 254 nm than 280 nm	Yes	Superose 12, Amicon YM 30, Amicon YM 2, HPLC
Xie et al. (1998)	RBC	Human Pb workers	240 ~ 260 kDa, <30 kDa	High M.Wt. peak identified as ALAD. Low M.Wt. peak seen after adding Pb in vitro	Yes	Bio-gel A column. Pb determined by A.A.
Goering and Fowler, (1987a)	Kidney	Rat		Pre-treatment with zinc before injecting ^{203}Pb leads to zinc-thionein binding Pb	No	^{203}Pb binding, Sephadex G-75
Goering and Fowler, (1987b)	Kidney and liver	Rat		Pre-Rx with Zn or Cd induces Zn or Zn, Cd-MT. The MT decreases Pb inhibition of ALAD	No	^{203}Pb binding, Sephadex G-75
Qu et al. (2002); Waalkes et al. (2004)	Kidney	MT-null phenotypic mice		Pb-exposed MT-null developed no Pb inclusion bodies, accumulated less renal Pb than WT		

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