

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of lead. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found in Appendix C at the end of this profile.

This chapter will focus primarily on inorganic lead compounds (lead, its salts, and oxides/sulfides), the predominant forms of lead in the environment. The available data on organic (i.e., alkyl) lead compounds indicate that some of the toxic effects of alkyl lead are mediated through metabolism to inorganic lead and that during the combustion of gasoline containing alkyl lead, significant amounts of inorganic lead are released to contaminate the environment. In addition, the lead alkyl halides in automobile exhausts are quickly oxidized by sunlight and air, and do not appear to be present at hazardous waste sites in significant amounts. By far, most lead at hazardous waste sites is inorganic lead. The limited data available on alkyl lead compounds indicate that the toxicokinetic profiles and toxicological effects of these compounds are qualitatively and quantitatively different from those of inorganic lead (EPA 1985b).

The database for lead is unusual in that it contains a great deal of data concerning dose-effect relationships in humans. These data come primarily from studies of occupationally exposed groups and the general population. For the general population, exposure to lead occurs primarily via the oral route, with some contribution from the inhalation route, whereas occupational exposure is primarily by inhalation with some contribution by the oral route. Because the toxic effects of lead are the same regardless of the route of entry into the body, the profile will not attempt to separate human dose data by routes of exposure. The dose data for humans are generally expressed in terms of absorbed dose and not in terms of external exposure levels, or milligrams per kilogram per day (mg/kg/day). The most common metric of absorbed dose for lead is the concentration of lead in the blood (PbB), although other indices, such as lead in bone, hair, or teeth also are available (further information regarding these indices can be found in Section 3.3.2 and Section 3.6.1). The concentration of lead in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone. Lead in bone is considered a biomarker of cumulative or long-term

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exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. For this reason, bone lead may be a better predictor than blood lead of some health effects.

The database on effects of lead in animals is extensive and, in general, provides support for observations in human studies, with some consistency in types of effects and PbB-effect relationships. However, animal data on lead toxicity are generally considered less suitable as the basis for health effects assessments than are the human data. There is no absolutely equivalent animal model for the effects of lead on humans. In this profile, animal studies will be discussed only to the extent that they support the findings in humans.

Due to the extent of the lead database, it is impossible to cite all, or even most, of the studies on a specific topic. ATSDR acknowledges that all studies that add a new piece of information are valuable, but the relative impact on the overall picture regarding lead toxicity varies among studies. Given that the goal of Chapter 3 is to provide an overall perspective on the toxicology of lead, some sections focus on studies that have provided major contributions to the understanding of lead toxicity over those that only add a small piece of information into a very big puzzle or that only reiterate findings previously published. Health outcomes associated with internal lead doses from selected studies are presented in Table 3-1.

3.2 DISCUSSION OF HEALTH EFFECTS

3.2.1 Death

Mortality studies for workers exposed occupationally to lead as well as studies of the general population are available (see also Section 3.2.8, Cancer). Two cohorts of male lead workers, 4,519 battery plant workers and 2,300 lead production workers, all of whom had been employed for at least 1 year during the period 1946–1970, were studied for mortality from 1947 through 1980 (Cooper 1988; Cooper et al. 1985). Overall mortality and standardized mortality ratios (SMRs) were determined. From 1947 through 1972, mean PbBs were 63 µg/dL for 1,326 battery plant workers and 80 µg/dL for 537 lead production workers (PbB data were not available for many of the workers and most of the monitoring was done after 1960). For both groups, the number of observed deaths from all causes combined was significantly greater ($p < 0.01$) than expected, based on national mortality rates for white males. The increased mortality rates resulted in large part from malignant neoplasms; chronic renal disease, including

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Cardiovascular^a					
519 males, 67 years old (mean)	General population	20.3 ppm (mean tibia Pb)	Increased risk of hypertension; no significant association with PbB or patella lead	Longitudinal study (Normative Aging Study). Covariates: age and body mass index; race; family history of hypertension; education; tobacco smoking and alcohol consumption; and dietary intakes of sodium and calcium. Subjects were free from definite hypertension at baseline.	Cheng et al. 2001
667 pregnant females, 15–44 years old	General population	10.7 ppm (mean calcaneus Pb)	Hypertension; a 10 ppm increase in calcaneus Pb was associated with a 0.70 mmHg increase in systolic blood pressure and 0.54 mmHg diastolic blood pressure	Longitudinal study of pregnancy. Co-variables: age and body mass index, parity, postpartum hypertension, tobacco smoking, and education.	Rothenberg et al. 2002b
496 adults, 56 years old (mean)	Occupational	4.6 µg/dL (mean PbB at baseline) 14.7 ppm (mean tibia Pb at year 3 of study)	Increase in systolic blood pressure associated with PbB and tibia Pb	Longitudinal study. Covariates: age and body mass index; diagnosis of diabetes, arthritis, or thyroid disease; education; and blood pressure measurement interval.	Glenn et al. 2003
294 females, 61 years old (mean)	General population	17.3 ppm (mean patella Pb)	Increased risk of hypertension; no significant association with tibia Pb or PbB	Case-control study (Nurses Health Study). Covariates: age and body mass index, dietary sodium intake, and family history of hypertension.	Korrick et al. 1999

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
146 males, 67 years old (mean)	General population	24 ppm (mean tibia Pb)	Increased risk of hypertension; an increase in tibia Pb from 8 to 37 ppm associated with a 1.5 odds ratio for hypertension	Case-control study. Covariates: body mass index and family history of hypertension.	Hu et al. 1996a
13,781 males and females, >20 years old	General population	2.1–4.2 µg/dL median PbB in white and black males and females	Bordeline association between PbB and systolic BP in black males and significant association in black females; no association in whites	NHANES III analysis. Covariates: age and body mass index; hematocrit, total serum calcium, and protein concentrations; tobacco smoking; alcohol and coffee consumption; dietary calcium, potassium, and sodium intakes; diabetes; and use of antihypertensive drugs.	Den Hond et al. 2002
543 females, 50 years old (mean)	General population	6.4 µg/dL (mean PbB) 4.0–31 µg/dL (range)	Increased risk of diastolic hypertension	NHANES III analysis. Co-variates: race, age, and body mass index; tobacco smoking, and alcohol consumption.	Nash et al. 2003
508 males and females, 19–24 years old	General population	>10 ppm (tibia Pb)	Increase in systolic and diastolic blood pressure	Cohort follow-up study of Bunker Hill children. Covariates: gender, age, and body mass index; blood hemoglobin and serum albumin concentrations; education; tobacco smoking and alcohol consumption; current use of birth control pills; income; and current PbB.	Gerr et al. 2002

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
775 males, 68 years old (mean)	General population	22.2 ppm (mean tibia Pb)	Significant association with EKG changes and conduction defects. Less strong association with patella Pb; no association with PbB	Cross-sectional study (Normative Aging Study). Covariates: age, body mass index, diastolic blood pressure, fasting blood glucose level, alcohol consumption, and serum HDL concentration.	Cheng et al. 1998
122 children, 9 years of age	General population	1.98 µg/dL (mean PbB prenatal); 4.62 µg/dL (mean PbB at evaluation)	Higher prenatal PbB associated with higher resting systolic BP; higher childhood PbB associated with greater peripheral resistance response to stress	Covariates included in the models were: maternal age, education, IQ, SES, HOME score, health and nutrition, substance use during pregnancy, and infant and childhood characteristics.	Gump et al. 2005
Gastrointestinal					
Children	General population	60–100 µg/dL (PbB range)	Colic	Compilation of unpublished data.	NAS 1972
Hematological					
159 adults	General population and occupational	5–95 µg/dL (PbB range)	Decreased ALAD activity	Four groups of subjects were analyzed. One unexposed group and three worker groups.	Hernberg and Nikkanen 1970
579 children, 1–5 years old	Residence near lead ore smelter	PbB >20 µg/dL	Anemia	Anemia defined as hematocrit <35%. Iron status was not available.	Schwartz et al. 1990
143 children, 10–13 years old	Residence near lead smelter	5–40 µg/dL (PbB range)	Decreased ALAD activity	There was no obvious threshold for ALAD-PbB relationship. A threshold for elevation of EP was evident between 15 and 20 µg/dL PbB.	Roels and Lauwerys 1987

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Musculoskeletal					
290 children, 6–10 years old	General population	2.9 µg/dL (mean PbB)	Increased caries in urban children	No increase in caries was seen in 253 rural children (PbB, 1.7 µg/dL). Covariates: sex, race, SES, maternal smoking, parental education, and dental hygiene variables.	Gemmel et al. 2002
6,541 children 2–11 years old	General population	2.9 µg/dL (geometric mean PbB for 2–5-year-olds); 2.1 µg/dL for 6–11-year-olds)	Increasing PbB associated with increased number of dental caries in both groups	NHANES III analysis. Covariates included age, gender, race-ethnicity, poverty income ratio, exposure to tobacco smoke, geographic region, parental education, carbohydrate and calcium intake, and dental visits.	Moss et al. 1999
10,033 males and females 20–69 years old	General population	2.5 µg/dL (geometric mean PbB)	Increasing PbB associated with periodontal bone loss	NHANES III analysis. Covariates included age, gender, race/ethnicity, education, SES, age of home, smoking, and periodontal disease.	Dye et al. 2002
Renal ^b					
744 males, 64 years old (mean)	General population	8 µg/dL (mean PbB) <4–26 µg/dL (range)	Decrease in GFR; an increase in PbB of 10 µg/dL was associated with a decrease in creatinine clearance rate of 10.4 mL/minute	Cross-sectional study (Normative Aging Study). Covariates: age and body mass index; systolic and diastolic blood pressure; alcohol consumption and tobacco smoking; and analgesic or diuretic medications.	Payton et al. 1994
459 males, 57 years old (mean)	General population	10 µg/dL (mean PbB) 0.2–54 µg/dL (range)	Decrease in GFR; a 10-fold increase in PbB was associated with a significant increase in serum creatinine	Longitudinal study (Normative Aging Study). Covariates: age and body mass index; hypertension; alcohol consumption and tobacco smoking; and education.	Kim et al. 1996a

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
707 males, 62 years old (mean)	General population	6.5 µg/dL (mean PbB) 21 ppm (mean tibia Pb)	Decrease in GFR; PbB and tibia, but not patella Pb, predicted increases in serum creatinine in men with diabetes and hypertension	Prospective study (Normative Aging Study). Covariates: age and body mass index; diabetes and hypertension; alcohol consumption and tobacco smoking; and education.	Tsaih et al. 2004
4,813 males and females, >20 years old	General population	4.2 µg/dL (mean PbB)	Decrease in GFR in subjects with hypertension	NHANES III analysis. Covariates: age, gender, and body mass index; systolic blood pressure; cardiovascular disease and diabetes mellitus; alcohol consumption and cigarette smoking; and household income, marital status, and health insurance.	Muntner et al. 2003
1,981 males and females, 48 years old (mean)	General population	11 µg/dL (mean PbB), 2–72 µg/dL (range in men); 7.5 µg/dL (1.7–60 µg/dL range in women)	Decrease in GFR; a 10-fold increase in PbB associated with decrease of 10–13 mL/minute in creatinine clearance	Cross-sectional study (Cadmibel Study). Covariates: age and body mass index; urinary glutamyltransferase activity; diabetes mellitus; and analgesic or diuretic therapy.	Staessen et al. 1992
803 males and females, 18–65 years old	Occupational	32 µg/dL (mean PbB) 37 ppm (mean tibia lead)	Increasing tibia lead associated with increased serum creatinine and uric acid; increasing PbB associated with increasing BUN	Cross-sectional study of Korean workers. Associations significant only for >46-year-old workers. Covariates included age, gender, body mass index, current/former exposed status, and hypertension.	Weaver et al. (2003a, 2005a)

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Endocrinological					
75 men	Occupational	50–98 µg/dL (PbB range)	Decreased serum T ₃ and T ₄	No significant correlation for FT ₄ and TSH in this PbB range. TSH, T ₃ , FT ₄ , and T ₄ increased in the range 8–50 µg/dL.	López et al. 2000
58 males, mean age 31.7 years	Occupational	51.9 µg/dL (mean PbB)	TSH significantly higher than in controls (mean PbB 9.5 µg/dL in controls)	Cross-sectional study. The association between PbB and TSH was independent of employment length. T ₃ was lower in a subgroup of 17 workers employed for 17.5 years than in those employed for 2.4 years.	Singh et al. 2000a
68 children, 11 months–7 years old	General population	2–77 µg/dL (PbB range) 25 µg/dL (mean PbB)	No effect on serum T ₄ or FT ₄	Covariates: sex, race, SES, and hemoglobin; 56% of the children had PbB <24 µg/dL.	Siegel et al. 1989
30 children, 1–5 years old	General population	33–120 µg/dL (PbB range)	Decreased serum Vitamin D levels	15 children with mean PbB of 18 µg/dL served as a comparison group.	Rosen et al. 1980
Immunological					
38 children, 3–6 years old	General population	PbB >10 µg/dL	Increased IgE and decreased IgG and IgM in females	35 children with PbB <10 µg/dL served as controls. No such effect was seen in males or in the combined analysis of males and females.	Sun et al. 2003
279 children, 9 months–6 years old	General population	1–45 µg/dL (PbB range)	Increased serum IgE	No other parameter of cellular or humoral immunity showed a significant association with PbB. Covariates: age, race, sex, nutrition, and SES.	Lutz et al. 1999

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Neurological					
172 children, 5 years old	General population	7.7 µg/dL (lifetime average PbB)	7.4 IQ points decline with PbB increase 1–10 µg/dL	Children tested with Stanford-Binet Intelligence Scale. Covariates: sex, birth-weight, iron status; mother's IQ, education, race, smoking, income, and HOME score.	Canfield et al. 2003
4,853 children, 6–16 years old	General population	1.9 µg/dL (geometric mean PbB)	PbB <5 µg/dL associated with decrease in arithmetic and reading skills	NHANES III (1988–1994). Covariates: sex, race, iron status, exposure to second-hand smoke, region of the United States, marital status, country, parental education, poverty index, and birth weight. Exposure history was unknown.	Lanphear et al. 2000a
237 children, 7.5 years old	General population	5.4 µg/dL (current mean PbB)	PbB associated with decrements in domains of attention, executive, function, visual-motor integration, social behavior, and motor skills	Associations were present at PbB as low as 3 µg/dL; 19 variables were controlled for in addition to alcohol and drug use.	Chiodo et al. 2004
780 children, 7 years old	General population	8 µg/dL (mean PbB at age 7)	Concurrent PbB always has the strongest association with IQ	Children had been treated for elevated PbB (20–44 µg/dL at 2 years of age and were followed until 7 years of age with serial IQ tests.	Chen et al. 2005

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
146 children, 12 and 24 months old	General population	6.1 µg/dL (mean maternal PbB during first trimester of pregnancy)	One SD (0.014 µg/dL) in first trimester plasma Pb associated with a reduction of 3.5 points in MDI score at 24 months of age	Study of women in Mexico City. Potential confounders included child's sex, PbB at 24 months, height for age and weight, and maternal age and IQ.	Hu et al. 2006
294 children, 12 and 24 months old	General population	PbB <10 µg/dL	24-month PbB inversely associated with MDI and PDI scores at 24 months; 12-month PbB associated with PDI scores at 12 months	MDI and PDI scores of the BSID II were evaluated at 12 and months. Conditions for inclusion included PbB <10 µg/dL, gestation age ≥37 weeks, and birth weight >2,000 g.	Téllez-Rojo et al. 2006
736 older adults	General population	4.5 µg/dL (mean PbB) 29.5 ppm (mean patella Pb)	Impaired cognitive test performance	Associations were found for both PbB and bone lead. Age, education, and alcohol intake were included in regression models.	Wright et al. 2003c

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Reproductive					
74 adult men	Occupational	46.3 µg/dL (mean PbB)	Decreased fertility	Wife's variables controlled for included parity, time since previous birth, age, birth cohort, employment status, and education. Husband's variables included smoking, alcohol intake, education, and parameters reflecting exposure intensity and duration.	Gennart et al. 1992b
251 men	Occupational	10–40 µg/dL (PbB range)	Weak evidence of decreased fertility	Only couples with one pregnancy were included in study. Association existed only with younger maternal age (<30 years).	Sallmén et al. 2000b
98 men	Occupational	36.7 µg/dL (mean PbB)	Significantly higher alterations in sperm density, motility, viability, and indicators of prostate function than in a reference group	Cross-sectional study. Reference group consisted of 51 men with mean PbB of 10.3 µg/dL. Exposed and controls were comparable in age, smoking status, and alcohol consumption.	Telisman et al. 2000
121 women	General population	≥5.1 µg/dL (cord blood PbB)	Increased pre-term births	The effect was evident only among primiparous, but not multiparous women.	Torres-Sánchez et al. 1999
Developmental					
329 infants, 1 month old	General population	5.6 µg/dL (mean infant PbB at 1 month) 15.3 ppm (maternal patella Pb)	Infant PbB at 1 month and maternal patella bone inversely associated with weight gain	Infant age, sex, breast feeding practices, and infant health were included in regression models. Maternal variables: age, parity, maternal anthropometry, education, and hospital of recruitment.	Sanín et al. 2001

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
233 infants, 1 month old	General population	7.0 µg/dL (mean cord blood Pb) 14.1 ppm (maternal patella Pb)	Cord PbB associated with low birth length; patella lead associated with low head circumference	Variables included in models were maternal height, calf circumference, smoking, parity, reproductive history, age and education, hospital of delivery, infant sex, and gestational age.	Hernández-Avila et al. 2002
4,391 children, 1–7 years old	General population	1–72 µg/dL (PbB range)	Decrease of 1.57 cm in stature and 0.52 cm in head circumference per 10 µg/dL increase in PbB	Data from NHANES III. Models included: age, sex, ethnicity, and poverty-income ratio. Models also considered head of household education, exposure to cigarette smoke, nutrient intake, iron status, anemia, history of anemia, previous testing for high PbB, and previous treatment for lead poisoning.	Ballew et al. 1999
1,706 girls, 8–16 years old	General population	1–22 µg/dL (PbB range)	Delayed sexual maturation	Data from NHANES III. Covariates: race/ ethnicity, age, family size, residence in metropolitan area, poverty-income ratio, and body mass index.	Wu et al. 2003b
2,741 girls, 8–18 years old	General population	3 µg/dL (geometric mean PbB)	Delayed sexual maturation	Data from NHANES III. Covariates: age, height, body mass index, history of tobacco smoking or anemia, dietary intake of iron, vitamin C, calcium, and family income.	Selevan et al. 2003

^aSee also Table 3-2.

^bSee also Table 3-3.

ALAD = δ -aminolevulinic acid dehydratase; BP = blood pressure; BUN = blood urea nitrogen; EKG = electrocardiogram; EP = erythrocyte protoporphyrin; GFR = glomerular filtration rate; HDL = high density lipoprotein; Ig = immunoglobulin; NHANES III = Third National Health and Nutrition Examination; NM = not measured; SES = socioeconomic status; TSH = thyroid stimulating hormone

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hypertension and nephritis; and "ill-defined" causes. Three additional studies provided suggestive evidence of increased mortality due to cerebrovascular disease in lead workers (Fanning 1988; Malcolm and Barnett 1982; Michaels et al. 1991). Malcolm and Barnett (1982) studied causes of death between 1921 and 1976 among lead acid battery plant workers and found a significant increase in deaths due to cerebrovascular disease among workers 65–69 years of age. In addition, a marginally significant increase in the incidence of deaths due to nephritis and nephrosis was observed in the lead workers during 1935–1958, but not at later periods, compared to workers with no lead exposure. Fanning (1988) compared the causes of death among 867 workers exposed to lead from 1926 to 1985 with 1,206 workers having low or no lead exposure and found a significant increase in deaths due to cerebrovascular disease among workers who died between 1946 and 1965 as compared to controls. No other cause produced an excess of deaths in lead workers. Environmental lead levels and biological monitoring for body lead burdens were not available for the entire period. The author suggested that the increased risk of death due to cerebrovascular disease was not present from 1965 to 1985 because of stricter occupational standards resulting in lower levels of exposure. Michaels et al. (1991) followed a cohort of 1,261 white male newspaper printers (typesetters) from January 1961 through December 1984. These workers had little or no occupational exposure to any other potentially toxic agents. It was assumed that lead exposure ceased in 1976 when the transition to computerized typesetting occurred. SMRs were calculated for 92 cause-of-death categories using the mortality rates of New York City as the comparison population. The authors found that there were no significantly elevated nonmalignant or malignant causes of death in this cohort. In fact, the SMRs were generally less than unity, indicating that there were fewer deaths than expected, which the authors attributed to the "healthy worker effect." However, the SMR for cerebrovascular disease was significantly elevated in those members of the cohort employed for >30 years. Since there was no excess of arteriosclerotic heart disease, it appeared that lead exposure selectively increased cerebrovascular disease.

Few studies of the general population have been conducted. McDonald and Potter (1996) studied the possible effects of lead exposure on mortality in a series of 454 children who were hospitalized for lead poisoning at Boston's Children Hospital between 1923 and 1966 and who were traced through 1991. Of the 454 patients eligible for the study, 88% had a history of paint pica or known lead exposure; 90% had radiologic evidence of skeletal changes consistent with lead poisoning; and 97% had characteristic gastrointestinal, hematologic, and/or neurologic symptoms. The average PbB level in 23 children tested was 113 µg/dL; PbB tests were performed routinely at the hospital only after 1963. A total of 86 deaths were observed, 17 of these cases were attributed to lead poisoning. Although the distribution of causes of mortality generally agreed with expectations, there was a statistically significant excess of death from

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cardiovascular disease (observed/expected [O/E], 2.1; 95% confidence interval [CI], 1.3–3.2). Three of four deaths from cerebrovascular accidents occurred in females, and 9 of 12 deaths from arteriosclerotic heart disease occurred in males. Two men died from pancreatic cancer (O/E, 10.2; 95% CI, 1.1–36.2) and two from non-Hodgkin's lymphoma (O/E, 13.0; 95% CI, 1.5–46.9).

Lustberg and Silbergeld (2002) used data from the Second National Health and Nutrition Examination Survey (NHANES II) to examine the association of lead exposure and mortality in the United States. A total of 4,292 blood lead measurements were available from participants aged 30–74 years who were followed up through December 31, 1992. After adjusting for potential confounders, individuals with PbB between 20 and 29 $\mu\text{g/dL}$ had 46% increased all-cause mortality, 39% increased circulatory mortality, and 68% increased cancer mortality compared with those with PbB $<10 \mu\text{g/dL}$. The results also showed that nonwhite subjects had significantly increased mortality at lower PbB than did white subjects, and that smoking was associated with higher cancer mortality in those with PbB of 20–29 $\mu\text{g/dL}$ compared with those with PbB $<20 \mu\text{g/dL}$. Recently, Schober et al. (2006) used data from NHANES III (1988–1994) to determine relative risk of mortality from all causes, cancer, and cardiovascular disease in 9,757 participants who were ≥ 40 years of age. After adjusting for covariates, relative to PbBs $<5 \mu\text{g/dL}$, the relative risks of mortality from all causes for those with PbB 5–9 and $\geq 10 \mu\text{g/dL}$ were 1.24 (95% CI, 1.05–1.48) and 1.59 (95% CI, 1.28–1.98), respectively. Similar observations were reported for deaths due to cardiovascular disease and cancer, and tests for trend were statistically significant ($p < 0.01$) for both causes of death. Of interest also is a study that describes trends in lead poisoning-related deaths in the United States between 1979 and 1998 (Kaufmann et al. 2003). Reviews of death certificates revealed that approximately 200 lead poisoning-related deaths occurred from 1979 to 1998. The majority were among males (74%), African Americans (67%), adults of age ≥ 45 years (76%), people living in the South region of the United States (70%), and residents in cities with populations $<100,000$ habitants (73%). Lead poisoning was the underlying cause of death in 47% of the deaths. The authors also found that alcohol (moonshine ingestion) was a significant contributing cause for 28% of adults.

In summary, the information available suggests a potential association between lead exposure and cerebrovascular disease. There is no information from studies in animals that would support or refute the existence of a possible association between lead exposure and mortality due to cerebrovascular disease.

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3.2.2 Systemic Effects

Respiratory Effects. Very limited information was located regarding respiratory effects in humans associated with lead exposure. A study of 62 male lead workers in Turkey reported significant alterations in tests of pulmonary function among the workers compared to control subjects (Bagci et al. 2004). The cohort consisted of 22 battery workers, 40 exhaust workers, and 24 hospital workers with current PbB of 37, 27, and 15 µg/dL, respectively. Workers and controls were matched for age, height, weight, and smoking habit. No association was found between PbB and duration of employment. No information was provided regarding exposure levels, medical histories of the workers or potential exposure to other chemicals. No relevant information was located from studies in animals.

Cardiovascular Effects. Although lead has been shown to produce various cardiovascular effects in animals (Vaziri and Sica 2004), end points of greatest concern for humans at low exposures and low PbBs are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistically related and, furthermore, can be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease. Effects of lead on glomerular filtration are discussed in Section 3.2.2, Renal Effects. Other cardiovascular changes have been noted in association with increasing lead body burdens and/or lead exposures in humans that include changes in cardiac conduction and rhythm (Böckelmann et al. 2002; Cheng et al. 1998; Kirkby and Gyntelberg 1985; Kosmider and Petelenz 1962), which may be secondary to lead-induced impairment of peripheral nerve conduction (see Section 3.2.4, Neurological Effects).

Effects on Blood Pressure. Numerous epidemiological studies have examined associations between lead exposure (as indicated by PbB or bone lead concentration) and blood pressure. Meta-analyses of the epidemiological findings have found a persistent trend in the data that supports a relatively weak, but significant association. Quantitatively, this association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994). The results of more recent epidemiology studies indicate that the lead contribution to elevated blood pressure is more pronounced in middle age than at younger ages. Numerous covariables and confounders affect studies of associations between PbB and blood pressure, including age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, and various dietary factors (e.g., dietary calcium). Including confounders in a regression model will attenuate the apparent association between lead exposure and the measured health outcome (e.g., Moller and

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Kristensen 1992). For example, adjusting for alcohol consumption will decrease the apparent association between blood lead concentration and blood pressure, if alcohol consumption contributes to lead intake and, thereby, blood lead concentration (Bost et al. 1999; Hense et al. 1993; Hertz-Picciotto and Croft 1993; Wolf et al. 1995). Conversely, failure to account for important effect modifiers (e.g., inherited disease) will result in overestimation of the apparent strength of the association. Varying approaches and breadth of inclusion of these may account for the disparity of results that have been reported.

Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements (Staessen et al. 2000). Few studies have employed such techniques and, when used, have not found significant associations between PbB and blood pressure (Staessen et al. 1996b).

An additional limitation of blood lead studies, in general, is that PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of lead. Bone lead, a metric of cumulative or long-term exposure to lead, appears to be a better predictor of lead-induced elevations in blood pressure than PbB (Cheng et al. 2001; Gerr et al. 2002; Hu et al. 1996a; Korrick et al. 1999; Rothenberg et al. 2002a). In a recent prospective analysis of the Normative Aging Study, higher patellar lead levels, but not PbB, were associated with higher systolic blood pressure and abnormalities in electrocardiographic conduction (Cheng et al. 1998, 2001).

Epidemiology studies, alone, cannot prove cause and effect relationships between lead exposure and blood pressure or cardiovascular disease. However, studies conducted in animal models support the plausibility of blood pressure effects of lead in humans. These studies have shown that long-term lead exposure can elevate blood pressure in nutritionally replete rats (Carmignani et al. 1988; Iannaccone et al. 1981; Khalil-Manesh et al. 1993; Victory et al. 1982a, 1982b), and have identified potential mechanisms for the effect (Carmignani et al. 2000; Ding et al. 1998; Gonick et al. 1997; Purdy et al. 1997; Vaziri and Ding 2001; Vaziri et al. 1999a, 1999b, 2001).

Meta-analyses. A recent meta-analysis of 31 studies published between 1980 and 2001, which included a total of 58,518 subjects (Nawrot et al. 2002), estimated the increase in systolic pressure per doubling of PbB to be 1 mmHg (95% CI, 0.5–1.5) and the increase in diastolic pressure to be 0.6 mmHg (95% CI, 0.4–0.8) (Table 3-2; Figures 3-1 and 3-2). This outcome is similar to two other meta-analyses. A meta-analysis reported by Staessen et al. (1994) included 23 studies (published between 1984 and 1993; 33,141 subjects) and found a 1 mmHg (95% CI, 0.4–1.6) increase in systolic blood pressure and 0.6 mmHg (95% CI, 0.2–1.0) in diastolic pressure per doubling of PbB. Schwartz (1995) conducted a

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Table 3-2. Characteristics of the Study Population in Meta-Analyses of Effects of Lead on Blood Pressure

Reference	No. ^a	Pop. ^b	Men (%) ^c	HT ^d	Age (years) ^e	SBP ^f	DBP ^f	Lead (µg/dL) ^g
1 ^h Pocock et al. 1984; Shaper et al. 1981	7,379	GP	100	Y	49 (40–59)	145	82	15.13 (2.07–66.3) ^{Ae}
2 Kromhout 1988; Kromhout et al. 1985	152	GP	100	Y	67 (57–76)	154	92	18.23 (10.77–27.97) ^{Ac}
3 Moreau et al. 1982, 1988; Orssaud et al. 1985	431	WC	100	Y	41 (24–55)	131	75	18.23 (8.91–49.94) ^{Ae}
4 Weiss et al. 1986, 1988	89	WC	100	Y	47 (30–64)	122	83	24.45 (18.65–29.01) ^{Mx}
5 de Kort and Zwennis 1988; de Kort et al. 1987	105	BC	100	N	40 (25–80)	136	83	29.22 (4.35–83.29) ^{Ae}
6 Lockett and Arbuckle 1987	116	BC	100	Y	32 (?–?)	119	80	37.5 (14.92–95.52) ^{Ae}
7 Parkinson et al. 1987	428	BC	100	Y	36 (18–60)	127	80	27.97 (6.01–49.52) ^{Ac}
8 Rabinowitz et al. 1987	3,851	GP	0	Y	28 (18–38)	121	76	7.04 (3.73–10.15) ^{Ac}
9 Elwood et al. 1988a, 1988b ⁱ	1,136	GP	100	Y	56 (49–65)	146	87	12.64 (6.01–26.11) ^{Gc}
10 Elwood et al. 1988a, 1988b ^j	1,721	GP	50	Y	41 (18–64)	127	78	10.15 (4.56–23.21) ^{Gc}
11 Gartside 1988; Harlan 1988; Harlan et al. 1985; Pirkle et al. 1985; Ravnskov 1992 ^k	6,289	GP	53	Y	30 (10–74)	127	80	13.47 (2.07–95.93) ^{Ge}
12 Neri et al. 1988 ^l	288	BC	100	?	? (?–?)	?	?	45.17 (6.01–65.06) ^{Ae}
13 Neri et al. 1988 ^m	2,193	GP	?	Y	45 (25–65)	?	?	23.41 (0–47.03) ^{Me}
14 Grandjean et al. 1989, 1991 ⁿ	1,050	GP	48	Y	40 (40–40)	?	?	11.6 (3.94–60.09) ^{Ae}
15 Reimer and Tittelbach 1989	58	BC	100	?	32 (?–?)	134	81	39.99 (12.85–70.24) ^{Ac}
16 Apostoli et al. 1990	525	GP	48	Y	45 (21–60)	132	84	13.05 (2.07–28.18) ^{Ae}
17 Morris et al. 1990	251	GP	58	Y	? (23–79)	?	?	7.46 (4.97–38.95) ^{Ae}
18 Sharp et al. 1988, 1989, 1990	249	WC	100	N	43 (31–65)	128	83	6.63 (2.07–14.92) ^{Pe}
19 Staessen et al. 1984 ^o	531	WC	75	Y	48 (37–58)	126	78	11.4 (4.14–35.22) ^{Ge}
20 Møller and Kristensen 1992 ^p	439	GP	100	Y	40 (40–40)	?	?	13.68 (4.97–60.09) ^{Ae}

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Table 3-2. Characteristics of the Study Population in Meta-Analyses of Effects of Lead on Blood Pressure

Reference	No. ^a	Pop. ^b	Men (%) ^c	HT ^d	Age (years) ^e	SBP ^f	DBP ^f	Lead (µg/dL) ^g
21 Hense et al. 1993	3,364	GP	51	Y	48 (28–67)	129	80	7.87 (1.24–37.09) ^{Ae}
22 Maheswaran et al. 1993	809	BC	100	Y	43 (20–65)	129	84	31.7 (0–98.01) ^{Ae}
23 Menditto et al. 1994	1,319	GP	100	Y	63 (55–75)	140	84	11.19 (6.22–24.66)
24 Hu et al. 1996a; Proctor et al. 1996 ^q	798	GP	100	Y	66 (43–93)	134	80	5.59 (0.41–35.02) ^{Pe}
25 Staessen et al. 1996a, 1996b ^r	728	GP	49.3	Y	46 (20–82)	130	77	9.12 (1.66–72.52) ^{Ge}
26 Sokas et al. 1997 ^s	186	BC	99	Y	43 (18–79)	130	85	7.46 (2.07–30.04) ^{Pe}
27 Bost et al. 1999	5,326	GP	48	Y	48 (16–?)	135	75	63.82 (?–?) ^G
28 Chu et al. 1999	2,800	GP	53	Y	44 (15–85)	123	78	6.42 (0.41–69) ^{Ae}
29 Rothenberg et al. 1999a, 1999b	1,627	GP	0	Y	27 (?–?)	110	59	2.28 (?–?) ^G
30 Schwartz and Stewart 2000	543	BC	100	Y	58 (41–73)	128	77	4.56 (1.04–20.1) ^{Ae}
31 Den Hond et al. 2001 ^t	13,781	GP	53.2	Y	48 (20–90)	125	73	3.11 (0.62–55.94) ^{Ge}

^aNo.: Number of persons in whom relevant data were available.

^bPop.: Study population: BC = blue collar workers; GP = sample from general population; WC = white collar employees

^cMen: Percentage of men

^dHT: Indicates whether the sample included (Y = yes) or did not include (N = no) hypertensive patients.

^eAge: Mean age or midpoint of age span (range or approximate range given between parentheses).

^fSBP, DBP: Mean systolic and diastolic blood pressures

^gLead: Measure of central tendency: A = arithmetic mean; G = geometric mean; M = midpoint of range; P = P₅₀ (median). The spread of blood lead is given between parentheses: c = P₅–P₉₅ interval; P₁₀–P₉₀ interval, or interval equal to 4 times the standard deviation; e = extremes; x = approximate limits of distribution.

^hNumber refers to reference in Figures 3-1 and 3-2.

ⁱCaerphilly Study

^jWelsh Heart Program

^kNHANES (National Health and Nutrition Examination Survey)

^lfoundry workers

^mCanadian Health Survey

ⁿGlostrup Population Study, cross-sectional analysis (1976)

^oLondon Civil Servants

^pGlostrup Population Study, longitudinal analysis (1976–1987)

^qNormative aging study

^rPheeCad (Public Health and Environmental Exposure to Cadmium) Study

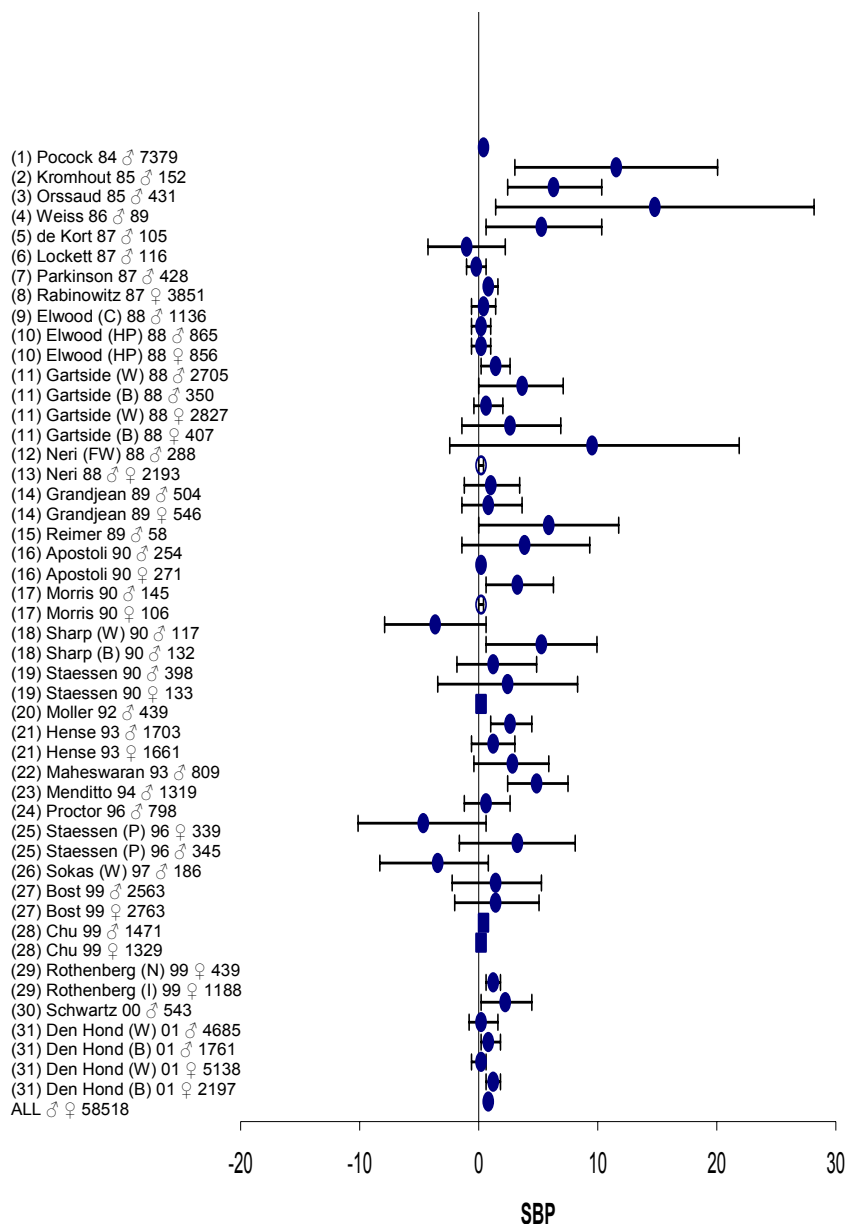
^sBecause of missing information, only the effect in whites is included.

^tNHANES III Survey

Source: Nawrot et al. 2002

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Figure 3-1. Change in the Systolic Pressure Associated with a Doubling of the Blood Lead Concentration*

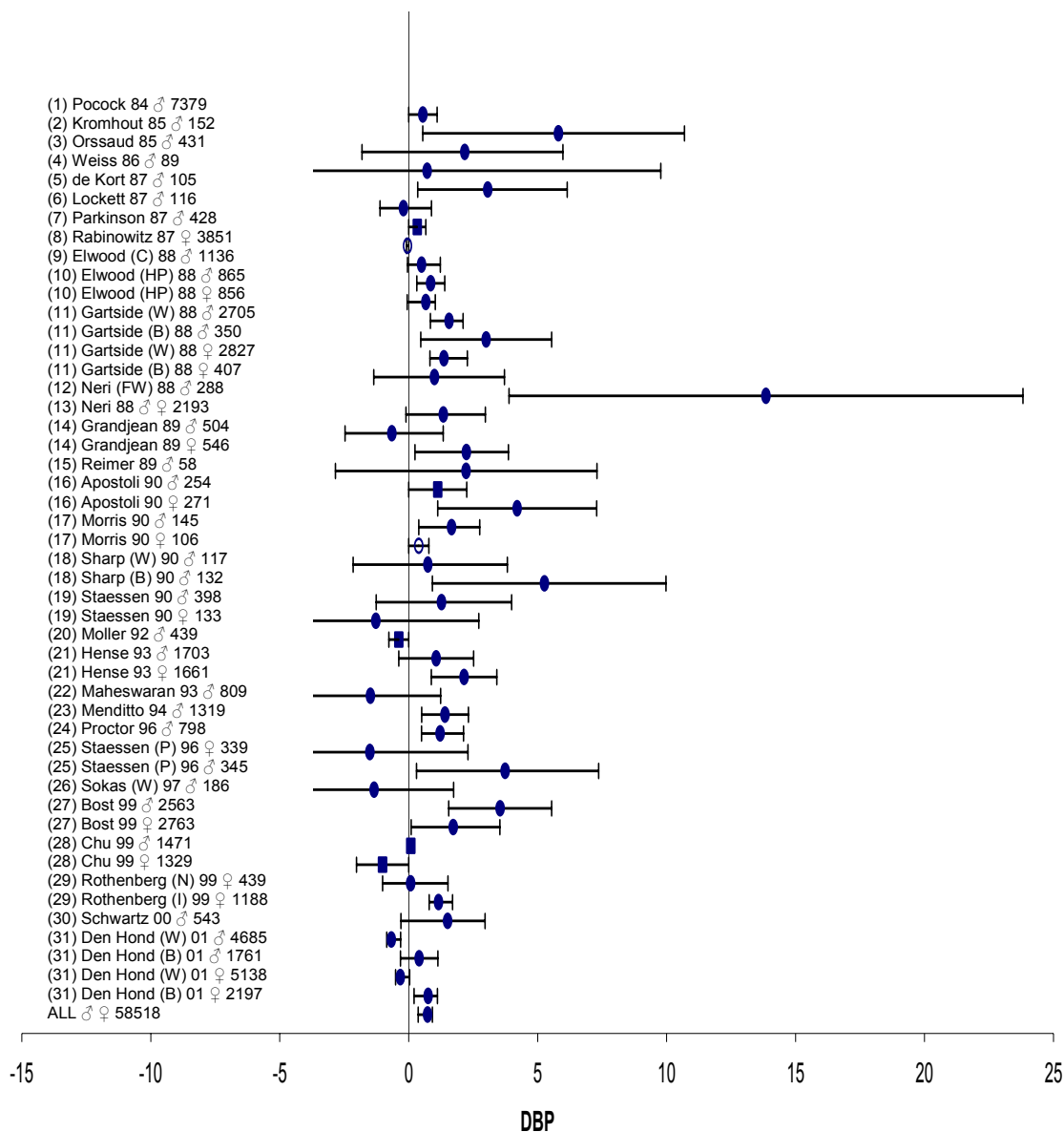


*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 3-2 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

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Figure 3-2. Change in the Diastolic Pressure Associated with a Doubling of the Blood Lead Concentration*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 3-2 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

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meta-analysis that encompassed a similar time frame (15 studies published between 1985 and 1993) and found a 1.25 mmHg (95% CI, 0.87–1.63) increase in systolic blood pressure per doubling of PbB (diastolic not reported). The latter analysis included only those studies that reported a standard error on effect measurement (e.g., increase in blood pressure per doubling of PbB). Of the 15 studies included in the Schwartz (1995) analysis, 8 were also included in the Staessen et al. (1994) analysis.

Longitudinal Studies—General Populations—Adults. The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67 years) and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitis. Physical examinations, including seated blood pressure and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone x-ray fluorescence (XRF) measurements (mid-tibia and patella) were included in the examinations. Data collected for a subset of the study population (840 subjects) observed between 1991 and 1997 were analyzed for associations between blood pressure and blood or bone lead concentrations (Cheng et al. 2001). Mean baseline PbB was 6.1 µg/dL (standard deviation [SD], 4.0) for the entire study group and 5.87 µg/dL (SD, 4.01) in the normotensive group (n=323). Mean bone lead concentrations in the normotensive subjects (n=337) were: tibia, 20.27 µg/g (SD, 11.55); patella, 28.95 (SD, 18.01). Based on a cross-sectional linear multivariate regression analysis of 519 subjects who had no hypertension at the time of first bone and blood lead measurement, covariate-adjusted systolic blood pressure was not significantly associated with PbB or patella lead concentration; however, increasing tibia lead concentration was associated with increasing systolic blood pressure. Follow-up examinations were completed on 474 subjects, allowing a longitudinal analysis of hypertension risk. Covariate-adjusted risk (risk ratio, RR; proportional hazards model) of hypertension (systolic >160 mm Hg or diastolic >95 mm Hg) was significantly associated with patella bone lead concentrations (RR, 1.29; 95% CI, 1.04–1.61), but not with PbB (RR, 1.00; 95% CI, 0.76–1.33) or tibia bone lead concentration (RR, 1.22; 95% CI, 0.95–1.57). Increases in patella lead concentration from 12.0 µg/g (mid-point of lowest quintile) to 53.0 µg/g (mid-point of highest quintile) were associated with a rate ratio of 1.71 (95% CI, 1.08–2.70). Covariates considered in the analyses included age and body mass index; race; family history of hypertension; education; tobacco smoking and alcohol consumption; and dietary intakes of sodium and calcium. A cross-sectional case-control analysis of the Normative Aging Study also found significant associations between bone lead concentration and risk of hypertension (see discussion of Hu et al. 1996a). The observation that risk of hypertension in middle-aged males increased in association with increasing patella bone lead concentration, but not tibia bone lead or PbB, is consistent with a similar finding in middle-aged females, derived from the Nurses Health

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Study (Korrick et al. 1999). Associations between PbB and hypertension risk in middle-aged women have been found in larger cross-sectional studies (Nash et al. 2003). These observations suggest that, in some populations, blood pressure increases may be more strongly associated with cumulative lead exposure (reflected in bone lead levels) than more contemporaneous exposures (reflected in blood lead concentrations).

A random sample from the general population of Belgium (728 subjects, 49% male, age 20–82 years old) was studied during the period 1985 through 1989 (baseline; from Cadmibel study, Dolenc et al. 1993) and reexamined from 1991 through 1995 (follow-up) (Staessen et al. 1996b). Multiple seated blood pressure measurements were taken during the baseline and follow-up periods; multiple ambulatory measurements were taken during the follow-up period. The baseline PbB for the study group was 8.7 µg/dL (range, 1.7–72.5). Based on a linear multivariate regression analysis (with log-transformed blood lead concentrations), covariate-adjusted time-integrated systolic or diastolic blood pressure, or changes in systolic or diastolic blood pressure (follow-up compared to baseline) were not significantly associated with PbB or zinc photoporphyrin (ZPP) concentrations. The covariate adjusted risk for hypertension of doubling of the baseline PbB was not significantly >1. Covariates considered in the above analyses included gender, age, and body mass index; menopausal status; smoking and alcohol consumption; physical activity; occupational exposure to heavy metals; use of antihypertensive drugs, oral contraceptives, and hormonal replacement therapy; hematocrit or blood hemoglobin concentration; and urinary sodium, potassium, and γ-glutamyltransferase activity.

A random sample of the general population of Denmark (451 males, 410 females, age 40 years) was studied in 1976 (baseline) and reexamined in 1981 (Grandjean et al. 1989). Baseline and follow-up observations included sitting blood pressure measurements, physical examination and health histories, and PbB measurements. The median baseline PbB was 13 µg/dL (90th percentile, 20) and 9 µg/dL (90th percentile, 13) in males and females, respectively. Covariate adjusted linear regression coefficients for relating systolic or diastolic blood pressure with PbB (log-transformed) were not statistically significant in males or females. Covariates considered in the analysis included height-adjusted weight index, exercise, smoking, alcohol intake, occupation, blood hemoglobin, serum cholesterol, and serum triglycerides. Similar conclusions were reported from a prospective study of this same population; adjustment for cardiovascular risk factors (i.e., body mass index, tobacco smoking, alcohol consumption, physical fitness) attenuated an apparent association between PbB and systolic and diastolic blood pressure (Moller and Kirstensen 1992).

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Longitudinal Studies—General Population—Pregnancy. A longitudinal study examined associations between blood pressure and lead exposure during pregnancy and postpartum (Rothenberg et al. 2002b). The study included 667 subjects (age 15–44 years) registered at prenatal care clinics in Los Angeles during the period 1995–2001, and who had no history of renal or cardiovascular disease, postnatal obesity (body mass index >40), or use of stimulant drugs (e.g., cocaine, amphetamines). Measurements of sitting blood pressure and PbB were made during the third trimester and at 10 weeks postnatal. Tibia and calcaneus bone lead concentrations (XRF) were measured at the postnatal visit. Mean (geometric) PbBs were 1.9 µg/dL (+3.6/-1.0, geometric standard deviation [GSD]) during the third trimester and 2.3 µg/dL (+4.3/-1.2, GSD) postnatal. Mean (arithmetic) bone lead concentrations were 8.0 µg/g (11.4, SD) in tibia and 10.7 µg/g (11.9, SD) in calcaneus. Covariate-adjusted risk (odds ratio, OR) of hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) in the third trimester was significantly associated with increasing calcaneus bone lead concentration (OR, 1.86; 95% CI, 1.04–3.32). A 10 µg/g increase in calcaneus bone lead concentration was associated with a 0.77 mmHg (95% CI, 0.04–1.36) increase systolic blood pressure in the third trimester and a 0.54 mmHg (95% CI, 0.01–1.08) increase in diastolic blood pressure. Covariates included in the final model were age and body mass index, parity, postpartum hypertension, tobacco smoking, and education.

Longitudinal Studies—General Population—Children. Possible associations between blood pressure and lead exposure in young children were studied as part of a prospective study of pregnancy outcomes (Factor-Litvak et al. 1996). The study group consisted of 281 children, age 5.5 years, from the Kosovo, Yugoslavia prospective study (see Section 3.2.4 for more details on this cohort). Approximately half of the children (n=137) lived in a town with heavy lead contamination (exposed group) and the other half (n=144) were from a relatively uncontaminated town (reference group). Mean PbBs were 37.3 µg/dL in the exposed group and 8.7 µg/dL in the reference group. Covariate-adjusted linear regression coefficients relating blood pressure and PbB at 5.5 years of age were not significantly >0: systolic, 0.054 (95% CI, -0.024–0.13); diastolic, -0.042 (95% CI, -0.01–0.090). Regression coefficients for the integrated average PbB (assessed every 6 months from birth) were similar in magnitude: systolic, 0.047 (95% CI, -0.037–0.13), diastolic, 0.041 (95% CI, -0.016–0.098). Covariates included in the analysis were gender, height and body mass index, birth order, and ethnicity.

A prospective study designed to assess various environmental factors on development examined possible associations between PbB and blood pressure in a group of 122 children (66 females) at 9 years of age (Gump et al. 2005). The mean PbB at the time of evaluation was 4.62 µg/dL (SD±2.51). Outcomes measured included heart rate, diastolic and systolic blood pressure, stroke volume, cardiac output, and

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total peripheral resistance; these were assessed at rest and following an acute pressor stress (arm immersion in ice water). General linear models were used to explore associations between PbB and outcomes. Increasing cord PbB was significantly associated with increasing covariate-adjusted resting systolic blood pressure (β , 12.16; Standard error [SE], 4.96; $p=0.016$). Increasing childhood PbB was significantly associated with an increased total peripheral vascular resistance in response to the acute pressor stress (β , 0.88 dyn-s/cm⁵ per $\mu\text{g/dL}$; 95% CI, 0.024–0.152; $p=0.007$). Covariates considered in the models included: maternal age, education, IQ, socioeconomic status (SES), HOME score, health, nutrition; substance use during pregnancy; infant birth characteristics (e.g., gestational age, birth weight, head circumference, Ballard score); and childhood characteristics (e.g., body mass index, SES).

Longitudinal Studies—Occupational. A population of 496 current and former employees of an organic lead manufacturing facility (mean age, 55.8 years) located in the eastern United States, was studied during the period 1994–1996 with follow-up examinations at approximately 4–14-month intervals through 1998 (Glenn et al. 2003). Multiple seated blood pressure measurements were taken at each examination. PbB was measured at the initial examination (baseline) and tibia bone XRF measurements were taken in 1997. The mean PbB was 4.6 $\mu\text{g/dL}$ and the mean tibia bone lead concentration was 14.7 $\mu\text{g/g}$. Based on a generalized estimating equation model, covariate-adjusted systolic blood pressure was significantly associated with baseline PbB or tibia bone lead concentration. A one standard deviation increase in PbB was associated with a 0.64 mmHg (95% CI, 0.14–1.14) increase in systolic blood pressure and a 0.009 (95% CI, -0.24–0.43) increase in diastolic blood pressure. A one standard deviation increase in tibia bone lead concentration was associated with a 0.73 mmHg (95% CI, 0.23–1.23) increase in systolic blood pressure and a 0.07 mmHg (95% CI, -0.29–0.42) increase in diastolic blood pressure. Covariates considered in the analyses included race; age and body mass index; diagnosis of diabetes, arthritis, or thyroid disease; education; and blood pressure measurement interval.

A population of 288 foundry workers was studied during the period 1979–1985, during which multiple blood pressure and PbB measurements were taken (Neri et al. 1988). Linear regression coefficients were estimated for the relationship between PbB and systolic or diastolic blood pressure, for each of 288 subjects. The average covariate (age and body weight) adjusted regression coefficient (mmHg per $\mu\text{g/dL}$ blood lead) was 0.210 (SE, 0.139, $p=0.064$) for systolic pressure and 0.298 (SE, 0.111, $p<0.05$) for diastolic pressure.

A population of 70 Boston policemen was studied during the period 1969–1975, during which multiple seated blood pressure measurements were taken (years 2–5) and PbB measurements were taken in

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year 2 (Weiss et al. 1986, 1988). Covariate adjusted linear regression coefficients (mmHg per $\mu\text{g/dL}$) were determined, with exposure represented as low (20–29 $\mu\text{g/dL}$) or high (≥ 30 $\mu\text{g/dL}$). After adjusting for covariates, high PbB was a significant predictor of subsequent elevation in systolic blood pressure of 1.5–11 mmHg in the working policemen with normal blood pressure. Low PbB (20–29 $\mu\text{g/dL}$) was not a predictor of subsequent systolic blood pressure elevations. Diastolic pressure was unrelated to PbB. Covariates retained in the model were previous systolic blood pressure, body mass index, age, and cigarette smoking.

Case-control Studies—General Population. A case-control study examined potential associations between blood pressure and blood and bone lead concentrations in a population of middle-aged women (mean age, 61 years; Korrick et al. 1999). Cases ($n=89$) and age-matched controls ($n=195$) were a subset of women who resided in the Boston area of the United States (recruited during the period 1993–1995) who were enrolled in the National Nurses Health Study (NHS). Cases were selected based on self-reported physician diagnosis of hypertension as part of the NHS. Potential controls were excluded from consideration if they had a history of hypertension or other cardiovascular disease, renal disease, diabetes, malignancies, obesity, or use of antihypertensive or hypoglycemic medication. Controls were stratified based on measured blood pressure: low normal (<115 mm Hg systolic and <75 mmHg diastolic), or high normal (>134 and <140 mmHg systolic or >85 and <90 mmHg diastolic). Multiple sitting blood pressure measurements, PbB, and tibia and patella bone lead concentration measurements were taken at the beginning of the study. Self-reported information on medical history was provided as part of the NHS every 2 years. The mean PbB (cases and controls combined) was 3 $\mu\text{g/dL}$ (range, <1 –14 $\mu\text{g/dL}$). Mean bone lead concentrations were: tibia, 13.3 $\mu\text{g/g}$ and patella, 17.3 $\mu\text{g/g}$. Risk of hypertension was assessed using a logistic regression model. Covariate-adjusted risk of hypertension (defined as systolic pressure ≥ 140 mm Hg or diastolic ≥ 90 mm Hg) was significantly associated with increasing patella lead concentration, but not with tibia bone concentration or PbB. An increase from the 10th to the 90th percentile of patella bone lead concentration (from 6 to 31 $\mu\text{g/g}$) was associated with an increase in the odds of hypertension of 1.86 (95% CI, 1.09–3.19). Covariates considered in the regression models included: age and body mass index; dietary calcium and sodium intakes; alcohol consumption and tobacco smoking, and family history of hypertension. Of these, age and body mass index, dietary sodium intake, and family history of hypertension were included in the final model. The OR (odds of being a case/odds of being in control group) of hypertension with increasing patella lead concentration was 1.03 (95% CI, 1.00–1.05). When stratified by age, the ORs were 1.04 (95% CI, 1.01–1.07) in the >55 years of age groups and 1.01 (95% CI, 0.97–1.04) in the age group ≤ 55 years. Stratification by menopausal status resulted in ORs of 1.04 (95% CI, 1.01–1.06) for the postmenopausal group and

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0.98 (95% CI, 0.91–1.04) for the premenopausal group (78 of 89 of the cases, 93%, were postmenopausal). The observation that risk of hypertension in women increased in association with increasing patella bone lead concentration, but not tibia bone lead or PbB, is consistent with a similar finding in men, derived from the longitudinal Normative Aging Study (Cheng et al. 2001). Associations between PbB and hypertension risk in postmenopausal women also have been found in larger cross-sectional studies (Nash et al. 2003; see below).

As part of the Normative Aging Study, a case-control study examined potential associations between blood pressure and blood and bone lead concentrations in a population of middle-aged males (mean age, 66 years; Hu et al. 1996a). The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67 years) and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitis. Physical examinations, including seated blood pressure and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone x-ray fluorescence (XRF) measurements (mid-tibia and patella) were included in the examinations. Cases (n=146) and age-matched controls (n=444) were a subset of the study group who resided in the Boston area of the United States (recruited during the period 1993–1995) who were observed between 1991 and 1994. Hypertension cases were taking daily medication for the management of hypertension and/or had a systolic blood pressure >160 mmHg or diastolic pressure $\geq$ 96 mmHg. The mean PbBs in cases and controls were 6.9 $\mu\text{g/dL}$ (4.3, SD) and 6.1 $\mu\text{g/dL}$ (4.0, SD), respectively. Mean bone lead concentrations in cases and controls were: tibia, 23.7 $\mu\text{g/g}$ (14.0, SD) and 20.9 $\mu\text{g/g}$ (11.4, SD), respectively; and patella, 35.1 $\mu\text{g/g}$ (19.5, SD) and 31.1 $\mu\text{g/g}$ (18.3, SD), respectively. Risk of hypertension (OR) was assessed using a logistic regression model. Covariate-adjusted risk of hypertension was significantly associated with increasing tibia lead concentration, but not with patella bone concentration or PbB. An increase in tibia bone lead concentration from the mid-point of the lowest quintile (8 $\mu\text{g/g}$) to the mid-point of the highest quintile (37 $\mu\text{g/g}$) was associated with an OR of 1.5 (95% CI, 1.1–1.8). Covariates in the final regression model included body mass index and family history of hypertension. A longitudinal analysis of the Normative Aging Study also found significant associations between bone lead concentration and risk of hypertension (see discussion of Cheng et al. 2001).

A case-control study examined the association between PbB and hypertension risk in middle-aged and menopausal women (Al-Saleh et al. 2005). Hypertension cases (n=100; age, 47–92 years) and controls (n=85; age, 45–82 years) were selected from the King Faisal Hospital Hypertension Clinic (Saudi Arabia)

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during the period 2001–2002. Hypertension case inclusion criteria were: taking medication, or >160 mm Hg systolic pressure, or >95 mm Hg diastolic pressure. Control inclusion criteria were: average systolic/diastolic pressure <120/80 mm Hg, and no record of >130/85 mm Hg). Mean PbB of the case group was 4.8 µg/dL (range, 1.4–28) and of the control group was 4.6 µg/dL (range, 1.2–18). Covariate adjusted ORs in association with a median PbB ≥ 3.86 µg/dL was 5.27 (95% CI, 0.93–30; $p=0.06$).

Cross-sectional Studies—General Population. Several analyses of possible associations between blood pressure and PbB have been conducted with data collected in the NHANES (II and III). The NHANES III collected data on blood pressure and PbB on approximately 20,000 U.S. residents during the period 1988–1994. The results of two analyses of the NHANES III data on adult subjects provides evidence for an association between increasing PbB and increasing blood pressure that is more pronounced in blacks than whites (Den Hond et al. 2002; Vupputuri et al. 2003). Den Hond et al. (2002) analyzed data collected on 13,781 subjects of age 20 years or older who were white (4,685 males; 5,138 females) or black (1,761 males; 2,197 females). Median PbBs (µg/dL, inter-quartile range) were: white males, 3.6 (2.3–5.3); white females, 2.1 (1.3–3.4); black males, 4.2 (2.7–6.5); and black females, 2.3 (1.4–3.9). Based on multivariate linear regression (with log-transformed blood lead concentration), the predicted covariate-adjusted increments in systolic blood pressure per doubling of PbB (95% CI) were: white males, 0.3 (95% CI, -0.2–0.7, $p=0.29$); white females, 0.1 (95% CI, -0.4–0.5, $p=0.80$); black males, 0.9 (95% CI, 0.04–1.8, $p=0.04$); and black females, 1.2 (95% CI, 0.4–2.0, $p=0.004$). The predicted covariate-adjusted increments in diastolic blood pressure per doubling of PbB (95% CI) were: white males, -0.6 (95% CI, -0.9– -0.3, $p=0.0003$); white females, -0.2 (95% CI, -0.5– -0.1, $p=0.13$); black males, 0.3 (95% CI, -0.3–1.0, $p=0.28$); and black females, 0.5 (95% CI, 0.01–1.1, $p=0.047$). Covariates included in the regression models were: age and body mass index; hematocrit, total serum calcium, and protein concentrations; tobacco smoking; alcohol and coffee consumption; dietary calcium, potassium, and sodium intakes; diabetes; and use of antihypertensive drugs. Poverty index was not included as a covariate in the above predictions because its independent effect was not significant; however, when included in the regression model for black males, the effect size was not significant.

Vupputuri et al. (2003) analyzed the NHANES III subset of 14,952 subjects of age 18 years or older who were white (5,360 males; 5,188 females) or black (2,104 males; 2,197 females). Mean PbBs (µg/dL, $\pm$ SE) were: white males, 4.4 ± 0.1 ; white females, 3.0 ± 0.1 ; black males, 5.4 ± 0.2 ; and black females, 3.4 ± 0.1 . Based on multivariate linear regression, the predicted covariate-adjusted increments in systolic blood pressure per one standard deviation increase of PbB (95% CI) were: white males, 0.29 (95% CI, -0.24–0.83, $p \geq 0.05$); white females, 0.34 (95% CI, -0.49–1.17, $p \geq 0.05$); black males, 0.83 (95% CI, 0.19–

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1.44, $p < 0.05$); and black females, 1.55 (95% CI, 0.47–2.64, $p < 0.010$). The predicted covariate-adjusted increments in diastolic blood pressure per one standard deviation increase in PbB (95% CI) were: white males, 0.01 (95% CI, -0.38–0.40, $p \geq 0.05$); white females, -0.04 (95% CI, -0.56–0.47, $p \geq 0.05$); black males, 0.64 (95% CI, -0.08–1.20, $p < 0.05$); and black females, 1.07 (95% CI, 0.37–1.77, $p < 0.01$).

Covariates included in the regression models were: age and body mass index; alcohol consumption; dietary calorie, potassium, and sodium intakes; and physical activity. The analyses of Den Hond et al. (2002) and Vupputuri et al. (2003) suggest an association between blood pressure and PbB in blacks but not in whites; among blacks, the association was significant for women and or borderline significance for men.

A more recent analysis of the NHANES III data focused on females between the ages of 40 and 59 years (Nash et al. 2003). The study group ($n=2,165$) had a mean age of 48.2 years and mean PbB of 2.9 $\mu\text{g/dL}$ (range, 0.50–31.1). Based on multivariate linear regression, covariate-adjusted systolic and diastolic blood pressure was significantly associated with increasing PbB. Increasing PbB from the lowest (0.5–1.6 $\mu\text{g/dL}$) to highest (4.0–31.1 $\mu\text{g/dL}$) quartile was associated with a 1.7 mmHg increase in systolic pressure and a 1.4 mmHg increase in diastolic pressure. The study group was stratified by blood lead concentration (quartile), and into pre- and postmenopausal categories. Increased risk of diastolic (but not systolic) hypertension (systolic ≥ 140 mmHg diastolic ≥ 90 mmHg) was significantly associated with increased blood lead concentration. When stratified by menopausal status, the effect was more pronounced in the postmenopausal group. Covariates included in the models were race, age, and body mass index; tobacco smoking, and alcohol consumption. The Nursing Health Study (Korrick et al. 1999) found significant associations between hypertension risk and patella lead concentration in postmenopausal women, but not with PbB. However, the Nash et al. (2003) study included 850 postmenopausal subjects, compared to 78 in the Korrick et al. (1999) case-control study.

The NHANES II collected data on PbB and blood pressure during the period 1976–1980. In general, PbBs were higher in the NHANES II sample than in NHANES III sample (Pirkle et al. 1998), providing a means to explore possible associations between blood pressure and higher PbB than is possible with the NHANES III data. While various analyses have yielded somewhat conflicting results (Gartside 1988; Harlan 1988; Harlan et al. 1985; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988), they support the general findings of the more recent longitudinal and case-control studies (including those of the NHANES III) that increasing PbB is associated with increasing blood pressure in middle-aged adults.

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An analysis of the NHANES II data on white males (40–59 years of age, $n=564$) found a significant association between increasing systolic or diastolic blood pressure and increasing PbB, after accounting for significant covariates (Pirkle et al. 1985). Covariates considered in the analysis included 87 nutritional and diet variables, cigarette smoking, alcohol consumption, socioeconomic status, and family history of hypertension. Those included in the final linear regression model for diastolic blood pressure were age and body mass index; blood hemoglobin concentration and serum albumin concentration; and dietary potassium and vitamin C intakes. Additional covariates included in the systolic blood pressure model were dietary riboflavin, oleic acid, and vitamin C. Blood lead statistics for the study group were not reported; however, the association appeared to have been evaluated over a range of 7–38 $\mu\text{g/dL}$. Lead was also a significant predictor of diastolic hypertension (≥ 90 mm Hg). Gartside (1988) stratified the NHANES II data into age and race categories and also found significant associations between systolic (but not diastolic) blood pressure and PbB in white males in age categories between 36 and 55 years. In these age categories, doubling PbB was associated with an increase in systolic blood pressure of approximately 4 mmHg. The statistical model used was a forward linear regression; however, the covariates retained in the final models were not reported. Other analyses of the NHANES II data for men have addressed the issue of possible time-trend effects confounded by variations in sampling sites (Landis and Flegal 1988; Schwartz 1988). These analyses confirm that correlations between systolic or diastolic blood pressure and PbB in middle-aged white males remain significant when sampling site is included as a variable in multiple regression analyses. Accuracy of blood pressure data in the NHANES II has been challenged (e.g., digit preference by people recording the measurements, differing variability among survey sites). When these sources of variability are accounted for, the magnitude of the covariate-adjusted PbB—blood pressure relationship decreases; however, it remains significant, and strongest, for white males in the 49–50-year-old group (Coate and Fowles 1989).

Relationships between PbB and hypertension were evaluated in a survey of 7,731 males, aged 40–59 years, from 24 British towns in the British Regional Heart Study (BHRS) (Pocock et al. 1984, 1988). The PbB distributions in the study group were approximately: <12.4 $\mu\text{g/dL}$, 27%; 12.4–16.6 $\mu\text{g/dL}$, 45%; 18.6–22.8 $\mu\text{g/dL}$, 19%; and >24.9 $\mu\text{g/dL}$, 8%. The most recent, multivariate analysis of the data from this survey (Pocock et al. 1988), found that covariate-adjusted systolic blood pressure increased by 1.45 mmHg and diastolic blood pressure increased by 1.25 mmHg for every doubling in PbB. Covariates included in the regression model included age, body mass index, alcohol consumption, cigarette smoking, and socioeconomic factors. Covariate-adjusted risk of ischemic heart disease (OR) was not significantly associated with PbB. PbBs in cases ($n=316$) of ischemic heart disease were not statistically different,

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when compared to those of the rest of the study group, after adjustment was made for age, number of years smoking cigarettes, and town of residence.

A more recent survey conducted in Great Britain (Health Survey for England, HSE) collected data annually on blood pressure and PbB. An analysis of the HSE data collected in 1995 included 2,563 males (mean age, 47.5 years) and 2,394 females (mean age, 47.7) (Bost et al. 1999). Multiple seated blood pressure measurements were taken. Mean (geometric) PbBs were 3.7 µg/dL in males and 2.6 µg/dL in females. Based on multivariate linear regression (with log-transformed PbB), increasing covariate-adjusted diastolic blood pressure was significantly associated with increasing PbB in males, but not in females. Covariates included in the above model were: age and body mass index, alcohol consumption and tobacco smoking, socioeconomic status, and region of residence; subjects who were on antihypertensive agents were excluded.

A cross-sectional study of potential associations between blood and bone lead, and blood pressure in older adults was conducted as part of the longitudinal Baltimore Memory Study (Martin et al. 2006). The study group consisted of 964 adults (age, 50–70 years, 65% female) who were evaluated for blood pressure and PbB during the period 2001–2002, and tibia lead during the period 2002–2004. Mean PbB concentration in the study group was 3.5 µg/dL (SD±2.3) and tibia lead was 18.8 µg/g (SD±12.4). Increasing PbB (but not tibia lead) was significantly associated (linear regression model) with increasing covariate-adjusted systolic (β , 0.99 mm Hg per µg/dL; 95% CI, 0.47–1.51; $p<0.01$) and diastolic blood pressure (β , 0.51; 95% CI, 0.24–0.79; $p<0.01$). Covariates included in the model included age, gender, body mass index, sodium and potassium intakes, SES, and race/ethnicity). Covariate-adjusted ORs for hypertension (>140 mm Hg systolic pressure or >90 mmHg diastolic pressure) were significantly associated with tibia lead (but not PbB) only when the multivariate logistic model excluded SES (OR, 1.21; 95% CI, 1.02–1.43; $p=0.03$) or SES and race/ethnicity (OR, 1.24; 95% CI, 1.05–1.47; $p=0.01$) from the model. When SES and race/ethnicity were included in the model, the odds ratios were not significant for tibia lead (OR, 1.16; 95% CI, 0.98–1.77; $p=0.09$) or PbB (OR, 1.01; 95% CI, 0.86–1.19).

The potential effects of childhood exposure to lead on bone lead—blood pressure relationships in adulthood have been examined in a cohort study (Gerr et al. 2002). The exposed cohort consisted of 251 people (ages 19–24 years in 1994), who resided in any of five towns near the former Bunker Hill smelter in Silver Valley, Idaho and were between the ages of 9 months and 9 years during the period 1974–1975, when uncontrolled emissions from the smelter resulted in contamination of the region and elevated PbB in local children. The reference cohort consisted of 257 Spokane, Washington residents in

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the same age range as the exposed cohort. Individuals were excluded from participating in the study if they were black, pregnant, had a history of hypertension or chronic renal failure, or had a PbB exceeding 15 µg/dL at the initial examination. Subjects were given a physical examination, which included medical history, multiple measurements of sitting blood pressure, PbB measurement, and XRF measurement of tibia bone lead concentration. Relationships between blood pressure and bone lead were assessed using the general linear model, in which bone lead was expressed categorically (µg/g): <1, 1–5, >5–10, and >10. Covariate-adjusted systolic and diastolic blood pressures were significantly higher in the highest bone lead category compared to the lowest category; the differences being 4.26 mmHg ($p=0.014$) systolic pressure and 2.80 mmHg ($p=0.03$) diastolic pressure. Covariates retained in the final models included gender, age and body mass index; blood hemoglobin and serum albumin concentrations; education; tobacco smoking and alcohol consumption; current use of birth control pills; income; and current PbB. While residence (exposed vs. reference) was not a significant variable in predicting blood pressure, 82% of subjects in the highest bone lead group were members of the exposed group (i.e., residents of the contaminated towns in 1974–1975). Mean PbB during the exposure period, 1974–1975, was also higher in the high bone lead group (65 µg/dL) compared to the lower bone lead groups (2–2.4 µg/dL). Similar findings were reported by Hu et al. (1991a) in a pilot study of subjects with well-documented lead poisoning in 1930–1942 in a Boston area. Exposed subjects (mean current age, 55 years; mean current PbB, 6 µg/dL) and controls were matched for age, race, and neighborhood. Comparison of 21 matched pairs showed that the risk of hypertension was significantly higher in subjects who had experienced plumbism (RR, 7.0; 95% CI, 1.2–42.3). Kidney function, evaluated by measurements of creatinine clearance rate was significantly higher in subjects with plumbism than in controls, but serum creatinine was not significantly different than in controls subjects. The results from these two studies (Gerr et al. 2002; Hu 1991a) suggest the possibility that high childhood exposures to lead may contribute to higher blood pressure in adulthood. However, epidemiological studies of children have not found significant associations between increasing PbB and blood pressure (Factor-Litvak et al. 1996; Friedlander 1981; Rogan et al. 1978; Selbst et al. 1993).

Studies in Animal Models. Early studies in experimental animals suggested that long-term lead exposure could elevate blood pressure in nutritionally replete rats (Carmignani et al. 1988; Iannaccone et al. 1981; Khalil-Manesh et al. 1993; Victory et al. 1982a, 1982b). These observations have been corroborated with more recent studies, as well as studies that have identified numerous potential mechanisms for the effect that are relevant to humans (Carmignani et al. 2000; Ding et al. 1998; Gonick et al. 1997; Purdy et al. 1997; Vaziri and Ding 2001; Vaziri et al. 1999a, 1999b, 2001).

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Other Cardiovascular Effects. Several studies have explored possible associations between lead exposure and cardiovascular disease mortality and morbidity. In a multivariate analysis of the data from the British Regional Heart Study (7,731 males, age 40–59 years; 8% of cohort had PbB >24.9 µg/dL), covariate-adjusted risk of ischemic heart disease (OR) was not significantly associated with PbB (Pocock et al. 1988). Cooper (1988) reported significantly elevated SMRs for “other hypertensive disease” (i.e., malignant hypertension, or essential benign hypertension, or hypertensive renal disease) among male battery plant workers (n= 4,519; mean PbB, 63 µg/dL) and lead production workers (n=2,300; mean PbB, 80 µg/dL). The study did not explore associations between SMRs and biomarkers of lead exposure (e.g., PbB). SMRs for cardiovascular disease were not elevated among 1,987 male lead smelter workers who worked at the Bunker Hill smelter facility in northern Idaho (i.e., who were hired between 1950 and 1965 and who worked at least 1 year) (Selevan et al. 1985, 1988). The study did not explore associations between SMRs and biomarkers of lead exposure (e.g., PbB). SMRs for ischemic heart disease were significantly elevated (SMR, 1.72; 95% CI, 1.16–1.79) among male smelter workers (n=644) who worked for at least 3 months during the period 1942–1987; however, the SMRs were across time-integrated PbB quartiles (Gerhardsson et al. 1995a).

Data from a subset of the Normative Aging Study were analyzed to assess possible associations between electrocardiographic abnormalities and body lead burdens (Cheng et al. 1998). The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States. Subjects enrolled in the study, between 1963 and 1968, ranged in age from 21 to 80 years (mean, 67; SD, 7), and had no history of heart disease or hypertension. Physical examinations, including electrocardiograms and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone XRF measurements (midtibia and patella) were included in the examinations. Data collected for a subset of the study population (775 subjects) observed between 1991 and 1995 and for whom complete data were acquired, were analyzed for associations between blood and bone lead concentrations and electrocardiographic abnormalities (e.g., heart rate, conduction defects, arrhythmia). The mean age of the subjects at the time of evaluation was 68 years (range, 48–93). Lead levels were: blood, 5.79 µg/dL (SD, 3.44); tibia bone, 22.19 µg/g (SD, 13.36); and patella bone, 30.82 µg/g (SD, 19.19). The study group was stratified by age (<65 or ≥65 years) for multivariate regression (linear and logistic) analyses. Covariate-adjusted QT and QRS intervals were significantly associated with tibia bone lead in subjects <65 years of age. A 10 µg/g increase in tibia lead concentration was associated with a 5.01 millisecond increase in the QT interval and 4.83 millisecond increase in QRS interval. Covariates included in the analyses were age, body mass index, diastolic blood pressure, fasting blood glucose level, and alcohol consumption. Covariate-adjusted OR for

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intraventricular conduction defect was significantly associated with increasing tibia bone lead in the <65 year-age group; ORs were not significant for the older age group. In the age group ≥ 65 years, the OR for atrioventricular conduction defect with increasing tibia bone lead concentration was 1.22 (95% CI, 1.02–1.47; $p=0.03$), and for patella bone lead concentration, 1.16 (95% CI, 1.00–1.29; $p<0.01$); ORs were not significant for the younger age group. Covariates included in the models were age and serum HDL concentration. Risk of arrhythmia was not significantly associated with blood or bone lead concentrations.

A study of 95 lead smelter workers and matched (age, occupational status, duration of employment) unexposed reference group found a significantly higher incidence of ischemic ECG changes (20%) in the lead workers than in the reference group (6%) (Kirkby and Gyntelberg 1985). Mean PbB was 53 $\mu\text{g/dL}$ in the exposed group and 11 $\mu\text{g/dL}$ in the reference group.

A cross-sectional analysis of the NHANES (for the period 1999–2000) data found a significant association between PbB and risk of peripheral artery disease (Navas-Acien et al. 2004). The analysis included 2,125 subjects (1,055 females, 1,070 males) whose ages were ≥ 40 years. Geometric mean PbB was 2.1 $\mu\text{g/dL}$ (25th–75th percentile range, 1.5–2.9). The increasing PbB was significantly associated with increasing covariate-adjusted OR for peripheral artery disease (ankle brachial index <0.9 in one or both legs). For the upper quartile PbB (>2.9 $\mu\text{g/dL}$), the ORs were 4.07 (95% CI, 1.21–13.73), without adjustment for smoking status and 2.52 (95% CI, 0.75–8.51) with adjustment for smoking. Other covariates included in the analysis were age, gender, race, education, body mass index, alcohol consumption, hypertension, diabetes, hypercholesterolemia, glomerular filtration, and C-reactive protein.

As part of the Baltimore-Washington Infant Study, a case-control study examined possible associations between lead exposure and risk of total anomalous pulmonary venous return (TAPVR), a rare congenital malformation in which pulmonary veins deliver oxygenated blood to the right atria rather than the left atria (Jackson et al. 2004). Cases ($n=54$) were recruited during the period 1981–1989. Controls ($n=522$) consisted of a stratified random sample of live-born infants without birth defects (excluding twins, low birth weight infants, and infants whose race was other than black or white). Subjects were classified as having been exposed to lead (or not) during critical maternal (i.e., from 3 months prior to conception through third trimester) or paternal (i.e., within 6 months prior to conception) periods based on self-reporting of occupational or environmental exposures, reported in an administered questionnaire. Prevalence of maternal lead exposure was 17% among cases and 11% among controls; prevalence of paternal lead exposure was 61% among cases and 46% among controls. The OR for TAPVR in

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association with any maternal lead exposure during the critical maternal period was 1.57 (95% CI, 0.64–3.47; $p=0.27$); the OR for any paternal lead exposure was 1.83 (95% CI, 1.00–3.42, $p=0.045$).

Several small-scale studies have reported changes in peripheral hemodynamics in association with occupational exposures to lead. Effects observed in these studies may represent effects of lead on either the cardiovascular and/or autonomic nervous systems. A study conducted in Japan compared the results of finger plethysmographic assessments in 48 male workers in a lead refinery and 43 male controls who had no occupational lead exposure (Aiba et al. 1999). Ages of the exposed and reference groups were similar (mean $\pm$ SD; 46 $\pm$ 15 and 49 $\pm$ 11 years, respectively). Mean PbB in the exposed group was 43.2 μ g/dL (25.2, SD), PbBs for the control group were not measured. Covariate-adjusted acceleration plethysmography parameters were significantly different in the exposure group compared to the reference group and were significantly associated with PbB. The prevalence of abnormal parameter values (<25th percentile value) was significantly higher in the exposure group and prevalence increased with increasing duration of employment or increasing PbB. A study of ceramic painters in Japan evaluated postural changes in finger blood flow in relation to PbB (Ishida et al. 1996). Subjects of the study were 50 males (age, 55 $\pm$ 12 years) and 78 females (age, 52 $\pm$ 8 years) who were not currently receiving pharmacological treatment. Finger blood flow parameters evaluated were the percent change in finger blood flow in response to standing from a supine position, and the rate of decrease in blood flow in response to standing. The mean (geometric) PbB was 16.5 μ g/dL (2.1, SD; range, 3.5–69.5 μ g/dL) in males and 11.1 μ g/dL (1.7, SD; range, 2.1–31.5 μ g/dL) in females. Both percent change in blood flow and rate of decrease in blood flow significantly decreased with increasing PbB in both males and females. Covariate-adjusted postural change in finger blood flow was significantly associated with PbB. Covariates included in the regression model were age, body mass index total blood cholesterol concentration, skin temperature, alcohol consumption and tobacco smoking.

Gastrointestinal Effects. Colic is a consistent early symptom of lead poisoning in occupationally exposed cases or in individuals acutely exposed to high levels of lead, such as occurs during the removal of lead-based paint. Colic is characterized by a combination of the following symptoms: abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss. Although gastrointestinal symptoms typically occur at PbBs of 100–200 μ g/dL, they have sometimes been noted in workers whose PbBs were between 40 and 60 μ g/dL (Awad El Karim et al. 1986; Baker et al. 1979; Haenninen et al. 1979; Holness and Nethercott 1988; Kumar et al. 1987; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Pollock and Ibels 1986; Rosenman et al. 2003; Schneitzer et al. 1990).

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Colic is also a symptom of lead poisoning in children. EPA (1986a) has identified a LOAEL of approximately 60–100 µg/dL for children. This value apparently is based on a National Academy of Sciences (NAS 1972) compilation of unpublished data from the patient groups originally discussed in Chisolm (1962, 1965) and Chisolm and Harrison (1956) in which other signs of acute lead poisoning, such as severe constipation, anorexia, and intermittent vomiting, occurred at ≥ 60 µg/dL.

Hematological Effects. Lead has long been known to alter the hematological system. The anemia induced by lead is microcytic and hypochromic and results primarily from both inhibition of heme synthesis and shortening of the erythrocyte lifespan. Lead interferes with heme synthesis by altering the activities of δ -aminolevulinic acid dehydratase (ALAD) and ferrochelatase. As a consequence of these changes, heme biosynthesis is decreased and the activity of the rate-limiting enzyme of the pathway, δ -aminolevulinic synthetase (ALAS), which is feedback inhibited by heme, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and δ -aminolevulinic acid (ALA); increased blood and plasma ALA; and increased erythrocyte protoporphyrin (EP).

Studies of lead workers have shown that ALAD activity correlated inversely with PbB (Alessio et al. 1976; Gurer-Orhan et al. 2004; Hernberg et al. 1970; Meredith et al. 1978; Schuhmacher et al. 1997; Tola et al. 1973; Wada et al. 1973), as has been seen in subjects with no occupational exposure (Secchi et al. 1974). Erythrocyte ALAD and hepatic ALAD activities were correlated directly with each other and correlated inversely with PbBs in the range of 12–56 µg/dL (Secchi et al. 1974).

General population studies indicate that the activity of ALAD is inhibited at very low PbB, with no threshold yet apparent. ALAD activity was inversely correlated with PbB over the entire range of 3–34 µg/dL in urban subjects never exposed occupationally (Hernberg and Nikkanen 1970). Other reports have confirmed the correlation and apparent lack of threshold in different age groups and exposure categories (children—Chisolm et al. 1985; Roels and Lauwerys 1987; adults—Roels et al. 1976). Studies of children in India and China also have reported significant decreases in ALAD activity associated with PbB ≥ 10 µg/dL (Ahamed et al. 2005; Jin et al. 2006). Inverse correlations between PbB and ALAD activity were found in mothers (at delivery) and their newborns (cord blood). PbB ranged from approximately 3 to 30 µg/dL (Lauwerys et al. 1978). In a study in male volunteers exposed to particulate lead in air at 0.003 or 0.01 mg lead/m³ for 23 hours/day for 3–4 months mean PbB increased from 20 µg/dL (pre-exposure) to 27 µg/dL at the 0.003 mg/m³ exposure level and from 20 µg/dL (pre-exposure) to 37 µg/dL at the 0.01 mg/m³ exposure level. ALAD decreased to approximately 80% of

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preexposure values in the 0.003 mg/m³ group after 5 weeks of exposure and to approximately 53% of preexposure values in the 0.01 mg/m³ group after 4 weeks of exposure (Griffin et al. 1975). Similar observations were made in a study of volunteers who ingested lead acetate at 0.02 mg lead/kg/day every day for 21 days (Stuik 1974). The decrease in erythrocyte ALAD could be noticed by day 3 of lead ingestion and reached a maximum by day 14. Mean PbB was approximately 15 µg/dL before exposure and increased to approximately 40 µg/dL during exposure. Cools et al. (1976) reported similar results in a study of 11 volunteers who ingested lead acetate that resulted in a mean PbB of 40 µg/dL; the mean pre-exposure PbB was 17.2 µg/dL.

Inhibition of ALAD and stimulation of ALAS result in increased levels of ALA in blood or plasma and in urine. For example, in a case report of a 53-year-old man with an 11-year exposure to lead from removing old lead-based paint from a bridge, a PbB of 55 µg/dL was associated with elevated urinary ALA (Pollock and Ibels 1986). The results of the Meredith et al. (1978) study on lead workers and controls indicated an exponential relationship between PbB and blood ALA. Numerous studies reported direct correlations between PbB and log urinary ALA in workers. Some of these studies indicated that correlations can be seen at PbB of <40 µg/dL (Lauwerys et al. 1974; Selander and Cramer 1970; Solliway et al. 1996), although the slope may be different (less steep) than at PbBs >40 µg/dL. In a study of 98 occupationally exposed subjects (mean PbB, 51 µg/dL) and 85 matched referents (mean PbB, 20.9 µg/dL), it was found that log ZPP and log ALA in urine correlated well with PbB (Gennart et al. 1992a). In the exposed group, the mean ZPP was 4 times higher than in the comparison group, whereas urinary ALA was increased 2-fold.

Correlations between PbBs and urinary ALA similar to those observed in occupationally exposed adults have also been reported in nonoccupationally exposed adults (Roels and Lauwerys 1987) and children (unpublished data of J.J. Chisolm, Jr., reported by NAS 1972). Linear regression analyses conducted on data obtained from 39 men and 36 women revealed that increases in urinary ALA may occur at PbB >35 µg/dL in women and >45 µg/dL in men (Roels and Lauwerys 1987). A significant linear correlation between PbB and log ALA was obtained for data in children 1–5 years old with PbBs 25–75 µg/dL. The correlation was seen primarily at PbBs >40 µg/dL, but some correlation may persist at <40 µg/dL (NAS 1972).

A dose-related elevation of EP or ZPP in lead workers has been documented extensively (Herber 1980; Matte et al. 1989). Correlations between PbB and log EP or ZPP indicate an apparent threshold for EP elevation in male workers at 25–35 µg/dL (Grandjean and Lintrup 1978; Roels et al. 1975) for FEP and a

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threshold of 30–40 µg/dL for EP (Roels and Lauwerys 1987; Roels et al. 1979). The threshold for EP elevation appears to be somewhat lower (20–30 µg/dL) in women than in men (Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Stuik 1974), regardless of whether exposure is primarily by inhalation (occupational) or oral (nonoccupational). These studies were controlled for possible confounding factors such as iron deficiency or age, both of which increase erythrocyte ZPP.

Many studies have reported the elevation of EP or ZPP as being exponentially correlated with PbBs in children. However, peak ZPP levels lag behind peak levels of PbB. The threshold for this effect in children is approximately 15 µg/dL (Hammond et al. 1985; Piomelli et al. 1982; Rabinowitz et al. 1986; Roels and Lauwerys 1987; Roels et al. 1976), and may be lower in the presence of iron deficiency (Mahaffey and Annest 1986; Marcus and Schwartz 1987). A study of 95 mother-infant pairs from Toronto showed a significant inverse correlation between maternal and umbilical cord lead levels and FEP (Koren et al. 1990). Most (99%) infants had cord PbBs below 7 µg/dL; in 11 cases, the levels were below the detection limit. The cord blood FEP levels were higher than the maternal levels. This may reflect immature heme synthesis and increased erythrocyte volume rather than lead poisoning, or perhaps an early effect of lead poisoning.

The threshold PbB for a decrease in hemoglobin in occupationally exposed adults is estimated by EPA (1986a) to be 50 µg/dL, based on evaluations of the data of Baker et al. (1979), Grandjean (1979), Lilis et al. (1978), Tola et al. (1973), and Wada et al. (1973). For example, 5% of smelter workers with PbBs of 40–59 µg/dL, 14% with levels of 60–79 µg/dL, and 36% with levels of >80 µg/dL had anemia. In a study of 98 workers from a lead acid battery factory with a mean PbB of 51 µg/dL, the mean hemoglobin concentration was not significantly different than in an unexposed group of 85 subjects (mean PbB, 21 µg/dL). However, four exposed workers, but no controls, had hemoglobin levels below the level considered as the limit value for defining anemia (13 µg/dL) (Gennart et al. 1992a). Similar lack of correlation between PbB and hemoglobin was reported in a study of 94 Israeli lead workers with a mean PbB of 38.1 µg/dL (range, 6–113 µg/dL) (Froom et al. 1999). Solliway et al. (1996) also reported no significant differences in hemoglobin concentration between a group of 34 workers from a battery factory (mean PbB 40.7 µg/dL, range 23–66 µg/dL) and a group of 56 nonexposed persons (mean PbB 6.7 µg/dL, range 1–13 µg/dL). However, red blood cell count was significantly lower in exposed workers than in the controls. Lead-induced anemia is often accompanied by basophilic stippling of erythrocytes (Awad El Karim et al. 1986; Pagliuca et al. 1990). In a study of workers with a relatively low mean PbB of 8.3 µg/dL (range, 2–25 µg/dL), it was found that PbB did not correlate with either hemoglobin or hematocrit; however, patellar lead significantly correlated with a decrease in hemoglobin and hematocrit

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even after adjusting a number of confounders (Hu et al. 1994). The PbB threshold for decreased hemoglobin levels in children is judged to be approximately 40 µg/dL (EPA 1986a; WHO 1977), based on the data of Adebonojo (1974), Betts et al. (1973), Pueschel et al. (1972), and Rosen et al. (1974). In a pilot study of subjects who suffered lead poisoning in 1930–1942 in a Boston area, hemoglobin and hematocrit were significantly decreased compared to unexposed matched controls (Hu 1991a). The mean current age of the subjects was 55 years and the mean current PbB was 6 µg/dL. No difference was noticed in red blood cell size or shape between exposed and control subjects. Hu et al. (1991a) suggested that the effect observed may have represented a subclinical effect of accumulated bone lead stores on hematopoiesis.

Other studies have shown that adverse effects on hematocrit may occur at even lower PbBs in children (Schwartz et al. 1990). Anemia was defined as a hematocrit of <35% and was not observed at PbB below 20 µg/dL. Analyses revealed that there is a strong negative nonlinear dose-response relationship between PbBs and hematocrit. Between 20 and 100 µg/dL, the decrease in hematocrit was greater than proportional to the increase in PbB. The effect was strongest in the youngest children. The analysis also revealed that at PbBs of 25 µg/dL, there is a dose-related depression of hematocrit in young children. Similar results also have been reported by others (Kutbi et al. 1989).

Lead also inhibits the enzyme pyrimidine-5'-nucleotidase within the erythrocyte, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte and subsequent destruction of these cells. This has been reported in lead workers, with the greatest inhibition and marked accumulations of pyrimidine nucleotides apparent in workers with overt intoxication, including anemia (Paglia et al. 1975, 1977). PbBs in these workers ranged between 45 and 110 µg/dL, and 7 of 9 were anemic. Pyrimidine-5'-nucleotidase activity was correlated inversely with PbB when corrected for an enhanced population of young cells due to hemolytic anemia in some of the workers (Buc and Kaplan 1978). Erythrocyte pyrimidine-5'-nucleotidase is inhibited in children at very low PbBs. A significant negative linear correlation between pyrimidine-5'-nucleotidase and PbB level was seen in 21 children with PbBs ranging from 7 to 80 µg/dL (Angle and McIntire 1978). Similar results were seen in another study with 42 children whose PbB ranged from <10 to 72 µg/dL (Angle et al. 1982). Additional findings included a direct correlation between cytidine phosphate levels and PbBs (log-log). There was no indication of a threshold for these effects of lead in these two studies.

In summary, of all the parameters examined, ALAD activity appears to be the most sensitive indicator of lead exposure. In studies of the general population, ALAD activity was inversely correlated with PbBs

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over the entire range of 3–34 µg/dL. In contrast, the threshold PbB for increase in urinary ALA in adults is approximately 40 µg/dL; for increases in blood EP or ZPP, the threshold in adults is around 30 µg/dL, and the threshold for increased ZPP in children is about 15 µg/dL in children. Threshold PbBs for decreased hemoglobin levels in adults and children have been estimated at 50 and 40 µg/dL, respectively. Although the measurement of ALAD activity seems to be a very sensitive hematological marker of lead exposure, the inhibition of the enzyme is so extensive at PbBs ≥ 30 µg/dL that the assay cannot distinguish between moderate and severe exposure.

Studies in animals, in general, support the findings in humans and indicate that the effects depend on the chemical form of lead, duration of exposure, and animal species. Of particular interest are the results of a study in a cohort of 52 monkeys administered lead acetate orally for up to 14 years (Rice 1996b). PbB was dose-related and ranged between 10 and 90 µg/dL. Decreased hematocrit and hemoglobin was observed in monkeys at 7 (PbB 25 µg/dL) and 11 years (PbB 90 µg/dL) of age; hemoglobin also was decreased at 6 years of age when PbB was 23 µg/dL. All changes that occurred were within normal ranges, which led Rice (1996b) to conclude that under the conditions of the study, there were no lead-related hematological effects.

Musculoskeletal Effects. Several case reports of individuals who experienced high exposures to lead either occupationally or through the consumption of illicit lead contaminated whiskey described the occurrence of a bluish-tinged line in the gums (Eskew et al. 1961; Pagliuca et al. 1990). The etiology of this "lead line" has not been elucidated. This effect has also been observed in workers exposed to high lead levels who had exposures via dust or fume. Individuals having high exposures to lead have also been reported to complain of muscle weakness, cramps, and joint pain (Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990). Rosenman et al. (2003) described musculoskeletal effects (frequent pain/soreness and/or muscle weakness) in lead workers with PbB ≥ 40 µg/dL.

A study of the association between lead exposure and bone density in children was recently published (Campbell et al. 2004). The cohort consisted of 35 African American children 8–10 years of age from Monroe County, New York State. The cohort was divided into two groups, one (n=16) with mean cumulative PbB of 6.5 µg/dL (low-exposure group) and the other (n=19) with mean cumulative PbB of 23.6 µg/dL (high-exposure group). The groups were similar by sex, age, body mass index, socio-economic status, physical activity, or calcium intake. Contrary to what was expected, subjects with high cumulative exposure had a higher bone mineral density than subjects with low-lead cumulative exposure. Among 17 bony sites examined, four were significantly different ($p < 0.05$). Campbell et al. (2004)

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speculated that lead accelerates skeletal maturation by inhibiting proteins that decrease the rate of maturation of chondrocytes in endochondral bone formation. A lower peak bone mineral density achieved in young adulthood might predispose to osteoporosis in later life.

A limited number of studies have explored the effects of oral lead exposure on bone growth and metabolism in animals (Escribano et al. 1997; Gonzalez-Riola et al. 1997; Gruber et al. 1997; Hamilton and O'Flaherty 1994, 1995; Ronis et al. 2001). These data, all from intermediate-duration studies in rats, indicate that oral lead exposure may impair normal bone growth and remodeling as indicated by decreased bone density and bone calcium content, decreased trabecular bone volume, increased bone resorption activity, and altered growth plate morphology. In general, rats appear to be less sensitive than humans to lead effects in bone. A recent study in mice reported that lead delays fracture healing at environmentally relevant doses and induces fibrous nonunions at higher doses by the progression of endochondral ossification (Carmouche et al. 2005). In studies in cultured osteoblast-like cells, lead disrupted the modulation of intracellular calcium by 1,25-dihydroxyvitamin D in a biphasic manner (Long and Rosen 1994). Another effect seen in this culture system was the inhibition by lead of 1,25-dihydroxyvitamin D₃-stimulated synthesis of osteocalcin, a protein constituent of bone that may play a major role in normal mineralization of bone. Reduced plasma levels of osteocalcin have been reported in "moderately lead-poisoned" children (Pounds et al. 1991). Lead also inhibited secretion of osteonectin/SPARC, a component of bone matrix, and decreased the levels of osteonectin/SPARC mRNA from osteoblast-like cells in culture (Sauk et al. 1992). Lead inclusion bodies are commonly found in the cytoplasm and nuclei of osteoclasts, but not other bone cells, following *in vivo* lead exposure (Pounds et al. 1991).

The studies that have examined relationships between lead exposure, as reflected by PbB, and the occurrence of dental caries in children have, for the most part, found a positive association (Campbell et al. 2000a; Gemmel et al. 2002; Moss et al. 1999). Moss et al. (1999) conducted a cross-sectional analysis of measurements of PbB and dental caries in 24,901 people, including 6,541 children 2–11 years of age, recorded in the NHANES III (1988–1994). Mean (geometric) PbBs were 2.9 µg/dL in children 2–5 years of age and 2.1 µg/dL in children 6–11 years of age. Increasing PbB was significantly associated with increased number of dental caries in both age groups, after adjustment for covariates. An increase in PbB of 5 µg/dL was associated with an adjusted OR of 1.8 (95% CI, 1.3–2.5) for the age group 5–17 years. Covariates included in the models were age, gender, race/ethnicity, poverty income ratio, exposure to cigarette smoke, geographic region, educational level of head of household, carbohydrate and calcium intakes, and dental visits. A retrospective cohort study conducted in Rochester, New York compared the

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risk of dental caries among 154 children 7–12 years of age associated with PbB less than or exceeding 10 µg/dL, measured at ages 18 and 37 months of age (Campbell et al. 2000a). The OR (adjusted for age at examination, grade in school, and number of dental surfaces at risk) for caries on permanent teeth associated with a PbB exceeding 10 µg/dL was 0.95 (95% CI, 0.43–2.09; $p=0.89$) and for deciduous teeth, 1.77 (95% CI, 0.97–3.24; $p=0.07$). Other covariates examined in the models, all of which had no significant effect on the outcome, were gender, race/ethnicity, SES, parental education and residence in community supplied with fluoridated drinking water, and various dental hygiene variables. Gemmel et al. (2002) conducted a cross-sectional study of associations between PbB and dental caries in 543 children, 6–10 years of age, who resided either in an urban ($n=290$) or rural ($n=253$) setting. Increasing PbB was significantly associated with the number of caries in the urban cohort, but not in the rural cohort. The mean PbBs were 2.9 µg/dL (SD, 2.0) in the urban group and 1.7 µg/dL (SD, 1.0) in the rural group. Covariates examined in the models were gender, race/ethnicity, SES, maternal smoking, parental education, and various dental hygiene variables.

Dye et al. (2002) conducted a cross-sectional analysis of measurements of blood lead concentration and indices of periodontal bone loss in 10,033 people, 20–69 years of age, recorded in the NHANES III (1988–1994). Mean (geometric) PbB was 2.5 µg/dL (SE, 0.08). Increasing blood lead concentration was significantly associated with periodontal bone loss, after adjustment for covariates. Covariates examined in the analysis included age, gender, race/ethnicity, education, SES, age of home, smoking, and dental furcation (an indicator of severe periodontal disease) as well as an interaction term for smoking and dental furcation.

Studies in animals also have examined the effect of lead exposure on teeth. For example, young rats whose mothers were exposed to lead since young adults, during pregnancy, and lactation had a significantly higher mean caries score than a control group (Watson et al. 1997). The mean PbB achieved in the dams was 48 µg/dL and in the breast milk 500 µg/dL; PbB in the offspring was not determined. Lead also has been reported to delay mineralization in teeth, resulting in less hard enamel (Gerlach et al. 2002) and eruption rate in hypofunctional teeth (Gerlach et al. 2000).

Hepatic Effects. In children, exposure to lead has been shown to inhibit formation of the heme-containing protein cytochrome P-450, as reflected in decreased activity of hepatic mixed-function oxygenases. Two children with clinical manifestations of acute lead poisoning did not metabolize the test drug antipyrine as rapidly as did controls (Alvares et al. 1975). Another study found a significant reduction in 6β-hydroxylation of cortisol in children who had positive urinary excretion of lead

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(≥ 500 $\mu\text{g}/24$ hours) upon ethylenediamine tetraacetic acid (EDTA) provocative tests compared with an age-matched control group (Saenger et al. 1984). These biochemical transformations are mediated by hepatic mixed-function oxygenases.

The association between lead exposure and serum lipid profile was examined in a study of Israeli workers (Kristal-Boneh et al. 1999). The mean PbB of the 87 workers was 42.3 $\mu\text{g}/\text{dL}$ and that of 56 control subjects was 2.7 $\mu\text{g}/\text{dL}$. After adjusting for confounders including nutritional variables, the authors found statistically higher values for total cholesterol (212 vs. 200 mg/dL) and HDL cholesterol (47 vs. 42 mg/dL) in the workers compared to controls; no significant differences were seen for LDL cholesterol and triglycerides. These findings are of dubious biological significance, particularly since the HDL/total cholesterol ratio was the same in the two groups. A study in rats administered lead acetate for 7 weeks that resulted in PbBs of 17 and 32 $\mu\text{g}/\text{dL}$ reported a dose-related increase in triglycerides and decrease in HDL cholesterol (Skoczynska et al. 1993). The authors speculated that the increase in serum triglycerides could have been caused by lead-induced inhibition of lipoprotein lipase activity or decreased activity of hepatic lipase; no possible explanation was offered for the decrease in HDL cholesterol.

A study of workers in the United Arab Emirates reported that a group of 100 workers with a mean PbB of 78 $\mu\text{g}/\text{dL}$ had significantly higher concentrations of amino acids in serum than 100 controls whose mean PbB was 20 $\mu\text{g}/\text{dL}$ (Al-Neamy et al. 2001). Tests for liver function that included serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities found small ($\leq 10\%$) but statistically significant increases in alkaline phosphatase and lactate dehydrogenase activities in the serum of the workers. A study in rats treated with lead acetate for 4 months found decreased AST and ALT activities in hepatic homogenates, but activities in serum were not monitored (Singh et al. 1994).

Collectively, the information regarding effects of lead on the liver in humans and animals is scarce and does not allow for generalizations.

Renal Effects. Lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis and interstitial fibrosis (Diamond 2005; Goyer 1989; Loghman-Adham 1997). Functional deficits in humans that have been associated with excessive lead exposure include enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate. A few studies have revealed histopathological features of renal injury in humans, including intranuclear inclusion bodies and cellular necrosis in the proximal tubule and interstitial fibrosis (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979).

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A large number of studies of lead nephropathy in humans have been published (Table 3-3). Most of these studies are of adults whose exposures were of occupational origin; however, a few environmental and/or mixed exposures are represented and a few studies of children are also included (Bernard et al. 1995; Fels et al. 1998; Verberk et al. 1996). In most of these studies, PbB was the biomarker for exposure, although more recent epidemiological studies have explored associations between toxicity and bone lead concentrations. These studies provide a basis for establishing blood lead, and in some cases, bone lead concentration ranges associated with specific nephrotoxicity outcome. The studies are sorted in Figure 3-3 by the central tendency blood lead concentration reported in each study; details about the subjects and exposures are provided in Table 3-3. End points of kidney status captured in this data set include various measures of glomerular and tubular dysfunction. Data on changes in glomerular filtration rate represent measurements of either creatinine clearance or serum creatinine concentration. Measurements of enzymuria represent, mainly, urinary N-acetyl-D-glucosaminidase (NAG), are also represented. Increased excretion of NAG has been found in lead-exposed workers in the absence of increased excretion of other proximal tubule enzymes (e.g., alanine aminopeptidase, alkaline phosphatase, glutamyltransferase) (Pergande et al. 1994). Data points indicating proteinuria refer to total urinary protein, urinary albumin, or urinary LMW protein (e.g., 2 μ G or RBP). Indices of impaired transport include clearance or transport maxima for organic anions (e.g., p-aminohippurate, urate) or glucose (Biagini et al. 1977; Hong et al. 1980; Wedeen et al. 1975). A few studies have provided histopathological confirmation of proximal tubular injury (Biagini et al. 1977; Wedeen et al. 1975, 1979).

Figure 3-3 illustrates a few general trends regarding the relationship between PbB and qualitative aspects of the kidney response. A cluster of observations of decrements in glomerular filtration rate appear at the low end of the PbB range (<20 μ g/dL); the significance of these studies is discussed in greater detail below. Outcomes for the various renal toxicity end points are mixed over the PbB range 20–50 μ g/dL. Enzymuria or proteinuria were detected in most studies in which these end points were evaluated, whereas indications of depressed glomerular filtration rate were, with only one exception, not observed over this PbB range. At PbBs >50 μ g/dL, functional deficits, including enzymuria, proteinuria, impaired transport, and depressed glomerular filtration rate, dominate the observations. The overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs below 20 μ g/dL, enzymuria and proteinuria becoming evident above 30 μ g/dL, and severe deficits in function and pathological changes occurring in association with PbBs exceeding 50 μ g/dL.

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Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans^a

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL) ^b	Biomarker evaluated ^c
1	Muntner et al. 2003	Unknown	4,831	>20	NA	5 (<1–56)	SCr*
2	Hu 1991b	Environmental	22	55	NA	6 (2–11)	CCr* ^d
3	Lin et al. 2001	Unknown	55	57	NA	7 (1–16)	CCr*
4	Staessen et al. 1992	Environmental	1,981	48	NA	8 (~2–70)	CCr*, SCr*
5	Payton et al. 1994	Environmental	744	64	NA	8 (4–26)	CCr*
6	Kim et al. 1996a	Unknown	459	57	NA	10 (<1–54)	SCr*
7	Staessen et al. 1990	Environmental	531	48	NA	10 (<4–35)	SCr*
8	Bernard et al. 1995	Environmental	154	13	NA	12 (3–35)	UNAG*, URBP*
9	Fels et al. 1998	Environmental	62	10	NA	13 (SD=6)	SCr, UE, UP, ULMWP
10	Sonmez et al. 2002	Occupational	13	32	0.14	25 (SD=10)	SCr, UNAG*
11	Chia et al. 1994	Occupational	128	28	3	30 (4–66)	UNAG*
12	Chia et al. 1995a, 1995b	Occupational	137	28	>0.5	30 (4–66)	SCr, Sβ ₂ µG*, UAlb, Uβ ₂ µG, URBP
13	Weaver et al. 2003a, 2005	Occupational	803	40	1–36	32 (4–86)	BUN* ^e , SCr* ^e , CCr, UNAG* ^e , URBP
14	Mortada et al. 2001	Occupational	43	33	10	32 (SD=17)	SCr, UNAG*, UAlb*
15	Gerhardsson et al. 1992	Occupational	100	37–68	14–32	32 (5–47)	CCr, SCr, Uβ ₂ µG*, UNAG*
16	Verberk et al. 1996	Environmental	151	4.6	NA	34 (<5–~110)	UNAG*
17	Factor-Litvak et al. 1999	Environmental	394	6	6	35 (20–40)	UP*
18	Omae et al. 1990	Occupational	165	18–57	0.1–26	37 (9–60)	CCr, CUA, Uβ ₂ µG, Cβ ₂ µG

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Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans^a

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL) ^b	Biomarker evaluated ^c
19	Cardozo dos Santos et al. 1994	Occupational	166	33	4.5	37 (16–88) ^f	SCr, UNAG*, UAlb, UP
20	Wedeen et al. 1975	Occupational	4	36	5–8	40 (29–52)	GFR, RPF, TMPAH, HP
21	Hsiao et al. 2001	Occupational	30	38	13	40 (<10–98)	SCr ^g
22	Huang et al. 2002	Occupational	40	30	5	42 (24–63)	Uβ ₂ µG, UP
23	Fels et al. 1994	Occupational	81	30	7	42 (21–73)	UP*
24	Pergande et al. 1994	Occupational	82	30	7	42 (21–73)	SCr, UP*, UE*
25	Roels et al. 1994	Occupational	76	44	6–36	43 (26–68)	CCr ^{*d} , UNAG*
26	Kumar and Krishnaswamy 1995	Occupational	22	32.5	NA	43 (30–69)	CCr, Uβ ₂ µG*, UNAG*
27	Buchet et al. 1980	Occupational	25	45	13	44 (34–61)	CCr, SCr, Uβ ₂ µG, UP
28	de Kort et al. 1987	Occupational	53	42	12	47 (44–51)	SCr, BUN
29	Verschoor et al. 1987	Occupational	155	30–51	<2–>10	47 (34–66)	UNAG*, URPB*
30	Cardenas et al. 1993	Occupational	41	39	14	48 (36–65)	SCr, UP, Uβ ₂ µG, UNAG*, UTBX*, UPG*
31	Wedeen et al. 1975	Occupational	1	40	5	48	GFR*, TMPAH*, HP*
32	Gennart et al. 1992	Occupational	98	38	8	51 (45–70)	SCr, UNAG, Uβ ₂ µG, URPB
33	Wedeen et al. 1979	Occupational	15	41	14	52 (20–98)	GFR*, HP*
34	Ehrlich et al. 1998	Occupational	382	41	12	54 (23–110)	SCr, * SUA*
35	Pinto de Almeida et al. 1987	Occupational	52	38	NA	64 (SD=16)	SCr*
36	Hong et al. 1980	Occupational	6	35	7	68 (34–110)	GFR*, TMG*
37	Wedeen et al. 1975	Occupational	3	28	3–5	72 (51–98)	GFR*, RPF*, TMPAH*, HP*

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Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans^a

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL) ^b	Biomarker evaluated ^c
38	Baker et al. 1979	Occupational	160	29–62	4–31	77 (16–280)	GFR*, BUN*
39	Lilis et al. 1968	Occupational	102	32–61	>10	79 (42–149)	GFR*, SCr*
40	Lilis et al. 1980	Occupational	449	NA	12	80 (<40>80)	SCr*, BUN*
41	Cramer et al. 1974	Occupational	7	45	9	103 (71–109)	GFR*, HP*
42	Biagini et al. 1977	Occupational	11	44	12	103 (60–200)	GFR*, CPAH*, HP*

^aSee Figure 3-3 for graphical representation of lead-induced renal effects.

^bBlood lead concentrations are reported central tendencies with range or SD in parentheses.

^cAsterisk indicates association with lead exposure.

^dSignificant increase in creatinine clearance.

^eSignificant in upper age tertile (>46 years).

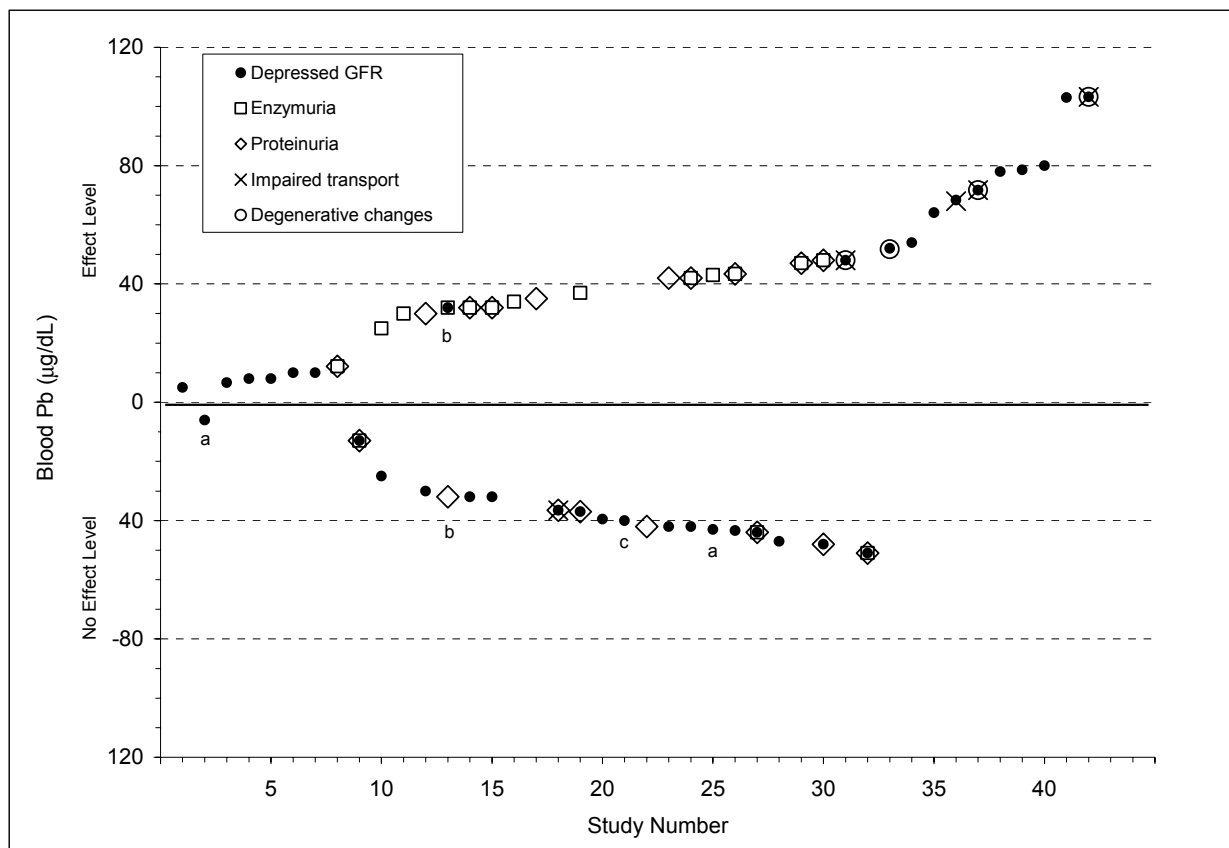
^f3rd and 97th percentile.

^gSignificant decrease in serum creatinine concentration.

BUN = blood urea nitrogen, CCr = creatinine clearance; C_{β₂µG} = β₂µG clearance, CPAH=p-aminohippurate (PAH) clearance; CUA = uric acid clearance; GFR = glomerular filtration rate; HP = histopathology; S_{β₂µG} = serum β₂µG; SCr = serum creatinine; SD = standard deviation; SUA = serum uric acid; RPF= renal plasma flow; TMG = transport maximum for glucose; TMPAH = transport maximum for PAH; UA1b = urine albumin; U_{β₂µG} = urine β₂µG; UE = urine enzymes; ULMWP = urine low molecular weight proteins; UNAG = urine N-acetyl-β-D-glucosaminidase; UP = urine protein; UPG = urine prostaglandins; URBP = urine retinol binding protein; UTBX = urine thromboxane

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Figure 3-3. Indicators of Renal Functional Impairment Observed at Various Blood Lead Concentrations in Humans*



*Refer to Table 3-3 for study details (indexed by study number)

a = Increase in creatinine clearance; b = >46 years of age; c = Decrease in serum creatinine; GFR = glomerular filtration rate

Source: Diamond 2005

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Inconsistencies in the reported outcomes across studies may derive from several causes. Varying uncertainty also exists, across studies, in exposure history of subjects and in the biomarkers assessed. In addition, occupational studies are subject to a healthy worker bias (i.e., tendency for workers who experience adverse effects to remove themselves, or be removed, from exposure).

Observations made in animal models provide evidence for the plausibility of effects of lead on renal glomerular and tubular function in humans. In rats, proximal tubular injury involves the convoluted and straight portions of the tubule (Aviv et al. 1980; Dieter et al. 1993; Khalil-Manesh et al. 1992a, 1992b; Vyskocil et al. 1989), with greater severity, at least initially, in the straight (S3) segment (Fowler et al. 1980; Murakami et al. 1983). Typical histological features include, in the acute phase, the formation of intranuclear inclusion bodies in proximal tubule cells (see below for further discussion); abnormal morphology (e.g., swelling and budding) of proximal tubular mitochondria (Fowler et al. 1980; Goyer and Krall 1969); karyomegaly and cytomegaly; and cellular necrosis, at sufficiently high dosage. These changes appear to progress, in the chronic phase of toxicity and with sufficient dosage, to tubular atrophy and interstitial fibrosis (Goyer 1971; Khalil-Manesh et al. 1992a, 1992b). Glomerular sclerosis has also been reported (Khalil-Manesh et al. 1992a). Adenocarcinomas of the kidney have been observed in long-term studies in rodents in which animals also developed proximal tubular nephropathy (Azar et al. 1973; Goyer 1993; Koller et al. 1985; Moore and Meredith 1979; Van Esch and Kroes 1969).

Effects on Glomerular Filtration Rate. In humans, reduced glomerular filtration rate (i.e., indicated by decreases in creatinine clearance or increases in serum creatinine concentration) has been observed in association with exposures resulting in average PbBs <20 µg/dL (Figure 3-3, Table 3-3).

The results of epidemiological studies of general populations have shown a significant effect of age on the relationship between glomerular filtration rate (assessed from creatinine clearance of serum creatinine concentration) and PbB (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992; Weaver et al. 2003a, 2005b). Furthermore, hypertension can be both a confounder in studies of associations between lead exposure and creatinine clearance (Perneger et al. 1993) and a covariable with lead exposure (Harlan et al. 1985; Muntner et al. 2003; Payton et al. 1994; Pirkle et al. 1985; Pocock et al. 1984, 1988; Tsaih et al. 2004; Weiss et al. 1986). These factors may explain some of the variable outcomes of smaller studies in which the age and hypertension effects were not fully taken into account. When age and other covariables that might contribute to glomerular disease are factored into the dose-response analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbB <20 µg/dL (Table 3-4). In the Kim et al. (1996a) and Muntner et al. (2003) studies, a

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Table 3-4. Summary of Dose-Response Relationships for Effects of Lead Exposure on Biomarkers of Glomerular Filtration Rate

Reference	Exposure	Number of Subjects	Mean PbB (range) (µg/dL)	End point	Change in end point (per 10-fold increase in blood lead)
Payton et al. 1994	Mixed ^a	744 M	8.1 (4–26)	CCr (mL/minute)	-10 ^b
Staessen et al. 1992	Environmental	1,016 F 965 M	7.5 (1.7–65)	CCr (mL/minute)	-10 F ^c -13 M
Kim et al. 1996a	Mixed ^a	459 M	9.9 (0.2–54)	SCr (mg/dL)	0.08 ^d 0.14 ^e
Staessen et al. 1990	Environmental	133 F 398 M	12 (6–35)	SCr (mg/dL)	0.07 M ^f

^aU.S. Veterans Administration Normative Aging Study

^bPartial regression coefficient, -0.040 ln mL/minute creatinine clearance per ln µmol/L blood lead concentration.

^cPartial regression coefficient, -9.51 mL/minute creatinine clearance per log µmol/L blood lead concentration.

^dPartial regression coefficient, 2.89 µmol/L serum creatinine per ln µmol/L blood lead concentration.

^eIn subjects with blood lead concentrations less than 10 µg/dL, the partial regression coefficient was 5.29 µmol/L serum creatinine per ln µmol/L blood lead concentration.

^fReported 0.6 increase in serum creatinine (µmol/L) per 25% increase in blood lead concentration (µmol/L, log-transformed) in males (two subjects with serum creatinine concentrations exceeding 180 µmol/L excluded; regression coefficient not reported for females).

CCr = creatinine clearance; F = females; ln = natural logarithm; M = males; PbB = blood lead concentration; SCr = serum creatinine concentration

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significant relationship between serum creatinine and PbB was evident in subjects who had PbB below 10 µg/dL (serum creatinine increased 0.14 mg/dL per 10-fold increase in PbB). Assuming a glomerular filtration rate of approximately 90–100 mL/minute in the studies reported in Table 3-4, a change in creatinine clearance of 10–14 mL/minute would represent a 9–16% change in glomerular filtration rate per 10-fold increase in PbB. Estimating the change in glomerular filtration rate from the incremental changes in serum creatinine concentration reported in Table 3-4 is far less certain because decrements in glomerular filtration do not necessarily give rise to proportional increases in serum creatinine concentrations. A 50% decrement in glomerular filtration rate can occur without a measurable change in serum creatinine excretion (Brady et al. 2000). Nevertheless, the changes reported in Table 3-4 (0.07–0.14 mg/dL) would represent a 6–16% increase, assuming a mean serum creatinine concentration of 0.9–1.2 mg/dL. This suggests at least a similar, and possibly a substantially larger, decrement in glomerular filtration rate. The confounding and covariable effects of hypertension are also relevant to the interpretation of the regression coefficients reported in these studies. Given the evidence for an association between lead exposure and hypertension, and that decrements in glomerular filtration rate can be a contributor to hypertension, it is possible that the reported hypertension-adjusted regression coefficients may underestimate the actual slope of the blood lead concentration relationship with serum creatinine concentration or creatinine clearance.

Another important complication in the assessment of associations between lead exposure and adverse effects on glomerular filtration is the potential confounding effect of decrements in glomerular filtration rate and increased lead body burden. Lead exposure has also been associated with increases in glomerular filtration rate (Hsiao et al. 2001; Hu 1991b; Roels et al. 1994). This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Increases in glomerular filtration rate have been observed in the early phases of development of chronic renal injury in rats (Khalil-Manesh et al. 1992a).

The observations suggestive of a relationship between PbB and decrements in glomerular filtration rate derived from the studies presented in Table 3-3 are consistent with those of a smaller prospective clinical study in which progression of renal insufficiency was related to higher lead body burden among patients whose PbB was <15 µg/dL (Lin et al. 2001; Yu et al. 2004). Mean PbB in a high lead body burden group (EDTA provocation test yielded >600 µg excreted/72 hours) were 6.6 µg/dL (range, 1.0–15 µg/dL) compared to 3.9 µg/dL (1–7.9 µg/dL) in a low body burden group.

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The above observations suggest that significant decrements in glomerular filtration rate may occur in association with PbB below 20 µg/dL and, possibly, below 10 µg/dL (Kim et al. 1996a; Muntner et al. 2003). This range is used as the basis for estimates of lead intakes that would place individuals at risk for renal functional deficits.

Longitudinal Studies—General Population. Three studies of glomerular function and lead exposure were conducted as part of the Normative Aging Study, a longitudinal study of health outcomes in 2,280 males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67), and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitis. Physical examinations, including seated blood pressure and medical history follow-ups, were conducted at approximately 3–5-year intervals. Beginning in 1987, participants were requested to provide 24-hour urine samples for analysis, including urine creatinine; and beginning in 1991, blood and bone concentrations were included in the examinations. Data collected from a subset of the study population (744 subjects, observed between 1988 and 1991) were analyzed for associations between serum creatinine, renal creatinine clearance, and blood lead concentrations (Payton et al. 1994). Mean age of the study group was 64.0 years (range, 43–90). Mean baseline PbB was 8.1 µg/dL (range, <4–26 µg/dL). Based on multi-variate linear regression (with log-transformed PbB), covariate-adjusted creatinine clearance was significantly associated with blood lead concentration (regression coefficient, -0.0403; SE, 0.0198; p=0.04). A 10-fold increase in PbB was associated with a decrease in creatinine clearance of 10.4 mL/minute. This would represent a decrease in creatinine clearance of approximately 11% from the group mean of 88 mL/minute. Co-variables included in the regression model were age and body mass index; systolic and diastolic blood pressure; alcohol consumption and tobacco smoking; and analgesic or diuretic medications.

In a subsequent longitudinal study, data collected from a random subset of the Normative Aging Study population (459 subjects, observed between 1991 and 1994) were analyzed for associations between serum creatinine and PbB (Kim et al. 1996a). Mean age of the study group was 56.9 years (range, 37.7–87.5). Mean PbB was 9.9 µg/dL (range, 0.2–54.1 µg/dL). Based on multivariate linear regression (with log-transformed PbB), covariate-adjusted serum creatinine concentration (mg/dL) was significantly associated with PbB. A 10-fold increase in PbB was associated with an increase of 0.08 mg/dL in covariate-adjusted serum creatinine (95% CI, 0.02–0.13). This would represent an increase of approximately 7% from the group mean of 1.2 mg/dL. When subjects were stratified by PbB, the association was significant for three blood lead categories: ≤40, ≤25, and ≤10 µg/dL. In subjects who had PbB ≤10 µg/dL, serum creatinine was predicted to increase 0.14 mg/dL per 10-fold increase in PbB

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(approximately 11% increase from the unstratified group mean). Covariates included in the models were age and body mass index; hypertension; alcohol consumption and tobacco smoking; and education.

A prospective study included 707 subjects from the Normative Aging Study who had serum creatinine, blood lead and bone lead measurements taken during the period 1991–1995 (baseline), and a subset of the latter group (n=448) for which follow-up serum creatinine measurements made 4–8 years later (Tsaih et al. 2004). Mean age of the study group was 66 years at the time of baseline evaluation and 72 years at follow-up. Mean PbB was 6.5 µg/dL at baseline and 4.5 at follow-up. Baseline bone lead concentrations were: tibia, 21.5 µg/g and patella, 32.4 µg/g and were essentially the same at follow-up. Associations between covariate-adjusted serum creatinine concentrations and lead measures were significant ($p<0.05$) in the study group only for blood lead and follow-up serum creatinine. Covariates included in the models were age and body mass index; diabetes and hypertension; alcohol consumption and tobacco smoking; and education. When stratified by diabetes and hypertension status, significant associations between serum creatinine concentration and lead measures (blood or bone lead) were found in the diabetic (n=26) and hypertensive groups (n=115), suggesting the possibility of interactions between lead exposure, glomerular function, diabetes, or hypertension. An increase in tibia bone lead concentration from the mid-point of the lowest to the highest quintile (9–34 µg/g) was associated with a significantly greater increment in serum creatinine concentration among diabetics (1.08 mg/dL per 10 years) compared to non-diabetics (0.062 mg/dL per 10 years).

Cross-sectional Studies—General Population. The NHANES III collected data on serum creatinine concentrations and PbB on approximately 20,000 U.S. residents during the period 1988–1994. Muntner et al. (2003) analyzed data collected on 15,211 subjects of age 20 years or older. Subjects were stratified into normotensive (n=10,398) or hypertensive categories (n=4,813; ≥ 140 mmHg systolic pressure or ≥ 90 mmHg diastolic pressure). Mean PbB was 3.30 µg/dL in the normotensive group and 4.21 µg/dL in the hypertensive group. Associations between PbB and risk of elevated serum creatinine concentrations or chronic renal disease (i.e., depressed glomerular filtration rate) were explored using multivariate regression. Elevated serum creatinine concentration was defined as ≥ 1.5 or ≥ 1.3 mg/dL in non-Hispanic Caucasian males and females, respectively; ≥ 1.6 mg/dL (males) or 1.4 mg/dL (females) for non-Hispanic African Americans; or ≥ 1.4 mg/dL (males) or ≥ 1.2 mg/dL (females) for Mexican Americans. Glomerular filtration rate was estimated from serum creatinine concentration using a predictive algorithm (Levey et al. 1999). Chronic renal disease was defined as glomerular filtration rate < 60 mL/minute per 1.73 m^2 of body surface area. Covariate-adjusted ORs were estimated for PbB quartiles 2 (2.5–3.8 µg/dL), 3 (3.9–5.9 µg/dL), and 4 (6.0–56.0 µg/dL), relative to the 1st quartile (0.7–2.4 µg/dL). The ORs for elevated

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serum creatinine concentration and chronic renal disease, but not in the normotensive group, exceeded unity in all quartiles of PbB and showed a significant upward trend with PbB. Covariate-adjusted ORs for chronic renal disease were: 2nd quartile, 1.44 (95% CI, 1.00–2.09); 3rd quartile, 1.85 (95% CI, 1.32–2.59); and 4th quartile, 2.60 (95% CI, 1.52–4.45). A 2-fold increase in PbB was associated with an OR of 1.43 (95% CI, 1.20–1.72) for elevated serum creatinine concentration or 1.38 (95% CI, 1.15–1.66) of chronic renal disease. Covariates included in the models were age, gender and body mass index; systolic blood pressure; cardiovascular disease and diabetes mellitus; alcohol consumption and cigarette smoking; and household income, marital status, and health insurance. A stronger association between PbB and depressed glomerular filtration rate (i.e., creatinine clearance) also was found in people who have hypertension, compared to normotensive people, in the smaller prospective study (Tsaih et al. 2004).

An analysis of relationships between PbB and renal creatinine clearance was conducted as part of the Belgian Cadmibel Study (Staessen et al. 1992). The Cadmibel Study was a cross-sectional study, originally intended to assess health outcomes from cadmium exposure. Subjects recruited during the period 1985–1989 resided for at least 8 years in one of four areas (two urban, two rural) in Belgium. One of the urban and rural areas had been impacted by emissions from heavy metal smelting and processing. PbB and creatinine clearance measurements were obtained for 965 males (mean age, 48 years) and 1,016 females (mean age, 48 years). Mean PbB was 11.4 µg/dL (range, 2.3–72.5) in males and 7.4 µg/dL (range, 1.7–6.0) in females. Based on multivariate linear regression (with log-transformed PbB), covariate-adjusted creatinine clearance was significantly associated with PbB in males. A 10-fold increase in PbB was associated with a decrease in creatinine clearance of 13 mL/minute in males and 30 mL/minute in females. This would represent a decrease in creatinine clearance of approximately 13% from the group mean of 99 mL/minute in males, or 38% from the group mean of 80 mL/minute in females. Covariates included in the regression model were age and body mass index; urinary γ -glutamyl-transferase activity; and diuretic therapy. A logistic regression model was applied to the data to examine the relationship between risk of impaired renal function, defined as less than the 5th percentile value for creatinine clearance in subjects who were not taking analgesics or diuretics (<52 mL/minute in males or 48 mL/minute in females). A 10-fold increase in PbB was associated with a covariate-adjusted risk for impaired renal function of 3.76 (95% CI, 1.37–10.4; $p=0.01$). Covariates included in the logistic model were age and body mass index; urinary γ -glutamyltransferase activity; diabetes mellitus; and analgesic or diuretic therapy.

A cross-sectional study of civil servants in London examined relationships between PbB and serum creatinine concentration (Staessen et al. 1990). Participants included 398 males (mean age, 47.8 years)

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and 133 females (mean age, 47.5 years). Mean PbB was 12.4 µg/dL in males and 10.2 µg/dL in females. Serum creatinine concentration was significantly ($p=0.04$, linear regression with log-transformed PbB) associated with PbB in males, but not in females. The association was no longer significant after excluding two subjects from the analysis who had serum creatinine concentrations exceeding 180 µmol/L (2 mg/dL). The predicted increase in serum creatinine concentration per 25% increase in PbB was 0.6 µmol/L (95% CI, -0.2–1.36). Although several covariates were considered in the analysis of the blood lead concentration data, covariates included in the regression model for serum creatinine concentration were not reported.

The Agency for Toxic Substances and Disease Registry (1995) conducted a cross-sectional analysis of possible associations between lead exposure and serum creatinine concentration or BUN among residents of four NPL sites (Granite City, Illinois; Galena, Kansas; Joplin, Mississippi; Palmerton, Pennsylvania). The study consisted of a target group of NPL site residents ($n=1,645$) and a comparison group ($n=493$) that had similar distributions of gender, age, SES, education, and housing age. Geometric mean blood lead concentrations were 4.26 µg/dL ($SD\pm 0.71$) in the target group and 3.45 µg/dL ($SD\pm 0.74$) in the comparison group. Multivariate regression analyses (linear and logistic) of subsets of the study group (e.g., age strata) did not reveal significant associations between PbB and either serum creatinine concentration or BUN.

Cross-sectional Studies—Occupational Exposures. As part of a longitudinal study of health outcomes among Korean lead workers, cross-sectional studies of potential associations between biomarkers of lead exposure (PbB, tibia lead, DMSA evoked urinary lead) have been conducted (Weaver et al. 2003a, 2003b, 2005a, 2005b). The cross-sectional study of the first of three longitudinal evaluations included 803 current and former lead workers (age range, 18–65 years; 639 males) and 135 controls (age range, 22–60 years; 124 males), enrolled in the study during the period 1997–1999 (Weaver et al. 2003a, 2005a). Mean PbB of the lead workers was 32 µg/dL (range, 4–86 µg/dL); mean tibia lead was 37 µg/g (range, -7–338 µg/dL). Significant associations were evident in the upper age tertile (>46 years), but not at younger ages, between increasing covariate-adjusted tibia lead and increasing serum creatinine (β , 0.0008 mg/dL per µg/dL; $p<0.01$) and increasing serum uric acid concentration (β , 0.0036 mg/dL per µg/dL; $p=0.04$); and between increasing PbB and increasing BUN (β , 0.0615 mg/dL per µg/dL; $p<0.01$). Covariates included age, gender, body mass index, current/former exposure status, and hypertension. In a subsequent cross-sectional study of the third evaluation of this same study group ($n=652$), performed during the period 1999–2001, similar age-dependent outcomes were observed (Weaver et al. 2005b). Significant associations between increasing serum creatinine and increasing tibia lead (β , 0.000451;

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$p=0.04$), patella lead (β , 0.000147; $p=0.04$), or PbB (β , 0.001266; $p=0.02$) were evident in the upper age tertile (46 years).

Experimental studies in laboratory animals have shown that exposures to lead that result in blood lead concentrations exceeding 50 $\mu\text{g}/\text{dL}$ can depress glomerular filtration rate and renal blood flow and produce glomerular sclerosis (Aviv et al. 1980; Khalil-Manesh et al. 1992a, 1992b).

Endocrine Effects. Occupational studies provide evidence for an association between high exposures to lead and changes in thyroid, pituitary, and testicular hormones. There are a number of inconsistencies in the available findings that are related in part to small sample sizes, possible confounding effects by age, tobacco use, and other factors, responses that remained within reference limits, and differences in laboratory methods of hormonal evaluation. Changes in circulating levels of thyroid hormones, particularly serum thyroxine (T_4) and thyroid stimulating hormone (TSH), generally occurred in workers having mean PbB ≥ 40 – $60 \mu\text{g}/\text{dL}$. Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone, have been observed at PbB ≥ 30 – $40 \mu\text{g}/\text{dL}$. Some data, mainly results of tests of hormonal stimulation tests, suggest that the changes in thyroid and testicular hormones are secondary to effects of lead on pituitary function.

Decreases in serum T_4 were found in studies of workers with very high PbB (Cullen et al. 1984; Robins et al. 1983). Serum T_4 and estimated free thyroxine (EFT_4) were reduced in three of seven men who had symptomatic occupational lead poisoning and a mean PbB of 87.4 $\mu\text{g}/\text{dL}$ (range, 66–139 $\mu\text{g}/\text{dL}$) (Cullen et al. 1984). There were no effects on thyroid binding globulin (TBG), total triiodothyronine (T_3), TSH, or TSH response to thyrotrophin releasing hormone (TRH) stimulation. A clinical study similarly found subnormal (low to borderline) serum T_4 and EFT_4 values in 7 of 12 (58%) foundry workers with a mean PbB of 65.8 $\mu\text{g}/\text{dL}$ (Robins et al. 1983). However, in a cross-sectional study of 47 men from the same foundry with PbB $< 50 \mu\text{g}/\text{dL}$ and a mean employment duration of 5.8 years, only 12 (26%) had evidence of reduced T_4 and EFT_4 (Robins et al. 1983). Serum T_3 and TSH levels (only measured in the clinical study) and thyroid binding capacity (TBC, only measured in the cross-sectional study) were normal, and regression analyses showed no clear correlation between T_4 or EFT_4 and PbB. The thyroid effects in these studies (i.e., reduced T_4 with inappropriately low TSH or poor TRH response) are consistent with a primary pituitary or hypothalamic insufficiency. Evaluation of 176 Kenyan male car battery factory and secondary lead smelter workers (mean PbB, 56 $\mu\text{g}/\text{dL}$; mean lead exposure duration 7.6 ± 5.1 years) showed that serum T_4 , FT_4 , T_3 , and TSH levels were similar in subgroups of 93 workers with PbB $\leq 56 \mu\text{g}/\text{dL}$ and 83 workers with PbB $\geq 56 \mu\text{g}/\text{dL}$ (Tuppurainen et al. 1988). Regression analysis found no

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significant correlations between PbB and any of the thyroid measures. However, there were weak but statistically significant negative correlations between duration of exposure and levels of T₄ and FT₄, and these associations were stronger in the ≥ 56 $\mu\text{g/dL}$ subgroup.

Several studies found alterations in serum thyroid hormone and TSH in the PbB range of 40–60 $\mu\text{g/dL}$ (Gustafson et al. 1989; López et al. 2000; Singh et al. 2000a). Mean serum levels of T₄ and FT₄ were significantly higher in 75 male lead-battery factory workers with a mean PbB of 50.9 $\mu\text{g/dL}$ (mean work duration 6.1 years) than in 62 unexposed referents (no workplace lead exposure) with a mean PbB of 19.1 $\mu\text{g/dL}$ (López et al. 2000). There were no group differences in serum T₃ and TSH. Regression analyses showed significant positive correlations for serum T₄, FT₄, T₃, and TSH vs. PbB in the range 8–50 $\mu\text{g/dL}$, and significant negative correlations for T₄ and T₃ vs. PbB in the range 50–98 $\mu\text{g/dL}$, indicating a drop in circulating hormones at PbBs around 50 $\mu\text{g/dL}$ that is consistent with the results of the Cullen et al. (1984) and Robins et al. (1983) studies cited above. There were no significant associations between PbB or hormone levels vs. time in workplace or age, and all hormone values were within normal reference ranges. Gustafson et al. (1989) measured serum levels of T₃, T₄, and TSH in 25 male lead smelter workers (mean PbB, 39 $\mu\text{g/dL}$) and 25 matched controls without occupational lead exposure (mean PbB, 4 $\mu\text{g/dL}$). There were no overall group differences in the three thyroid measures, although serum TSH was significantly increased in the most heavily exposed individuals (mean PbB, >41 $\mu\text{g/dL}$). Analysis of a subgroup that reported no intake of selenium pills showed that serum T₄ was significantly higher in the exposed workers. Additionally, serum T₄ was significantly increased in a subgroup of 14 workers under the age of 40 (mean PbB, 39 $\mu\text{g/dL}$). Serum T₄, T₃, and TSH were assessed in 58 male petrol pump workers or automobile mechanics who had a mean PbB of 51.9 $\mu\text{g/dL}$ and mean lead exposure duration of 13 years (Singh et al. 2000a). Comparison with an unexposed control group of 35 men (mean PbB, 9.5 $\mu\text{g/dL}$) showed no significant differences in T₄ and T₃ levels, although T₃ was significantly lower in a subgroup of 17 workers with a longer mean exposure time (17.5 years) than in 41 workers with shorter exposure (2.4 years). Serum TSH was significantly higher in the exposed workers compared to controls, as well as in a subgroup of 50 workers with higher mean PbB (55.4 $\mu\text{g/dL}$) than in 8 workers with a lower mean PbB (31.5 $\mu\text{g/dL}$), although all TSH values remained within the normal laboratory range.

Workers with PbBs of approximately 20–30 $\mu\text{g/dL}$ showed no clear indications of thyroid dysfunction (Dursun and Tutus 1999; Erfurth et al. 2001; Refowitz 1984; Schumacher et al. 1998). Serum T₄, EFT₄, and TSH were assessed in a cross-sectional study of 151 male lead smelter workers that examined dose-response relationships across specifically defined levels of lead exposure (Schumacher et al. 1998). The

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mean duration of employment in lead-exposed areas was 4.3 years, the mean current PbB was 24 µg/dL (15% exceeded 40 µg/dL), and the mean PbB for the preceding 10 years was 31 µg/dL (26% exceeded 40 µg/dL). The thyroid hormones were evaluated in relation to four levels of current and 10-year cumulative lead exposure (<15, 14–24, 25–39, and ≥40 µg/dL). Mean levels of T₄, EFT₄, and TSH were similar in all exposure categories and within laboratory normal limits for both current and cumulative exposure. There was no evidence of an exposure response with increasing lead burden, and controlling for age and alcohol consumption did not significantly alter the findings. Erfurth et al. (2001) found that serum concentrations of FT₄, FT₃, and TSH were similar in groups of 62 secondary lead smelter workers (median PbB, 33.2 µg/dL, median exposure time, 8 years) and 26 matched referents with no known occupational exposure to lead (median PbB, 4.1 µg/dL). There were no significant associations between these hormones and PbB, plasma lead, and bone lead levels after adjustment for age. Additionally, there was no difference in TSH response to TRH stimulation in subgroups of 9 exposed workers (median PbB, 35.2 µg/dL) and 11 referents (median PbB, 4.1 µg/dL). There were no adverse changes in thyroid hormones in workers with a mean PbB of 17.1 µg/dL who were exposed to lead for an average of 16.70 years (range, 1–22 years) in a Turkish metal powder-producing factory (Dursun and Tutus 1999). Comparison with 30 subjects from the general population (mean PbB, 2.37 µg/dL) showed that serum levels of T₄, FT₄, and FT₃, but not T₃ or TSH, were statistically significantly increased in the workers. However, all five thyroid measures were within normal reference limits. Refowitz (1984) found no correlation between levels of T₄ or EFT₄ and PbB in 58 secondary copper smelter workers in which the preponderance of PbBs were below 40 µg/dL.

No significant effects of lead on thyroid function have been found in children, but the number and/or quality of the available studies do not allow drawing firm conclusions. Thirty-six male and 32 female children ranging in age from 11 months to 7 years (median age of 25 months) took part in a study of the effects of lead exposure on thyroid function in inner city children (Siegel et al. 1989). PbB, T₄, and T₄ uptake were determined, and sex, race, socioeconomic status, and hemoglobin were also assessed for each child. The PbBs ranged from 2.0 to 77 µg/dL, with a mean of 25 µg/dL. Forty-four percent of the children had moderately elevated lead levels (>24 µg/dL). Linear regression analysis revealed that there was no association between PbB and either T₄ or FT₄. The results of this study are consistent with the findings of a small study of 12 children (2–5 years old) from the Omaha Lead and Poison Prevention Program with PbBs in the range of 41–72 µg/dL (Huseman et al. 1992). The authors found that basal TSH, T₄, T₃, and prolactin were within normal ranges. Also, TSH and prolactin responses to TRH, and cortisol responses to insulin were not altered by lead. However, Huseman et al. (1992) did find that the peak human growth hormone (HGH) response to an L-dopa and insulin test, although within normal

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limits, was significantly lower in children with toxic levels of lead compared with the peak response in children with lower PbB ($<30 \mu\text{g/dL}$). Furthermore, the mean 24-hour HGH in children with high PbB was not only significantly lower than those of normal children, but was comparable with that of children with HGH neurosecretory dysfunction. High PbB was also associated with a lower mean insulin-like growth factor I. A study of male adolescents in Turkey reported that 42 subjects who worked at auto repair workshops and had a mean PbB of $7.3 \mu\text{g/dL}$ ($\text{SD} \pm 2.92 \mu\text{g/dL}$) had a significantly lower ($p < 0.05$) serum level of FT4 (1.12 ng/mL) compared to 55 control subjects (1.02 ng/mL) with a mean PbB of $2.1 \mu\text{g/dL}$ ($\text{SD} \pm 1.24 \mu\text{g/dL}$) (Dundar et al. 2006). There were no significant effects on serum FT3 or TSH levels or in thyroid volume. Based on the small difference in FT4 values between exposed and unexposed subjects, the lack of increase in TSH, and the fact that many other chemicals normally present at auto repair workshops could have influenced the results, the significance of these findings is unknown.

Effects of occupational exposure to lead on pituitary gonadotrophins and testicular hormones were investigated in male workers (see also Section 3.2.5, Reproductive Effects). Changes in serum FSH, LH, and testosterone were found in several studies of highly exposed workers, but there are no clear patterns of response. The preponderance of evidence is consistent with an indirect effect(s) of lead on the hypothalamic-pituitary axis (i.e., a disruption of gonadotrophin secretions), although direct effects on testicular hormonal production are possible. Plasma concentrations of FSH, LH, testosterone, and prolactin were measured in a study of 122 male lead battery factory workers with a mean current PbB of $35.2 \mu\text{g/dL}$ and mean exposure duration of 6 years (Ng et al. 1991). Levels of FSH and LH were significantly increased compared to a control group of 49 nonexposed workers ($8.3 \mu\text{g/dL}$), and concentrations of these hormones increased with increasing PbB in the range of $10\text{--}40 \mu\text{g/dL}$. Age was not a confounding factor, although duration of exposure affected the results. Workers exposed for <10 years had significantly increased LH and FSH and normal testosterone and prolactin levels, whereas those exposed for ≥ 10 years had increased testosterone and normal LH, FSH, and prolactin. Rodamilans et al. (1988) assessed serum levels of LH, FSH, testosterone, and steroid binding globulin (SBG) in 23 male lead smelter workers with PbB in the range of $60\text{--}80 \mu\text{g/dL}$. Comparison with an unexposed group of 20 men (PbB $17 \mu\text{g/dL}$) showed that serum LH was significantly increased in the workers and that the magnitude of the effect did not increase with duration of exposure. A significantly lower free testosterone index (testosterone/SBG ratio) in the workers exposed for 1–5 years and significant changes in serum testosterone (lower), SGB (higher), and free testosterone index (lower) in the workers exposed for >5 years indicated an exposure duration-related effect on serum testosterone.

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Other studies of male workers have found different results. Erfurth et al. (2001) found no significant differences in basal serum levels of FSH, LH, prolactin, testosterone, sex hormone binding globulin, and cortisol in groups of 11 lead male workers (median PbB, 35.2 µg/dL) and 9 matched referents (median PbB, 4.1 µg/dL), although there was a tendency toward lower serum FSH concentrations in the exposed group. Additionally, measurements of serum FSH, LH, and prolactin after administration of gonadotrophin-releasing hormone (GRH) showed that the level of stimulated FSH was significantly lower in the workers. None of the basal or stimulated hormone levels correlated with lead exposure indices (blood lead, plasma lead, or bone lead) or age. Gustafson et al. (1989) found that plasma FSH, plasma LH, and serum cortisol levels were lower in male workers (mean PbB, 39 µg/dL) than in unexposed controls (mean PbB, 4 µg/dL); however, all hormone values were within normal reference limits. Serum FSH and LH values were similar in 98 male lead acid battery workers with a mean PbB of 51 µg/dL and a group of 85 nonoccupationally exposed subjects (mean PbB, 20.9 µg/dL) (Gennart et al. 1992a), although the high PbB in the comparison group might have obscured detection of an effect. Cullen et al. (1984) found increased serum FSH and LH and borderline low serum testosterone levels in one of seven men with symptomatic occupational lead poisoning and a mean PbB of 87.4 µg/dL. Although serum testosterone concentration was normal in most of these patients, five had defects in spermatogenesis and six had subnormal glucocorticoid production. Serum testosterone levels were significantly lower in groups of male workers with lead poisoning (n=6, mean PbB, 38.7 µg/dL) and lead exposure (n=4, mean PbB, 29.0 µg/dL) than in an unexposed control group (n=9, mean PbB 16.1 µg/dL), but testosterone-estradiol-binding globulin capacity and serum levels of estradiol, LH, FSH, and prolactin were normal (Braunstein et al. 1978). Both lead groups had appropriate responses for serum testosterone and FSH to stimulation by human chorionic gonadotrophin (HCG) and clomiphene, and serum FSH to stimulation by gonadotrophin releasing hormone (GRH) and clomiphene citrate. The lead exposed group also had a normal LH response to challenge by GRH and clomiphene citrate, although the LH response was suppressed in the lead poisoned group. Both lead groups had reduced estradiol response to stimulation by clomiphene citrate, although there was no effect following stimulation by HCG. Testicular biopsies performed on the two most heavily exposed men showed oligospermia and testicular lesions. Further information regarding effects of lead on sex hormone levels in humans and animals can be found in Section 3.2.5.

Information is also available on the effects of lead exposure on serum erythropoietin (EPO) concentration. EPO is a glycoprotein hormone that regulates both steady-state and accelerated erythrocyte production. More than 90% of EPO is produced in the proximal renal tubules. Serum EPO was evaluated in a group of women from the Yugoslavia Prospective Study (see Section 3.2.4 for a detailed description of the Yugoslavia Prospective Study) in mid-pregnancy (n=5) and at time of delivery (n=48) (Graziano et al.

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1991). Analysis of the variance showed that women with higher PbB had inappropriately low levels of EPO both at mid-pregnancy and at delivery. Graziano et al. (1991) speculated that lead may interfere with the mechanism of EPO biosynthesis, which appears to begin with increased calcium entry into the renal cells. In a study of lead workers, serum EPO levels from two groups of 28 exposed workers were significantly lower than in 113 control subjects (Romeo et al. 1996). Mean PbBs in the two exposed groups and in the controls were 38.3, 65.1, and 10.4 µg/dL, respectively. However, there was no correlation between PbB and EPO in any group. Hemoglobin levels were not affected by lead and were comparable among the three groups. In an additional study of male lead workers (n=20) with and without anemia, those with PbBs ≥ 60 µg/dL showed a significant reduction in erythroid progenitor cells and in granulocyte/macrophage progenitor cells (Osterode et al. 1999). However, EPO was in the normal range and did not increase in the presence of lead-induced anemia. Osterode et al. (1999) suggested that lead-induced kidney toxicity might be the reason why EPO was not adequately generated at higher PbB.

Ocular Effects. Lead is known to affect visual evoked potentials in adults and children (see Section 3.2.4 and review by Otto and Fox [1993]), but less is known regarding effects of lead on other eye structures. Recently, Schaumberg et al. (2004) examined the relationship of cumulative lead exposure with the development of cataracts in a group of 642 participants in the Normative Aging Study. Lead exposure was assessed by measuring PbB (mean, 5 µg/dL; range, 0–35 µg/dL) and lead in the tibia (mean, 20 ppm; range, 0–126 ppm) and patella (mean, 29 ppm; range, 0–165 ppm). The mean age of the subjects was 69 years (range, 60–93 years). A total of 122 cases of cataract were found. After controlling for age, tibia lead, but not patella lead, was a significant predictor of cataract. Also, PbB was not associated with increased risk of developing cataracts. Schaumberg et al. (2004) suggested that lead might be disrupting the lens redox status by inducing oxidative damage to lens epithelial cells. Changes consistent with lens opacity also were observed in Fisher 344 rats exposed to 2,000 ppm lead in the drinking water for 5 weeks, which produced a mean PbB of approximately 30 µg/dL (Neal et al. 2005). Examination of two-dimensional protein spot patterns of the rats' lenses showed significant alterations in the protein expression profile of both α A- and β A4-crystallins, alterations of which may decrease lens clarity through increased light scattering. The mechanism for this effect has not been elucidated.

In their review on lead effects on visual function, Otto and Fox (1993) mention that earlier studies reported alterations of the electroretinogram (ERG) in lead workers. Rothenberg et al. (2002a) reported alterations in scotopic (rod-mediated) retinal function in a group of 45 children (7–10 years old) participants in the Mexico City Lead Study (Rothenberg et al. 2002a). These alterations, consisting of increased a- and b-waves, appeared to be a new form of rod dysfunction and were associated with

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maternal blood lead levels measured during the first trimester of pregnancy; the threshold for the effect was 10.5 µg/dL. Alterations in rod function, evidenced by the appearance of central scotoma, also had been reported earlier in lead workers with moderate PbB (mean, 47 µg/dL) (Cavalleri et al. 1982). Changes in ERG components also have been reported in rats (Fox and Chu 1988; Fox and Farber 1988; Fox and Katz 1992; Fox and Rubinstein 1989) and monkeys exposed during development (Bushnell et al. 1977; Kohler et al. 1997; Lilienthal et al. 1988, 1994). Tests conducted in monkeys >2 years after cessation of life exposure to lead revealed alterations in the ERG under scotopic conditions similar to those recorded during lead exposure, and at a time when PbB was below 10 µg/dL (Lilienthal et al. 1994). Since the alteration could be reproduced by treatment with dopamine antagonists, Lilienthal et al. (1994) suggested that the observed effects may be mediated by a permanent change of dopamine function. The series of studies from Fox and coworkers in the rat showed that low-level lead exposure during postnatal development has a detrimental effect on the rods of the retina, but not on cones. They also showed that developing and adult retinas exhibited qualitatively similar structural and functional alterations, but developing retinas were much more sensitive, and in both cases, alterations in retinal cGMP metabolism was the underlying mechanism leading to lead-induced ERG deficits and rod and bipolar cell death (Fox et al. 1997). Using a preparation of rat retina *in vitro*, Fox and coworkers demonstrated that rod mitochondria are the target site for calcium and lead and that these ions bind to the internal metal binding site of the mitochondrial permeability transition pore, which initiates a cascade of apoptosis in rods (He et al. 2000).

Other Systemic Effects. Lead interferes with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. This conversion takes place via hydroxylation to 25-hydroxyvitamin D in the liver followed by 1-hydroxylation in the mitochondria of the renal tubule by a complex cytochrome P-450 system (Mahaffey et al. 1982; Rosen and Chesney 1983). Evidence for this effect comes primarily from studies of children with high lead exposure.

Lead-exposed children with PbBs of 33–120 µg/dL had marked reductions in serum levels of 1,25-dihydroxyvitamin D (Rosen et al. 1980). Even in the range of 33–55 µg/dL, highly significant depressions in circulating 1,25-dihydroxyvitamin D were found, but the most striking decreases occurred in children whose PbB was >62 µg/dL. In addition, children with PbB >62 µg/dL also had significant decreases in serum total calcium and ionized calcium and significant increases in serum parathyroid hormone. These conditions would tend to enhance production of 1,25-dihydroxyvitamin D; thus, the inhibition caused by lead may have been greater than was indicated by 1,25-dihydroxyvitamin D levels. Serum levels of 1,25-dihydroxyvitamin D returned to normal within 2 days after chelation therapy. These results are

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consistent with an effect of lead on renal biosynthesis of 1,25-dihydroxyvitamin D. A strong inverse correlation between 1,25-dihydroxyvitamin D levels and PbB was also found among children with PbB ranging from 12 to 120 µg/dL, with no change in the slope of the line at levels <30 µg/dL (Mahaffey et al. 1982).

Results obtained by Koo et al. (1991) indicate that low to moderate lead exposure (average lifetime PbB between 4.9 and 23.6 µg/dL, geometric mean, 9.8 µg/dL) of young children (n=105) with adequate nutritional status, particularly with respect to calcium, phosphorus, and vitamin D, had no effect on vitamin D metabolism, calcium and phosphorus homeostasis, or bone mineral content. The authors attributed the difference in results from those other studies to the fact that the children in their study had lower PbB (only 5 children had PbB >60 µg/dL and all 105 children had average lifetime PbB <45 µg/dL at the time of assessment) and had adequate dietary intakes of calcium, phosphorus, and vitamin D. They concluded that the effects of lead on vitamin D metabolism observed in previous studies may only be apparent in children with chronic nutritional deficiency and chronically elevated PbB. Similar conclusions were reached by IPCS (1995) after review of the epidemiological data.

In general, data in animals support the findings in humans. For example, depression of plasma levels of 1,25-dihydroxyvitamin D was observed in rats fed 0.82% lead in the diet as lead acetate for 7–14 days (Smith et al. 1981). High calcium diets protected against this effect. An additional finding was that lead blocked the intestinal calcium transport response to exogenous 1,25-dihydroxyvitamin D, but had no effect on bone response to the vitamin D hormone. Although the lead exposure and resulting PbB (≥ 174 µg/dL) were high in this study, the results provide support for the disturbances in vitamin D metabolism observed in children exposed to high levels of lead.

3.2.3 Immunological and Lymphoreticular Effects

Numerous studies have examined the effects of lead exposure on immunological parameters in lead workers and a smaller number of studies provide information on effects in members of the general population, including children. The results although mixed, give some indication that lead may have an effect on the cellular component of the immune system, while the humoral component is relatively unaffected. However, it should be noted that the clinical significance of these relationships is as yet unknown.

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Workers exposed occupationally for 4–30 years, and whose PbB at the time of testing ranged from 25 to 53 µg/dL (mean, 38.4 µg/dL), had serum concentrations of IgG, IgA, and IgM not significantly different from unexposed controls whose PbB at the time of testing ranged from 8 to 17 µg/dL (mean, 11.8 µg/dL) (Kimber et al. 1986). Alomran and Shleamoon (1988) also reported nonsignificant alterations in serum IgG and IgA levels in 39 workers exposed to lead oxides with a mean PbB of 64 µg/dL compared to 19 unexposed subjects (PbB not provided). Another study found no alterations in serum IgA and IgM levels among 25 workers with a mean PbB of 74.8 µg/dL (range, 38–100 µg/dL) compared to 16.7 µg/dL (range, 11–30 µg/dL) among 25 controls; however, IgG was significantly reduced among the workers (Basaran and Ündeger 2000; Ündeger et al. 1996). A study of 145 lead-exposed male workers from a large secondary lead smelter in the United States with a median PbB of 39 µg/dL (range, 25–55 µg/dL) also found no significant differences in serum immunoglobulin levels between the workers and a group of 84 unexposed workers with a mean PbB of <2 µg/dL (range, 2–12 µg/dL) (Pinkerton et al. 1998). Ewers et al. (1982) reported that lead workers with PbB of 21–90 µg/dL (median, 59 µg/dL) had more colds and influenza infections per year and had a significant suppression of serum IgM levels relative to a comparison group (median PbB, 11.7 µg/dL); neither serum IgA or IgG levels in workers were significantly different than in the comparison group. However, salivary IgA levels were significantly lower in the workers than in the control group. Secretory IgA is a major factor in the defense against respiratory and gastrointestinal infections (Koller 1985). A study of 606 Korean workers found that mean serum IgE levels were positively related to PbB in the range of <10–≥30 µg/dL (Heo et al. 2004).

Alterations in response to T-cell mitogens also have been reported in lead workers. Mishra et al. (2003) studied three groups of workers (n=84) who had mean PbBs of 6.5, 17.8, and 128 µg/dL and found that lymphocyte proliferation to phytohemagglutinin (PHA) was inhibited relative to a control group; natural killer (NK) cell activity was unaffected. The lymphocytes from the workers studied by Alomran and Shleamoon (1988) (mean PbB, 64 µg/dL) also were significantly less responsive to stimulation by PHA and concanavalin A (con A) than those from the controls (PbB not provided), and the severity of the depression was related to the duration of exposure. Impaired response to T-cell mitogens was also reported among a group of 51 firearm instructors (Fischbein et al. 1993). Fifteen of the 51 firearm instructors had PbBs ≥25 µg/dL (mean 31.4 µg/dL), whereas the rest had a mean PbB of 14.6 µg/dL. In contrast, Kimber et al. (1986) reported that responses to PHA and NK cell activity were not altered in their study of workers whose mean PbB was 34.8 µg/dL, compared with an unexposed group with a mean PbB of 11.8 µg/dL. Pinkerton et al. (1998) found no alterations in lymphoproliferative responses to tetanus toxoid or in NK cell activity in workers with a median PbB of 39 µg/dL. It should be noted,

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however, that firearm instructors are likely to be exposed to a number of metal haptens, such as nickel and antimony.

Changes in T-cell subpopulations also have been reported. Ündeger et al. (1996) and Basaran and Ündeger (2000) described a significant decrease in the number of CD4⁺ cells and C3 and C4 complement levels in workers with a mean PbB of 74.8 µg/dL. A significant decrease in percentage and number of CD3⁺ and CD4⁺ cells also was observed in the study of firearm instructors, but other cell types including CD8⁺, B-lymphocytes, or NK cells were not significantly altered relative to controls (Fischbein et al. 1993). Pinkerton et al. (1998) found no significant differences in the percentages of CD3⁺ cells, CD4⁺ T cells, CD8⁺ T cells, B cells, or NK cells between exposed and unexposed workers, but reported that the percentage and number of CD4⁺/CD45RA⁺ cells was positively associated with cumulative lead exposure. A study of 71 male workers engaged in the manufacturing of lead stearate who had a mean PbB of 19 µg/dL (range, 7–50 µg/dL) did not find significant differences in the number or percentages of CD4⁺ or CD3⁺ cells between the lead-exposed workers and a control group (PbB not measured) of 28 workers with no known occupational exposure to lead (Sata et al. 1998). However, the exposed workers had a significant reduction in the number of CD3⁺CD45RO⁺ (memory T) cells and a significant increase in the percentage of CD8⁺ cells compared to controls. Also, there was a significant correlation between the percentage of CD3⁺CD45RA⁺ cells and PbBs in the exposed workers. At the time of the study, no subject had any signs or symptoms indicative of infection.

A small study of 10 occupationally-exposed workers whose mean PbB was 33 µg/dL reported that chemotaxis of polymorphonuclear leukocytes (PMN), stimulated through a specific membrane receptor, was impaired, compared to a group of 10 unexposed subjects with a mean PbB of 12.6 µg/dL (Valentino et al. 1991). The investigators suggested that the reduction of chemotaxis might be partially due to a lead-related modification of plasma membrane lipids, because PMN locomotion is influenced by fatty acids.

The data available on the immunologic effects of lead exposure on children are sparse. In a comparison of 12 preschool children having a mean PbB of 45.3 µg/dL (range, 41–51 µg/dL) and elevated FEP with 7 preschool children with a mean PbB of 22.6 µg/dL (range, 14–30 µg/dL), it was found that there were no differences between groups with respect to complement levels, immunoglobulin levels (IgM, IgG, IgA), or antitoxoid titers following booster immunization with tetanus toxoid (Reigart and Graher 1976). The small number of children and the relatively high PbB of the control group, as judged by current views, limit the conclusions that can be drawn from this report. Lutz et al. (1999) conducted a survey of the immune system's function in a cohort of 279 children aged 9 months to 6 years, with PbB ranging

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from 1 to 45 µg/dL. Exposure was due primarily to lead-based paint. Of the comprehensive number of parameters of cellular and humoral immunity evaluated, only the serum IgE levels showed a statistically significant relationship with PbB, as PbB increased so did IgE levels. Variables controlled for in this study included age, race, gender, nutrition, and socioeconomic level. The assessment of IgE levels in this and other studies is important because IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma. Some investigators have suggested that lead may be a risk factor for childhood asthma (Dietert et al. 2002), although recently, Joseph et al. (2005) conducted a study of 4,634 children screened for lead from 1995 to 1998 and found that PbB was less a predictor of asthma than was race and did not affect the relationship of race to prevalent or incident asthma. IgE levels were not monitored in the study.

A study of Chinese children (3–6 years old) also examined the association between PbB and serum IgG, IgM, and IgE levels (Sun et al. 2003). The cohort consisted of 38 children with PbB ≥ 10 µg/dL (high-lead group) and 35 children with PbB < 10 µg/dL (controls). No significant association between immunoglobulins and PbB was found for the entire group (n=73). However, when the cohort was divided by sex, IgG and IgM were significantly lower and IgE was significantly higher in high-dose females (n=16) than in control females (n=17); no such relationship was seen among males. A study of 374 French mother-infant pairs reported a significant correlation ($p < 0.001$) between infant hair level and cord blood IgE levels (Annesi-Maesano et al. 2003). In this cohort, mean PbB was relatively high, 96 µg/dL (SD, 58 µg/dL) in the mothers and 67 µg/dL (SD, 48 µg/dL) in cord blood. No significant association was found between placental lead level or cord PbB and IgE levels. Further suggestive evidence for an association between IgE and lead burden is provided by a study of 331 German children (7–8 years of age) with a geometric mean PbB of 2.7 µg/dL, which found a significant association ($p < 0.05$) between PbB and increased serum IgE levels (Karmaus et al. 2005). Analysis of stratified data showed that the highest IgE levels were observed in the children with PbB in the range between 2.8–3.4 and > 3.4 µg/dL. No significant associations were seen between PbB and serum levels of IgA, IgG, or IgM (Karmaus et al. 2005).

A small study of 70 Chinese children (3–6 years old) reported that 35 of them with a mean PbB of 14.1 µg/dL (SD, 4.0 µg/dL) had a significantly lower ($p < 0.01$) serum levels of CD4⁺ cells than 35 children with a mean PbB of 6.4 µg/dL (SD, 1.3 µg/dL) (Li et al. 2005). There were no significant differences between the two groups regarding B, CD3⁺, CD8⁺, or NK cells. Sarasua et al. (2000) conducted a much bigger study of 2,041 children and adults who lived in areas with elevated soil levels of cadmium and lead (n=1,561) or in comparison communities (n=480) in the United States. Mean blood

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lead levels were 7 µg/dL for participants aged 6–35 months; 6 µg/dL for participants aged 36–71 months; 4 µg/dL for participants aged 6–15 years, and 4.3 µg/dL for participants aged 16–75 years. Parameters monitored included IgA, IgG, and IgM, and peripheral blood lymphocyte phenotypes (T cells B cells, NK cells, and CD4/CD8 subsets). The results of the multivariate analyses showed no significant differences in any of the immune marker distributions attributed to lead for subjects over 3 years of age. However, in children under 3 years, there were small but significant associations between increased PbB, particularly in those over 15 µg/dL, and increases in IgA, IgG, IgM, and circulating B-lymphocytes.

Many studies have been published on the effects of lead on immune parameters in animals. Developing organisms appear to be more sensitive than adult animals and a number of studies have been designed to determine critical windows of vulnerability during development, including fetal development. Studies conducted in the late 1970s showed that prenatal and postnatal exposure of rats to lead leading to a PbB of approximately 29 µg/dL induced several alterations in the offspring tested at 35–45 days of age, including depression of antibody responses to sheep red blood cells, decreased serum IgG (but not IgA or IgM) levels, decreased lymphocyte responsiveness to mitogen stimulation, impaired DTH, and decreased thymus weights as compared with controls (Faith et al. 1979; Luster et al. 1978). In a later study, exposure of mice to lead through gestation and lactation resulted in reduced humoral immunity in the pups tested at 8 weeks of age (Talcott and Koller 1983). The DTH response was reduced but the difference with controls was not statistically significant. Blood lead levels were not available in this study. Miller et al. (1998) compared responses of the immune system between fetal and adult exposures. Exposure of pregnant rats to lead acetate in the drinking water during breeding and pregnancy resulted in PbBs of up to 112.0 µg/dL during pregnancy and lactation. Immune function was assessed in the offspring at 13 weeks of age and in the dams at 7–8 weeks postpartum. At these times, PbB was approximately 12 µg/dL in the dams and 0.68–2.63 µg/dL in offspring. Results from a comprehensive battery of tests showed no significant effects in lead-exposed dams. However, alterations were observed in the offspring and included decreased DTH response, altered cytokine production, and elevated serum IgE. Also, total leukocyte counts were significantly decreased, but analyses of subpopulation distribution revealed no significant treatment-related effects. These findings indicate that exposure *in utero* may result in alterations in immune parameters that persist beyond the exposure period when PbB had returned to the normal range. Similar results were reported in a study in mice in which immunotoxic changes were found at PbB <20 µg/dL (Snyder et al. 2000). Altered DTH responses were seen in adult mice at PbBs of 87 µg/dL but not 49 µg/dL (McCabe et al. 1999) providing further evidence of increased sensitivity in developing animals compared to adults. More recent studies by Dietert and coworkers have shown that gestational exposure to lead resulting in PbB of approximately 38 µg/dL has a greater immunotoxic effect

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in female offspring than in male offspring (Bunn et al. 2001a) and that the embryo is more sensitive if exposure occurs late in gestation (gestation day [Gd] 15–21) than earlier during gestation (Gd 3–9) (Bunn et al. 2001b).

While many responses of the immune system observed in humans can be reproduced in experimental animals, recent observations from studies of perinatal exposure of animals suggest that caution should be exercised when extrapolating from animals to humans, since the immune functions depend on animal species, gender, and specially, developmental stage.

3.2.4 Neurological Effects

Neurological Effects in Adults. The most severe neurological effect of lead in adults is lead encephalopathy, which is a general term to describe various diseases that affect brain function. Early symptoms that may develop within weeks of initial exposure include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death (Kumar et al. 1987). Histopathological findings in fatal cases of lead encephalopathy in adults are similar to those in children.

Severe lead encephalopathy is generally not observed in adults except at extremely high PbBs (e.g., 460 µg/dL [Kehoe 1961]). Other data (Smith et al. 1938) suggest that acute lead poisoning, including severe gastrointestinal symptoms and/or signs of encephalopathy, can occur in some adults at PbBs that range from approximately 50 to >300 µg/dL, but the data are somewhat ambiguous.

Neurobehavioral Effects in Adults. Occupational exposure to lead has often been associated with signs of neurotoxicity. The literature contains numerous case reports and small cohort studies that describe a higher incidence of these symptoms, including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia at PbBs that range from approximately 40 to 120 µg/dL following acute-, intermediate-, and chronic-duration occupational exposure (Awad El Karim et al. 1986; Baker et al. 1979, 1983; Campara et al. 1984; Haenninen et al. 1979; Holness and Nethercott 1988; Lucchini et al. 2000; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Pasternak et al. 1989; Pollock and Ibels 1986; Rosenman et al. 2003; Schneitzer et al. 1990; Zimmerman-Tanselia et al. 1983).

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In addition to the findings mentioned above, numerous studies have reported neuropsychological effects in lead workers. PbB in these studies ranged between 40 and 80 µg/dL. For instance, Parkinson et al. (1986) reported that lead workers exhibited greater levels of conflict in interpersonal relationships compared with unexposed workers. In another study, lead workers (45–60 µg/dL) performed much worse than workers with lower PbB on neurobehavioral tests, with general performance on cognitive and visual-motor coordination tasks and verbal reasoning ability most markedly impaired (Campara et al. 1984). Disturbances in oculomotor function (saccadic eye movements) in lead workers with mean PbB of 57–61 µg/dL were reported in a study by Baloh et al. (1979) and a follow-up by Spivey et al. (1980), and in a study by Glickman et al. (1984). Deficits in hand-eye coordination and reaction time were reported in 190 lead-exposed workers (mean PbB, 60.5 µg/dL) (NIOSH 1974). Most of the workers had been exposed between 5 and 20 years. A similar study, however, reported no differences in arousal, reaction time, or grip strength between a reference group (mean PbB, 28 µg/dL) and workers who had been exposed to lead for 12±9.5 years (mean PbB, 61 µg/dL) (Milburn et al. 1976); however, the relatively high mean PbB in the referents may have obscured the results. Disturbances in reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, nervousness, mood, or coping ability were observed in lead workers with PbBs of 50–80 µg/dL (Arnvig et al. 1980; Haenninen et al. 1978; Hogstedt et al. 1983; Mantere et al. 1982; Valciukas et al. 1978). Baker et al. (1983) reported impaired verbal concept formation, memory, and visual/motor performance among workers with PbB >40 µg/dL. Similar findings were reported in a cohort of 43 Venezuelan workers from a lead smelter who had a mean-employment duration of 4 years and a mean PbB of 42 µg/dL (Maizlish et al. 1995). The authors observed a significant association between altered mood states and current, peak, and time-weighted average (TWA) blood lead levels. Other parameters such as memory, perceptual speed, reaction time, and manual dexterity tended to be poorer with increasing exposure, but the magnitude of the effect was small.

A study of 91 workers divided into three groups based on PbBs (<20, 21–40, and 41–80 µg/dL) noted that workers with high PbB concentrations showed evidence of impairment on tests of serial reaction time and category search, with only weak impairment on tasks measuring syntactic reasoning and delayed verbal free recall (Stollery et al. 1989, 1991). In general, the magnitude of the impairment correlated with PbB. The impairment of serial reaction time was the best predictor of PbB. The main deficit was a slowing of sensory motor reaction time, which was seen most clearly when the cognitive demands of the task were low. The response tended to be restricted to workers in the high PbB level group. A subsequent study of 70 workers showed that lead impaired both the speed of making simple movements, as well as decisions, and suggested that decision slowing is due to central rather than peripheral factors (Stollery 1996). A

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study of 427 Canadian lead workers whose mean current PbB was 27.5 µg/dL, and mean duration of employment was 17.7 years examined the correlation between short- and long-term measures of exposure to lead and performance on neuropsychological tests (Lindgren et al. 1996). Tasks that tested primarily visuomotor skills were significantly associated with a cumulative dose-estimate. Lindgren et al. (1996) indicated that the lack of an association between current blood lead or a TWA and neuropsychological performance was not necessarily inconsistent with other studies that found such an association since in their study the current mean PbBs were lower than in other studies. Current PbB as well as a TWA may have lacked the sensitivity to detect the decrement in performance.

Ehle and McKee (1990) reviewed the methodology and conclusions of 14 published reports to determine if any consensus regarding neurobehavioral effects of low-level lead exposure in adults could be reached. A PbB of 60 µg/dL was set as the upper limit of exposure. The investigators concluded that “the methodologies in the studies reviewed were so varied and the cultures in which the studies were conducted so diverse that it is impossible to generalize across findings.” However, Ehle and McKee (1990) found some evidence that increased irritability and fatigue may lead to interpersonal problems. They also found suggestive evidence for subtle changes in the ability to process information quickly and for impaired ability to input and integrate novel information and to store this information in short-term memory. Balbus-Kornfeld et al. (1995) reviewed 21 studies for evidence that cumulative exposure to lead is associated with decreased performance in neurobehavioral tests in adults. Only three studies used a measure of cumulative exposure and two others used duration of exposure as a surrogate for cumulative exposure. The conclusion of the analysis was that “the current (at the time of the Balbus-Kornfeld study) scientific literature provides inadequate evidence to conclude whether or not cumulative exposure to or absorption of lead adversely affects performance in neurobehavioral tests in adults.”

More recent studies of lead workers have reported significant associations between longitudinal decrements in cognitive function and past high PbB (Bleecker et al. 2005; Chen et al. 2005; Hänninen et al. 1998; Lindgren et al. 2003) and past high tibial lead (Schwartz et al. 2000b; Stewart et al. 1999). In the Lindgren et al. (2003) study, results of five neuropsychological measures showed that verbal memory was significantly better in a group with past high exposure followed by lower exposure than in a group with continuous high exposure, suggesting that reversibility of function may occur when PbB is maintained below 40 µg/dL. A small study of 27 Chinese lead workers also reported improvement in neurobehavioral performance over a period of 4 years during which the mean PbB was reduced from 26 to 8 µg/dL (Chuang et al. 2005). From a battery of 10 neurobehavioral tests, finger tapping, pattern comparison reaction time, and memory (visual patterns) significantly improved during the study period.

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Past high tibia lead (mean peak was 24 ppm), as a measure of cumulative lead dose, also was found significantly related to smaller total brain volume, frontal and total gray matter volume, and parietal white matter volume in 532 former organolead workers (Stewart et al. 2006). Of nine smaller regions of interest, higher tibia lead was associated with reduced volume of the cingulate gyrus and insula. Changes in brain morphology were assessed by brain MRI. Potential confounders assessed were age, systolic and diastolic blood pressure, smoking history, ApoE genotype, education, alcohol consumption, depression status, and race. Previous studies of this cohort had found tibia lead associated with a decline in cognitive function (Schwartz et al. 2000b; Stewart et al. 1999).

Lucchini et al. (2000) reported that in a group of 66 workers with a mean current PbB of 27 $\mu\text{g/dL}$ (range, 6–61 $\mu\text{g/dL}$) and exposure of 11 years, current, but not cumulative, exposure was associated with impaired visual contrast sensitivity; results from neurobehavioral tests were unaffected. Barth et al. (2002) also found in a group of 47 workers a significant correlation between current exposure (mean PbB, 31 $\mu\text{g/dL}$, range, 11–62 $\mu\text{g/dL}$) and cognitive deficits, particularly visuo-spatial abilities and executive functions related to the prefrontal cortex; however, no correlation was found between cumulative exposure measures and cognitive parameters. Recently, Schwartz et al. (2005) reported on a longitudinal study of the effects of lead on neurobehavioral test scores using both PbB and tibia lead as measures of dose. The cohort comprised 576 former and current lead workers who were evaluated from 1997 to 2001. At baseline (Schwartz et al. 2001), mean PbB was 32 $\mu\text{g/dL}$ ($\text{SD}\pm 15$ $\mu\text{g/dL}$) and mean tibia lead was 37 ppm ($\text{SD}\pm 40$ ppm). In the recent publication, the investigators developed regression models that separated recent from cumulative dose, acute from chronic effects, and cross-sectional from longitudinal relations. The results showed consistent associations of both PbB and tibia lead with current neurobehavioral test scores and also with declines in test scores over time; the associations with PbB were stronger than those with tibia lead. The stronger associations were mainly in executive abilities, manual dexterity, and peripheral vibration threshold; the magnitude across an interquartile range of exposure was equivalent to 1–5 years of aging. Schwartz et al. (2005) pointed out that: “the significant measurement error, especially for tibia lead and change measures, and the relatively short follow-up interval, could obscure the relations between lead dose and changes in test scores” and that this knowledge must be factored into their inferences about the likely health effects.

Meyer-Baron and Seeber (2000) did a meta-analysis to determine the size of performance effects caused by exposure to inorganic lead that translated into PbBs <70 $\mu\text{g/dL}$. A total of 22 studies that met some minimum requirements were considered, and of these, 12 studies provided data to analyze the results of 13 tests. The mean PbB in the lead workers ranged from 31 to 52 $\mu\text{g/dL}$ and those of the controls ranged

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from 6 to 20 $\mu\text{g}/\text{dL}$. Statistically significant effects were observed for the Block Design, Logical Memory, and Santa Ana (dominant hand) tests. The first two tests indicate impairments of central information processing, particularly for the functions visuo-spatial organization and short-term verbal memory; Santa Ana tests manual dexterity. Meyer-Baron and Seeber (2000) stated that the extent of decreased performance was comparable to changes of performance that can be expected during aging of up to 20 years. Goodman et al. (2002) conducted a meta-analysis of 22 studies that met inclusion criteria. The PbB among the study subjects ranged from 24 to 63 $\mu\text{g}/\text{dL}$ for exposed and from 0 to 28 $\mu\text{g}/\text{dL}$ for unexposed workers. Only 2 tests (Digit Symbol and D2) out of 22 neurobehavioral tests analyzed showed a significant effect between exposed and unexposed workers. Digit Symbol evaluated motor persistence, sustained attention, response-speed, and visuo-motor coordination, whereas D2 requires visual selectivity at a fast speed on a repetitive motor response task. The tests that were found altered in the Meyer-Baron and Seeber (2000) study were not significantly affected in the analysis of Goodman et al. (2002). The latter investigators concluded that the available data are inconclusive and unable to provide adequate information on the neurobehavioral effects of moderate PbB.

In summary, in studies where adults were exposed occupationally to lead, a number of neurobehavioral parameters were reportedly affected. Although as Goodman et al. (2002) pointed out, the lack of true measures of pre-morbid state, observer bias, and publication bias affect the overall assessment, the preponderance of the evidence indicates that lead is associated with neurobehavioral impairment in adult workers at PbBs below 70 $\mu\text{g}/\text{dL}$.

Krieg et al. (2005) used data from the NHANES III to assess the relationship between PbB in adults and performance on the three computerized neurobehavioral tests included in the survey: simple reaction time, symbol-digit substitution, and serial-digit learning. The age of the participants ranged from 20 to 59 years old and a total of 4,937 completed all three tests. The study also evaluated 26 previously published cross-sectional occupational studies conducted in various countries that used the same neurobehavioral tests included in the survey. Potential confounders evaluated in the analysis included sex, age, education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase. In the NHANES III, the PbB of those taking the neurobehavioral tests ranged from 0.7 to 42 $\mu\text{g}/\text{dL}$ and the geometric and arithmetic means were 2.5 and 3.3 $\mu\text{g}/\text{dL}$, respectively. The results showed no statistically significant relationships between PbB and neurobehavioral test performance after adjustment for confounders. In the occupational studies, the mean PbB in the controls was 11.4 $\mu\text{g}/\text{dL}$ (range, 3.7–20.4 $\mu\text{g}/\text{dL}$), whereas the mean in the exposed groups was 41.1 $\mu\text{g}/\text{dL}$ (range, 24.0–72 $\mu\text{g}/\text{dL}$). The groups exposed to lead in the occupational studies consistently

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performed worse than control groups on the simple reaction time and digit-symbol substitution tests. Some possible explanations for the lack of association between PbB and neurobehavioral scores in the survey mentioned by Krieg et al. (2005) include lack of toxicity of lead in adults at the levels investigated, a sample size or study design that did not allow enough precision to detect a relationship, or neurobehavioral tests that are not sensitive to the toxicity of lead at the levels investigated.

The effects of lead exposure on neurobehavioral parameters in nonoccupational cohorts of older persons also have been evaluated. Muldoon et al. (1996) conducted a wide range of cognitive tests designed to assess memory, language, visuo-spatial ability, and general intellectual status, as well as sensorimotor function in a group of 530 female participants in the Study of Osteoporotic Fractures. The cohort consisted of 325 rural dwellers and 205 urban dwellers with geometric mean PbB of 4.5 µg/dL and 5.4 µg/dL, respectively; the overall range was 1–21 µg/dL. The corresponding mean ages were 71.1 and 69.4 years. For the group, the scores on the various tests were average, consistent with normal values reported for older women. PbB showed a significant inverse association with performance only among the rural dwellers. After adjusting for age, education, and tobacco and alcohol consumption, women with PbB ≥ 8 µg/dL performed significantly worse in tests of psychomotor speed, manual dexterity, sustained attention, and mental flexibility than women with PbB ≤ 3 µg/dL. Similar results were found for reaction time tests after further adjusting for history of diabetes and/or arthritis. A similar study was conducted in a cohort of 141 men participants in the Normative Aging Study (Payton et al. 1998). In this study, in addition to PbBs, lead in bone (tibia and patella) was also measured. The mean PbB among the participants was 5.5 µg/dL (range not provided), and the mean age was 66.8 years. Tibial and patellar bone lead showed a stronger correlation with each other than either of them with blood lead. After adjusting for age and education, the results showed that men with higher PbB recalled and defined fewer words, identified fewer line-drawn objects, and required more time to attain the same level of accuracy on a perceptual comparison test as men with the lowest level of PbB. In addition, men with higher blood and tibial lead copied spatial figures less accurately, and men with higher tibial lead had slower response for pattern memory. The results showed that PbB was the strongest predictor of performance on most tests. Also of interest was the finding that lead in the tibia, which changes at a slower rate, showed more significant relationships with cognitive test scores than patellar bone lead, which changes more rapidly.

A more recent study of 526 participants of the Normative Aging Study with a mean age of 67.1 years and mean PbB of 6.3 µg/dL reported that patellar lead was significantly associated with psychiatric symptoms such as anxiety, depression, and phobic anxiety (Rhodes et al. 2003). In an additional study of Normative Aging Study participants (mean PbB, 4.5 µg/dL; mean patella Pb, 29.5 ppm), it was found that both bone

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and blood lead were associated with poor test performance (Weisskopf et al. 2004; Wright et al. 2003c). According to the investigators, these findings are consistent with the theory that bone lead chronically remobilizes into blood, thus accelerating cognitive decline. In yet an additional study, Shih et al. (2006) reported that in a group of 985 of sociodemographically diverse urban-dwelling adults in the United States (mean age, 59.4 years) higher tibia lead levels were consistently associated with worse performance in tests of cognitive function after adjusting for confounders; no such association was found with PbB. Mean tibia lead was 18.7 ppm (SD±11.2 ppm) and mean PbB was 3.5 µg/dL (SD±2.2 µg/dL). An increase in one interquantil range of tibia lead was equivalent to 2.2–6.1 more years of age across the tests conducted, the average tibia lead effects was 36% of the age effect. Shih et al. (2006) suggested that, in the population studied, a proportion of what was termed normal age-related decrements in cognitive function may be attributable to neurotoxicants such as lead.

Peripheral Physiological Effects in Adults. There are numerous studies available on peripheral nerve function that measured the conduction velocity of electrically stimulated nerves in the arm or leg of lead workers. Representative studies are summarized below. A prospective occupational study found decreased nerve conduction velocities (NCVs) in the median (motor and sensory) and ulnar (motor and sensory) nerves of newly employed high-exposure workers after 1 year of exposure and in the motor nerve conduction velocity of the median nerve of this group after 2 or 4 years of exposure (Seppalainen et al. 1983); PbBs ranged from 30 to 48 µg/dL. Although the severity of the effects on NCV appeared to lessen with continued exposure, several of the high-exposure workers in this study quit 1 or 2 years after starting. Thus, the apparent improvement in NCVs may have been due to a healthy worker effect. A similar healthy worker effect may have accounted for the negative results of Spivey et al. (1980) who tested ulnar (motor and slow fiber) and peroneal (motor) nerves in 55 workers exposed for 1 year or more and whose PbBs ranged from 60 to 80 µg/dL. The studies differed in design; one prospectively obtained exposure history, while the other did it retrospectively. The end points that were measured also differed; Spivey et al. (1980) did not test the median nerve, which was the most sensitive end point in the study by Seppalainen et al. (1983). Ishida et al. (1996) found no significant association between PbBs of 2.1–69.5 µg/dL and median nerve conduction velocity among a group of 58 male and 70 female ceramic painters.

In cross-sectional occupational studies, significant decreases in NCVs were observed in fibular (motor) and sural (sensory) nerves as a function of PbB with duration of exposure showing no effect (Rosen and Chesney 1983). In another study, decreases in NCVs of ulnar (sensory, distal) and median (motor) nerves were seen primarily at PbBs >70 µg/dL (Triebig et al. 1984). Duration of exposure and number of lead-

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exposed workers in these two studies were 0.5–28 years and 15 workers (Rosen and Chesney 1983), and 1–28 years and 133 workers (Triebig et al. 1984). Results of an earlier study by Araki et al. (1980) suggest that the decrease in NCV is probably due to lead since median (motor) NCVs in workers with a mean PbB of 48.3 µg/dL were improved significantly when PbB was lowered through CaNa₂EDTA chelation therapy. A study by Muijser et al. (1987) presented evidence of improvement of motor NCV after cessation of exposure. After a 5-month exposure, the PbB was 82.5 µg/dL and decreased to 29 µg/dL 15 months after the termination of exposure, at which time, NCVs were not different from a control group.

The results of these studies indicate that NCV effects occur in adults at PbBs <70 µg/dL, and possibly as low as 30 µg/dL. Ehle (1986), in reviewing many of the studies of NCV effects, concluded that a mild slowing of certain motor and sensory NCVs may occur at PbBs <60 µg/dL, but that the majority of studies did not find correlations between PbB and NCV below 70 µg/dL and that slowing of NCV is neither a clinical nor a subclinical manifestation of lead neuropathy in humans. Other reviewers have pointed out that decreases in NCV are slight in peripheral neuropathies (such as that induced by lead) that involve axonal degeneration (Le Quesne 1987), and that although changes in conduction velocity usually indicate neurotoxicity, considerable nerve damage can occur without an effect on conduction velocity (Anderson 1987). EPA (1986a) noted that although many of the observed changes in NCV may fall within the range of normal variation, the effects represent departures from normal neurological functioning. NCV effects are seen consistently across studies and although the effects may not be clinically significant for an individual, they are significant when viewed on a population basis. This is further supported by the meta-analysis of 32 studies of effects of lead exposure on NCV (Davis and Svendsgaard 1990).

More recent studies also have produced mixed results. Chia et al. (1996a) measured NCV in a group of 72 male workers from a lead battery-manufacturing factory and 82 unexposed referents. Measurements of NCV in the median and ulnar nerves, as well as of PbB were performed every 6 months over a 3-year period. The geometric mean PbB for the exposed workers at the beginning of the study was 36.9 µg/dL compared to 10.5 µg/dL for the referents. Baseline measurements revealed significant slower NCV in workers, mostly in the median nerve. Serial measurements in the exposed workers over the 3-year period showed a peak in PbB in the third test which was followed by a decrease in median sensory conduction velocity and ulnar sensory nerve conduction velocity in the fourth test. Evaluation at the end of the study of 28 workers who completed the 3-year period showed significant associations between PbB and five out

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of the eight parameters measured. The same was observed when only workers with PbB ≥ 40 $\mu\text{g/dL}$ were included in the analysis, but no significant association was found among workers with PbB < 40 $\mu\text{g/dL}$.

Yeh et al. (1995) evaluated nerve conduction velocity and electromyographic (EMG) activity in a group of 31 workers from a battery recycling factory and 31 sex- and age-matched controls. The mean duration of exposure to lead was 30.4 months and the mean PbB was 63 $\mu\text{g/dL}$ (range, 17–186 $\mu\text{g/dL}$); PbB was not measured in the control group. Eighty percent of the workers ($n=25$) had extensor weakness of the distal upper limbs and six of these workers had weakness in dorsiflexion of the foot; data for the control group were not provided. These 25 workers were classified as the lead neuropathy subgroup and the remaining 6 as the lead exposure subgroup. Studies of motor nerve conduction experiments showed a significantly increased distal latency in the median nerve from exposed workers relative to controls, but no such effect was seen in the ulnar, peroneal, and tibial nerves. Studies of sensory nerve conduction did not reveal any significant differences between exposed and control workers. Ninety-four percent of the exposed workers had abnormal EMG, but no mention was made regarding the control group. After controlling for age and sex, the authors found a significant positive association between an index of cumulative exposure to lead (ICL) and the distal motor latencies of tibial nerves and significant negative association between ICL and the NCVs of sural nerves. No correlation was found between current PbB or duration of exposure and neurophysiological data. Taken together, the data available suggest that in lead workers slowing of NCV starts at a mean PbB of 30–40 $\mu\text{g/dL}$.

Other Physiological Effects in Adults. Studies also have shown that exposure to lead affects postural balance. For example, Chia et al. (1996b) evaluated the possible association between postural sway parameters and current PbB, cumulative PbB at different years of exposure, and an index of total cumulative exposure to lead in a group of 60 workers; 60 unexposed subjects served as a control group. The current mean PbB was 36 $\mu\text{g/dL}$ (range, 6.4–64.5 $\mu\text{g/dL}$) among the workers and 6.3 $\mu\text{g/dL}$ (range, 3.1–10.9 $\mu\text{g/dL}$) among the referents. Exposed and referents differed significantly in postural sway parameters when the tests were conducted with the eyes closed, but not with the eyes open. Although the postural sway parameters were not significantly correlated with current PbB or with total cumulative lead exposure, a significant correlation existed with exposure during the 2 years prior to testing. The authors speculated that the lack of correlation between postural sway and cumulative lead exposure could be due to underestimation of cumulative exposure and/or to the effects of lead being reversible. A similar study of 49 male lead workers employed at a chemical factory producing lead stearate found that an increase in postural sway with the eyes open in the anterior-posterior direction observed in exposed workers was related to current PbB (mean, 18 $\mu\text{g/dL}$) (Yokoyama et al. 1997). Also, an increase in sway with the eyes

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closed in the right-left direction was significantly related to the mean PbB in the past. According to Yokoyama et al. (1997), the change in the vestibulo-cerebellum seemed to reflect current lead absorption, whereas the change in the anterior cerebellar lobe reflected past lead absorption. Changes in postural balance observed in a group of 29 female lead workers with a mean PbB of 55.7 µg/dL in a more recent study from the same group of investigators led them to suggest that lead affects the anterior cerebellar lobe, and the vestibulo-cerebellar and spinocerebellar afferent systems (Yokoyama et al. 2002). Other studies also have reported decreased postural stability in lead workers (Dick et al. 1999; Iwata et al. 2005; Ratzon et al. 2000), but whether the alterations are associated with current measures of exposure or measures of cumulative exposure remains to be elucidated.

The effect of lead exposure on somatosensory evoked potentials has been evaluated in numerous studies of lead workers. Comprehensive reviews on this topic are available (Araki et al. 2000; Otto and Fox 1993). For example, delayed latencies of visual evoked potentials have been reported in several studies of lead workers with PbB of approximately 40 µg/dL (Abbate et al. 1995; Araki et al. 1987; Hirata and Kosaka 1993). In contrast, no significant association was found between exposure to lead and the latencies of visual and brainstem auditory evoked potentials in a group of 36 female glass workers with a mean PbB of 56 µg/dL and mean exposure duration of 7.8 years (Murata et al. 1995). Also, in a similar study of 29 female lead workers with a mean PbB of 55.7 µg/dL (range, 26–79 µg/dL) and a mean employment duration of 7.9 years in a glass factory, Yokoyama et al. (2002) reported no significant differences in the latencies of brain auditory evoked potentials (BAEP) between the workers and 14 control workers (mean PbB, 6.1 µg/dL). Counter and Buchanan (2002) reported delayed wave latencies consistent with sensory-neural hearing impairment in adults with chronic exposure to lead through ceramic-glazing work and with mean PbB of 47 µg/dL, and suggested that this finding may be attributable to occupational noise exposure in combination with lead intoxication. Bleecker et al. (2003) found dose-dependent alterations in BAEP among lead workers with a mean PbB of 28 µg/dL and a mean-employment duration of 17 years. Analysis of the results led them to suggest that current lead exposure preferentially affected conduction in the distal auditory nerve while chronic lead exposure appeared to impair conduction in the auditory nerve and the auditory pathways in the lower brainstem.

An additional parameter that has been studied in lead-exposed workers is the electrocardiographic R-R interval variability, a measure of peripheral autonomic function. R-R interval variability was significantly depressed in a group of 36 female glass workers compared to a group of 17 referents with no known occupational exposure to lead (Murata et al. 1995). The mean PbB was 55.6 µg/dL and the mean exposure duration was 7.8 years. However, Gennart et al. (1992a) found no association between exposure

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and R-R interval variations in the electrocardiogram. The study group consisted of 98 workers from a lead acid battery factory (exposure group) and 85 people who had no occupation exposure to lead (reference group). The mean duration of occupational exposure was 10.6 years. Mean PbB at the time of the examination was 51 µg/dL (range, 40–75 mg/dL) in the exposure group, and 20.9 µg/dL (range, 4.4–39 mg/dL) in the reference group. More studies are needed to establish whether this parameter is truly affected by lead exposure, and if so, to evaluate the shape of the dose-response relationship.

Neurological Effects in Children. High-level exposure to lead produces encephalopathy in children. The most extensive compilation of dose-response information on a pediatric population is the summarization by the National Academy of Sciences (1972) of unpublished data from the patient populations reported in Chisolm (1962, 1965) and Chisolm and Harrison (1956). This compilation relates the occurrence of acute encephalopathy and death in children in Baltimore, Maryland, associated with PbBs determined by the Baltimore City Health Department between 1930 and 1970. Other signs of acute lead poisoning and blood lead levels formerly regarded as asymptomatic were also summarized. An absence of signs or symptoms was observed in some children at PbB of 60–300 µg/dL (mean, 105 µg/dL). Acute lead poisoning symptoms other than signs of encephalopathy were observed at PbB of approximately 60–450 µg/dL (mean, 178 µg/dL). Signs of encephalopathy such as hyperirritability, ataxia, convulsions, stupor, and coma were associated with PbB of approximately 90–800 µg/dL (mean, 330 µg/dL). The distribution of PbBs associated with death (mean, 327 µg/dL) was virtually the same as for levels associated with encephalopathy.

Additional evidence from medical reports (Bradley and Baumgartner 1958; Bradley et al. 1956; Gant 1938; Rummo et al. 1979; Smith et al. 1983) suggests that acute encephalopathy in the most susceptible children may be associated with PbBs in the range of 80–100 µg/dL. However, a study reported 19 cases of acute encephalopathy in infants of mean age 3.8 months and with mean PbB of 74.5 µg/dL (range, 49.7–331 µg/dL) following use of traditional medicines containing lead (surma, Bint al Thahab) (Al Khayat et al. 1997a). Seven cases had PbB ≤70 µg/dL. In this report, lead level at 2 months postchelation was a significant predictor of abnormal results in the Denver Developmental Screening Test carried out for a mean period of 20 months.

Histopathological findings in fatal cases of lead encephalopathy in children include cerebral edema, altered capillaries, and perivascular glial proliferation. Neuronal damage is variable and may be caused by anoxia (EPA 1986a).

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Numerous studies clearly show that childhood lead poisoning with encephalopathy results in a greatly increased incidence of permanent neurological and cognitive impairments. Additional studies indicate that children with symptomatic lead poisoning without encephalopathy (PbB, >80–100 µg/dL) also have an increased incidence of lasting neurological and behavioral damage.

Neurobehavioral Effects in Children. The literature on the neurobehavioral effects of lead in children is extensive. With the improvement in analytical methods to detect lead in the various biological media in recent years and in study design, the concentrations of lead, particularly in blood, associated with alterations in neurobehavioral outcomes keep decreasing. In fact, the results of some recent studies suggest that there may be no threshold for the effects of lead on intellectual function. Due to the enormous size of the database on neurobehavioral effects of lead in children, below are summaries of representative and/or major studies published on specific areas. For further information, the reader is referred to recent reviews on this topic (Bellinger 2004; Koller et al. 2004; Lidsky and Schneider 2003; Needleman 2004).

Many studies conducted decades ago reported negative associations between intellectual function, usually measured as IQ on various intelligence scales, and increased PbB, although other exposure indices were sometimes used. For example, de la Burde and Choate (1972) reported a mean Stanford-Binet IQ decrement of 5 points, fine motor dysfunction, and altered behavioral profiles in 70 preschool children exhibiting pica for paint and plaster and elevated PbBs (mean, 58 µg/dL), when compared with results for matched control subjects not engaged in pica for paint and plaster. A follow-up study on these children (ages 1–3 years) at 7–8 years of age reported a mean Wechsler Intelligence Scale for Children (WISC) full-scale IQ decrement of 3 points and impairment in learning and behavior, despite decreases in PbB since the original study (de la Burde and Choate 1975). Rummo et al. (1979) observed hyperactivity and a decrement of approximately 16 IQ points on the McCarthy General Cognitive Index (GCI) among children who had previously had encephalopathy and whose average maximum PbB at the time of encephalopathy were 88 µg/dL (average PbB, 59–64 µg/dL). Asymptomatic children with long-term lead exposures and average maximum PbB of 68 µg/dL (average PbB level, 51–56 µg/dL versus 21 µg/dL in a control group) had an average decrement of 5 IQ points on the McCarthy GCI. Their scores on several McCarthy Subscales were generally lower than those for controls, but the difference was not statistically significant. Children with short-term exposure and average maximum PbB of 61 µg/dL (average PbB, 46–50 µg/dL) did not differ from controls. PbB in the referent group averaged 21 µg/dL, which is high for so-called “controls.” Fulton et al. (1987) provided evidence of changes in intellectual function at lower PbB in a study of 501 children, 6–9 years old from Edinburgh, Scotland, exposed to lead primarily

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via drinking water. The geometric mean PbB of the study population was 11.5 µg/dL, with a range of 3.3–34 µg/dL and ten children had PbB >25 µg/dL. Multiple regression analyses revealed a significant relation between tests of cognitive ability and educational attainment (British Ability Scales [BAS]) and PbB after adjustment for confounding variables. The strongest relation was with the reading score. Stratification of the children into 10 groups of approximately 50 each based on PbB and plotting the group mean lead values against the group mean difference from the school mean score revealed a dose-effect relationship extending from the mean PbB of the highest lead groups (22.1 µg/dL) down through the mean PbB of the lowest-lead group (5.6 µg/dL), without an obvious threshold. It should be mentioned, however, that the size of the effect on the score was small compared with the effect of other factors. For the combined BAS score, only 0.9% of a total 45.5% variance explained by the covariates in the optimal regression model could be attributed to the effect of lead.

Needleman et al. (1979) examined the relationship between intellectual function and lead in dentin in a group of 158 first- and second-grade children. In comparison with children having dentin lead levels <10 ppm, children having dentin lead levels >20 ppm had significantly lower full-scale WISC-Revised scores; IQ deficits of approximately 4 points; and significantly poorer scores on tests of auditory and verbal processing, on a test of attention performance, and on a teachers' behavioral rating. A concentration of lead in dentin of 20 ppm corresponds to a PbB of approximately 30 µg/dL (EPA 1986a). Further analysis of Needleman's data showed that for children with elevated lead levels, the observed IQ was an average 3.94 points below the expected based on their mother's IQ scores, whereas for children with low lead levels, it was 1.97 points greater than the expected IQ (Bellinger and Needleman 1983). This meant that the children in the elevated lead group had a lower mean IQ than those in the low lead group when maternal IQ was partialled out. When 132 children from the initial study were reexamined 11 years later, impairment of neurobehavioral function was still related to the lead content of teeth shed at the ages of 6 and 7 years (Needleman et al. 1990). Higher lead levels in childhood were significantly associated with lower class standing in high school, increased absenteeism, lower grammatical-reasoning scores, lower vocabulary, poorer hand-eye coordination, longer reaction times, and slower finger tapping. However, no significant associations were found with the results of 10 other tests of neurobehavioral functioning. These later effects could stem from a poor academic start as opposed to effects of lead exposure; however, it could also be that the early lead exposure resulted in long-term consequences. Other studies of lead dentin and intellectual functions support Needleman's findings in that deficits have not been found below lead dentin concentrations of approximately 10 ppm (Damm et al. 1993; Hansen et al. 1989; Pocock et al. 1987). The association between bone lead and intellectual function also has been studied. A study of 156 male adolescents, 11–14 years of age, in the Pittsburgh school system reported

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that increasing bone lead levels (10–53 ppm) was significantly associated with poorer performance on complex language processing tasks (e.g., 4-syllable Nonword Repetition Task, subset 8 of Revised Token Task, responding to spoken commands) (Campbell et al. 2000b). Covariates considered in the analysis included child age, race, SES, and maternal IQ.

Low Lead Level and Intellectual Function. Several studies have been published in recent years that support the view that there is no apparent threshold in the relationship between PbB and neurobehavioral functions. Most of these studies have been cross-sectional studies with the inherent limitation that such type of study of school-age children might reflect latent damage done by a higher PbB at an earlier age, which could only be reliably detected at school age. However, recent data from Chen et al. (2005) showed that the effect of concurrent PbB on IQ may be greater than currently believed. These investigators analyzed data from a clinical trial of 780 children who were treated for elevated PbB (20–44 µg/dL) at approximately 2 years of age and followed until 7 years of age with serial IQ tests and measurements of PbB. Mean PbB at 5 and 7 years of age was 12 and 8 µg/dL, respectively. The results showed that concurrent PbB always had the strongest association with IQ and, as the children aged, the relationship grew stronger. The peak PbB from baseline (approximately 2 years old) to 7 years of age was not associated with IQ at 7 years of age. Furthermore, in the model including both prior and concurrent PbB, concurrent PbB was always more predictive of later IQ scores. The results were interpreted as support for the idea that lead exposure continues to be toxic to children as they reach school age, and that not all of the damage is done by the time the child is 2 or 3 years old.

Lanphear et al. (2000a) analyzed data on blood lead concentrations and various assessments of cognitive abilities conducted on 4,853 U.S. children, ages 6–16 years, as part of the NHANES III, 1988–1994. Four cognitive measures were tested: arithmetic skills, reading skills, nonverbal reasoning (block design), and short-term memory (digit span). Potential confounders that were assessed included gender, racial/ethnic background, child's serum ferritin levels, serum cotinine level, region of the country, marital status and education level of primary caregiver, and poverty index ratio. Although no data were available on important potential confounding factors such as maternal IQ or direct observations of caretaking quality in the home, control for the poverty index ratio and education of the primary caregiver may have served as surrogate. The geometric mean PbB of the sample was 1.9 µg/dL and 2.1% exceeded 10 µg/dL. After adjustment for potential covariables, an inverse association between PbB and cognitive scores was evident, which was significant for all end points when PbBs of only <10 µg/dL were included in the analysis. When the PbB range was restricted to <7.5 µg/dL, the inverse relationship was significant for

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arithmetic skills, reading skills, and nonverbal reasoning; when restricted to $<5.0 \mu\text{g/dL}$, the inverse relationship was significant for arithmetic skills and reading skills.

Canfield et al. (2003) reported the results of evaluations of 172 children from the Rochester Longitudinal Study. Fifty-eight percent of the children had PbBs below $10 \mu\text{g/dL}$. PbB was measured at ages 6, 12, 24, 36, 48, and 60 months. IQ of children was assessed with the Stanford-Binet Intelligence Scale at the age of 3 and 5 years. The highest mean PbB was observed at age 2 years ($9.7 \mu\text{g/dL}$) and the lowest at the age of 6 months ($3.4 \mu\text{g/dL}$). The mean PbB at 5 years of age was $6.0 \mu\text{g/dL}$. After adjustment for covariables, an increase in lifetime average PbB of $1 \mu\text{g/dL}$ was associated with a decrease in IQ of 0.46 IQ points (95% CI=-0.76-0.15). Similar findings were obtained when the children were tested at 3 and 5 years of age. When the analysis was limited to children whose highest observed PbB were $<10 \mu\text{g/dL}$, an increase in the lifetime average PbB of $1 \mu\text{g/dL}$ was associated with a decrease in IQ of 1.37 IQ points (95% CI=-2.56-0.17). The results also showed a nonlinear relationship between IQ and PbB (i.e., an increase from 1 to $10 \mu\text{g/dL}$ was associated with a decline of 8.0 points in IQ, whereas, an increase from 10 to $30 \mu\text{g/dL}$ was associated with a decline of approximately 2.5 points). At the age of 5.5 years, the children were given the Working Memory and Planning Battery of the Cambridge Neuropsychological Test Automated Battery to evaluate specific cognitive functions (Canfield et al. 2004). The results showed that children with the greatest exposure performed more poorly on tests of spatial working memory, spatial memory span, intradimensional and extradimensional shifts, and an analog of the Tower of London task.

Evidence for absence of a lower-bound threshold for postnatal lead exposure also was provided in a study of 237 African-American, inner-city children 7.5 years of age with a current mean PbB of $5.4 \mu\text{g/dL}$ (Chiodo et al. 2004). The children were assessed in areas of intelligence, reaction time, visual-motor integration, fine motor skills, attention (including executive function), off-task behaviors, and teacher-reported withdrawn behaviors. A total of 21 variables were considered as potential confounders. Multiple regression analysis showed negative association with lead exposure in the areas of overall IQ, performance IQ, reaction time, visual-motor integration, fine motor skills, and attention including executive function, off-task behaviors, and teacher-reported withdrawn behavior. Regression analyses in which lead exposure was dichotomized at $10 \mu\text{g/dL}$ were no more likely to be significant than analyses dichotomizing exposure at $5 \mu\text{g/dL}$. Chiodo et al. (2004) indicated that data on maternal and child nutritional status, including iron deficiency, were not available so that their possible influence on the association between lead neurobehavioral outcomes could not be controlled.

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Kordas et al. (2006) studied the association between lead and cognitive function in 594 first-grade children exposed to lead from a metal foundry in Torreón, Mexico. Their ages ranged from 6.2 to 8.5 years and their mean PbB was 11.4 µg/dL (SD±6.1 µg/dL). Fifty-one percent of the children had PbBs ≥10 µg/dL. Children were assessed on performance on 14 tests of global or specific cognitive function. Examiners were experienced testing children and were unaware the children's PbB. The nature of the lead-cognition relation was described using both linear and spline (segmented) regression methods. Covariates included in the analyses were age, gender, SES, maternal formal education, parental involvement in schooling family structure, birth order, arsenic exposure, and hemoglobin concentration. Also, all models were adjusted for the tester administering cognitive tasks and the school each child attended. After adjusting for covariates, PbB was significantly associated ($p<0.05$) with poorer scores measuring math abilities, vocabulary, and visual short-term memory. Using segmented regressions, the investigators observed that the slope describing the associations of PbB with the math and vocabulary test scores below a cutoff of 12 and 10 µg/dL, respectively, were steeper than slopes above those cutoff points. Examination of segmented lead coefficients using a stratified analysis at various levels of covariates showed that the pattern of steeper estimates at low PbBs vs. higher PbBs was generally conserved. Furthermore, the data showed that the nonlinear relationship was most pronounced for children who already tended to be at risk for poorer performance (fewer family resources, lower maternal education, and lower parental involvement in school work). Although some important covariates such as HOME inventory and maternal IQ were not controlled for in the study, control for other family background characteristics may have served as surrogates.

Using data from a prospective study conducted in Mexico City, Mexico, Téllez-Rojo et al. (2006) evaluated the relationship between PbB and neurodevelopment in 294 children at 12 and 24 months of age. Two cohorts comprised the sample: one recruited at the time of delivery and another recruited prenatally. To be included in the study, children needed to have a PbB <10 µg/dL at both 12 and 24 months of age, a gestation age of 37 weeks or longer, and a birth weight >2,000 g. MDI and PDI scores of a Spanish version of the Bayley Scales of Infant Development II (BSID II) were the primary dependent variables. Non-lead variables that were related to BSID II scores at $p<0.1$ in bivariate analysis were included in multivariate models. Also included in the multivariate models were maternal age and IQ and children's gender and birth weight. Adjusting for covariates, children's PbBs at 24 months were significantly inversely associated ($p<0.01$) with both MDI and PDI scores at 24 months. PbB at 12 months of age was not associated with concurrent MDI or PDI, or with MDI scores at 24 months of age, but was significantly associated ($p<0.01$) with PDI scores at 24 months. An increase of 1 logarithmic unit in 24-month PbB was associated with a reduction of 4.7 points in MDI score at

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24 months. For both the MDI and PDI scores at 24 months of age, the coefficients that were associated with PbB were significantly larger ($p \leq 0.01$) among children with PbBs $< 10 \mu\text{g/dL}$ than in children with PbBs $> 10 \mu\text{g/dL}$. Moreover, for MDI scores, the slope of the association was steeper over the range up to $5 \mu\text{g/dL}$ than between 5 and $10 \mu\text{g/dL}$.

Perhaps the strongest evidence for an association between low PbB and intellectual impairment in children as well as for a nonlinear dose-response is provided by a pooled analysis of 1,333 children who participated in seven international prospective cohort studies and were followed from birth or infancy until 5–10 years of age (Lanphear et al. 2005). The participant sites included Boston, Massachusetts; Cincinnati, Ohio; Cleveland, Ohio; Rochester, New York; Mexico City; Port Pirie, Australia; and Kosovo, Yugoslavia. The full-scale IQ score was the primary outcome measured. The median lifetime PbB was $12.4 \mu\text{g/dL}$ (5th–95th percentiles, 4.1 – $34.8 \mu\text{g/dL}$), while the concurrent mean PbB was $9.7 \mu\text{g/dL}$ (5th–95th percentiles, 2.5 – $33.2 \mu\text{g/dL}$); 244 children (18%) had PbBs that never exceeded $10 \mu\text{g/dL}$. Four measures of blood lead were examined: concurrent PbB (PbB closest to the IQ test), maximum PbB (peak PbB measured at any time before IQ test), average lifetime PbB (mean PbB from 6 months to concurrent PbB tests), and early childhood PbB (mean PbB from 6 to 24 months). In the subsequent analyses, concurrent PbB and average lifetime PbB were generally stronger predictors of lead-associated intellectual deficits than the other two indices. Potential confounding effects of other factors associated with IQ scores were examined by multiple regression analysis and included HOME inventory, child's sex, birth weight, birth order, maternal education, maternal IQ, maternal age, marital status, prenatal smoking status, and prenatal alcohol use. Using various models, including the linear model, cubic spline function, the log-linear model, and the piece-wise model, Lanphear et al. (2005) determined that the nonlinear model was a better fit for the data. Using a log-linear model, the investigators found a 6.9 IQ point decrement (95% CI, 4.2–9.4) for an increase in concurrent PbB from 2.4 to $30 \mu\text{g/dL}$. However, the decrease in IQ points was greatest in the lowest ranges of PbB. The estimated IQ decrements associated with increases in PbB of 2.4–10, 10–20, and 20– $30 \mu\text{g/dL}$ were 3.9 (95% CI, 2.4–5.3), 1.9 (95% CI, 1.2–2.6), and 1.1 (95% CI, 0.7–1.5), respectively. To further investigate whether the lead-associated decrement was greater at lower PbBs, the investigators divided the data at two cut-off points *a priori*, a maximal PbB of 7.5 and $10 \mu\text{g/dL}$. They then fit separate linear models to the data in each of those ranges and compared the PbB coefficients for the concurrent PbB index. The coefficient for the 103 children with maximal PbB $< 7.5 \mu\text{g/dL}$ was significantly greater than the coefficient for the 1,230 children with maximal PbB $\geq 7.5 \mu\text{g/dL}$ (linear $\beta = -2.94$ [CI 95%, -5.16–-0.71]) vs. -0.16 (95% CI, -2.4–0.08). The coefficient for the 244 children who had maximal PbB $< 10 \mu\text{g/dL}$ was not significantly greater than that for 1,089 children who had maximal PbB $\geq 10 \mu\text{g/dL}$. Potential limitations

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acknowledged by the authors included the fact that the HOME inventory and IQ tests had not been validated in all cultural or ethnic communities, lack of examination of other predictors of neurodevelopmental outcomes such as maternal depression, and the unique limitations of each individual study.

A nonlinear relationship between first trimester of pregnancy blood lead and the MDI at 24 months was recently reported by Hu et al. (2006). In the study, the investigators measured lead in maternal plasma and whole blood lead during each trimester in 146 pregnant women in Mexico City. Measurements were also conducted in cord blood at delivery and when the infants were 12 and 24 months old. The primary outcome was the MDI scores at 24 months of age. The criteria for inclusion in the study were: child born with at least 37 weeks of gestational age; at least one valid measurement of plasma lead during any of the three visits made during pregnancy; complete information on maternal age and IQ; and child's PbB at 24 months, sex, weight, and height. Potential confounders included in the analyses were child's sex, PbB at 24 months of age, height for age and weight, and maternal age and IQ. Mean maternal PbB during the first, second, third trimester, and delivery ranged from 6.1 $\mu\text{g/dL}$ ($\text{SD}\pm 3.2$ $\mu\text{g/dL}$) to 7.3 $\mu\text{g/dL}$ ($\text{SD}\pm 4.3$ $\mu\text{g/dL}$); plasma lead during pregnancy ranged between 0.014 and 0.016 $\mu\text{g/dL}$. Mean PbB in the cord, at 12 months, and 24 months were 6.2 $\mu\text{g/dL}$ ($\text{SD}\pm 3.9$ $\mu\text{g/dL}$), 5.2 $\mu\text{g/dL}$ ($\text{SD}\pm 3.4$ $\mu\text{g/dL}$), and 4.8 $\mu\text{g/dL}$ ($\text{SD}\pm 3.8$ $\mu\text{g/dL}$), respectively. The results of the analyses showed that both maternal plasma and whole blood lead during the first trimester (but not in the second or third trimester) were significant predictors ($p<0.05$) of poorer MDI scores. Also, in models combining all three trimester measures and using standardized coefficients, the effect of first-trimester maternal plasma was substantially greater than the effects of second- and third-trimester plasma lead. A one standard deviation change in first-trimester plasma lead was associated with a reduction in MDI scores of 3.5 points ($p=0.03$). Inspection of the relationship between first-trimester plasma lead and MDI at 24 months showed that the slope was steeper at plasma lead levels corresponding to whole blood lead levels <10 $\mu\text{g/dL}$ than at higher plasma lead concentrations, as observed also in the studies summarized above. As a possible explanation, Hu et al. (2006) speculated that lead might be affecting the process of neuronal differentiation, which is primarily a first-trimester event. Limitations of the study acknowledged by the investigators include the relatively small sample size, the lack of control for a measure of home conditions, and the fact that infant PbB at 24 months did not significantly predict lower MDI score (as observed, for example, in Téllez-Rojo et al. [2006]). Another recent study that reported an association between prenatal lead exposure and intellectual function is that of Schnaas et al. (2006) who reported that IQ of 6–10-year-old children decreased significantly ($p<0.0029$; 95% CI, -6.45--1.36) only with increasing natural-log third trimester PbB, but not with PbB at other times during pregnancy or postnatal PbB measurements. However,

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because their observations began after the 12th week of pregnancy, the effects of the first trimester PbB could not be examined. As with other studies, the dose-response PbB-IQ function was log-linear, with a steeper slope at PbB <10 µg/dL.

Other studies that have reported cognitive impairments associated with low lead exposure include Al-Saleh et al. (2001), Bellinger and Needleman (2003), Carta et al. (2003), Emory et al. (2003), Gomaa et al. (2002), and Shen et al. (1998). Although individually all of these studies have limitations, collectively, they support the association between low blood lead and intellectual impairment in children.

Major Prospective Studies. The Port Pirie, Australia, prospective study examined cohorts of infants born to mothers living in the vicinity of a large lead smelting operation in Port Pirie and infants from outside the Port Pirie area. The study population consisted initially of 723 singleton infants. The children were followed from birth to age 11–13 years old; at this later age, 375 children remained in the cohort. Maternal blood and cord lead levels were slightly, but significantly, higher in the Port Pirie cohort than in the cohort from outside Port Pirie (e.g., mean cord blood lead was 10 vs. 6 µg/dL). The main outcome measures were the Bayley Mental Developmental Index (MDI) at age 2 years, the McCarthy GCI at age 4 years, and IQ from the Wechsler Intelligence Scale at ages 7 and 11–13 years (Baghurst et al. 1987, 1992, 1995; McMichael et al. 1988, 1994; Tong et al. 1996). Covariates in the models included: child gender, birth weight, siblings, infant feeding style and duration of breast feeding; maternal IQ, age at child's birth and marital status; parental tobacco use; SES, and HOME score. Analysis of the associations between blood lead concentrations (tertiles) in children of ages 2 or 11–13 years, and developmental status showed that the covariate-adjusted differences in development scores between the top and bottom tertiles were 4 points on the MDI at age 2; 4.8 points on the McCarthy GCI at age 4; and 4.9 and 4.5 IQ points at age 7 and 11–13 years, respectively. At age 7 years, both prenatal and postnatal PbB were inversely associated with visual motor performance (Baghurst et al. 1995). Analysis of the relationship between individual changes in PbB and individual changes in measures of cognitive development during the life of the cohort found that the mean PbB in the children decreased from 21.2 µg/dL at age 2 years to 7.9 µg/dL at age 11–13 years; however, cognitive scores in children whose blood lead concentration declined the most were generally not improved relative to the scores of children whose PbB declined least (Tong et al. 1998). Changes in IQ and declines in PbB that occurred between the ages of 7 and 11–13 years suggested better cognition among children whose PbB declined most. The overall conclusion was that the cognitive deficits associated with exposure to lead in early childhood appeared to be only partially reversed by a subsequent decline in PbB. Throughout the various assessments, it was noted that children from disadvantaged backgrounds were more sensitive to the effects of lead than those of a higher

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socioeconomic status, and that girls were more sensitive to the effects of lead than boys (Tong et al. 2000).

The Mexico City, Mexico, Prospective Study evaluated children born to mothers residing in Mexico City (Rothenberg et al. 1989, 1994a; Schnaas et al. 2000). The study recruited 502 pregnant women; 436 ultimately were included in the study. An analysis of a subset of 112 children for whom complete data were available for evaluation of GCI (McCarthy scales) at 6-month intervals between ages 36 and 60 months revealed significant associations between PbB and GCI, after adjusting for covariates. Mean PbBs were 10.1 µg/dL at 6–18 months, 9.7 µg/dL at 24–36 months, and 8.4 µg/dL at 42–54 months of age. Increasing PbBs at 24–36 months, but not 6–18 months or prenatal, were associated with significant declines in GCI at 48 months; increasing PbBs at 42–54 months were associated with decreased GCI at 54 months. Covariates included in the models were child gender, 5-minute Apgar score, birth weight, and birth order; maternal education and IQ; and family SES. HOME scores were not included and were assumed to have been accounted for by maternal IQ because of the strong correlation between the latter and HOME score. The main finding of this series of studies was that postnatal, but not prenatal, PbBs were associated with intellectual function and that the strength of the association between mean PbB and GCI increases with age up to 4 years, after which, it becomes less strong and continues to decrease.

The Yugoslavia Prospective Study evaluated children born to women from two towns in Kosovo, Yugoslavia; Kosovska Mitrovica (K. Mitrovica), the site of a lead smelter, refinery, and battery plant; and Pristina, a town 25 miles to the south of K. Mitrovica, which was considered not to have been impacted by industrial lead emissions (Factor-Litvak et al. 1991, 1999; Wasserman et al. 1992). A total of 1,502 women were recruited at mid-pregnancy: 900 women from Pristina and 602 from K. Mitrovica. A sample of 392 infants was selected for follow-up based on umbilical cord lead, town of residence, and parental education. The infants from K. Mitrovica were assigned to one of three groups based on cord PbB: low (<15 µg/dL), middle (15–20 µg/dL), and high (>20 µg/dL). Outcomes examined in the follow-up included measures of intelligence at ages 2 (MDI of the Bayley Scales), 4 (McCarthy Scales of Children's Abilities), and 7 years (Wechsler Intelligence Scale for Children-III), and behavior problems at age 3 (Child Behavior Checklist) and 12 years (Wechsler Intelligence Scale for Children-III). Covariates included in the models were child gender, birth weight, iron status (blood hemoglobin), siblings and ethnicity (language spoken in home); maternal age, education and Raven's test score; and HOME score. The geometric mean PbB in children in K. Mitrovica increased from 22.4 µg/dL, at birth, to 39.9 µg/dL, at age 4; in children from Pristina, it increased from 5.4 to 9.6 µg/dL over this same age range (Wasserman et al. 1994). PbB was significantly associated with poorer intellectual function at ages

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2 years (Wasserman et al. 1992), 4 years (Wasserman et al. 1994), and 7 years (Wasserman et al. 1997). An increase in PbB from 10 to 30 µg/dL was predicted to be associated with loss in intellectual function of 2.5 points at age 2 years, 4.5 points at age 4 years, and 4.3 points at age 7 years. In both towns combined, PbB measured concurrently with the Child Behavior Checklist was associated with small increases in behavioral problems, which the authors considered small compared with the effects of social factors (Wasserman et al. 1998). In a subsequent publication, Wasserman et al. (2000a) observed that while postnatal elevations that occurred before the age of 2 years and continued afterwards were associated with the largest decrements in IQ (50% increase in postnatal lead associated with 2.71 point IQ loss), elevations in PbB that occurred only after the age of 2 years were also associated with decrements. Thus, prenatal and postnatal exposures that occurred at any time during the first 7 years were independently associated with small decrements in later IQ scores (Wasserman et al. 2000a); identification of a particularly critical period of vulnerability during brain growth and maturation within this age range was not evident from this analysis.

In addition, evaluation of 283 children at the age of 54 months showed that PbB was significantly associated with poorer fine motor and visual motor function, but was unrelated to gross motor coordination. An estimated 2.6 and 5.8% of the variance in fine motor composite and visual motor integration was due to PbB, respectively. At age 12, the assessment of the children included measurements of tibial bone in addition to current PbB (Wasserman et al. 2003). At this age, mean PbB in the exposed children was approximately 31 µg/dL and mean tibial bone lead was 39 ppm, both measures significantly higher than those of a comparison group. Both bone lead and PbB were associated with intelligence decrements, but the bone lead-IQ associations were stronger than those for PbB. For each doubling of tibial bone, Full Scale, Performance, and Verbal IQ decreased by an estimated 5.5, 6.2, and 4.1 points, respectively. Analyses conducted in a subsample stratified by quartiles showed that the greatest decrements in intelligence appeared to occur at relatively low lead exposure, from quartile 1 to quartile 2. These transitions corresponded to tibial lead up to 1.85 ppm, mean serial PbB up to 7 µg/dL, and current PbB up to 5.6 µg/dL.

The Boston, Massachusetts, study examined the association between lead exposure and neurobehavioral parameters in 249 middle-class and upper-middle class Boston children (Bellinger et al. 1984, 1985a, 1985b, 1986a, 1986b, 1987a, 1987b, 1989a, 1989b, 1991, 1992). Cord PbBs were determined at delivery and MDI and PDI scores were measured every 6 months thereafter. Infants born at <34 weeks of gestation were excluded from the study. Cord PbBs were <16 µg/dL for 90% of the subjects, with the highest value being 25 µg/dL. On the basis of cord PbBs, the children were divided into low-dose

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(<3 µg/dL; mean, 1.8 µg/dL), medium-dose (6–7 µg/dL; mean, 6.5 µg/dL), and high-dose (≥10 µg/dL; mean, 14.6 µg/dL) exposure groups. Multivariate regression analysis revealed an inverse correlation between cord PbB and MDI scores at 6, 12, 18, and 24 months of age (Bellinger et al. 1985a, 1985b, 1986a, 1986b, 1987a). The high-lead group had an average deficit of 4.8 points on the covariate-adjusted MDI score as compared with the low-lead group. MDI did not correlate with postnatal PbB lead levels. No correlations between PDI and cord or postnatal blood lead levels were seen. Subsequent studies of this cohort showed that the younger the infants, the more vulnerable they are to lead-induced developmental toxicity (Bellinger et al. 1989a, 1989b). Infants in lower socioeconomic groups showed deficits at lower levels of prenatal exposure (mean PbB, 6–7 µg/dL) than children in higher socioeconomic groups. The early postnatal PbBs (range, 10–25 µg/dL) were also associated with lower MDI scores, but only among children in lower socioeconomic groups. Evaluation of the children at approximately 5 years of age showed that deficits in GCI scores correlated significantly with PbB at 24 months of age (mean 7 µg/dL), but not with prenatal PbB (Bellinger et al. 1991). These results suggest that prenatal PbB is a better predictor of cognitive development in infants than in 4–5-year-old children and that early developmental deficits associated with elevated PbB may not persist to 4–5 years of age, especially in socioeconomically advantaged families. Evaluation of 148 of the Boston cohort children at age 10 years showed that all postnatal blood lead levels were inversely associated with Full Scale IQ measured at age 10; however, only the associations involving PbB at ages 10 years, 57 months, and 24 months were statistically significant (Bellinger et al. 1992). This was also seen for both Verbal and Performance IQ scores. After adjusting for confounding, only the coefficient associated with 24-month blood lead level remained significant. It was also shown that the association between 24-month PbB and Full Scale IQ at age 10 years was not due simply to the high correlation between GCI scores at age 5 years and IQ. The decline in Full Scale IQ corresponded to 5.8 points per 10 µg/dL of increase in 24-month PbB. PbB at 24 months was also significantly associated with Verbal IQ and five WISC-R subtest scores. Only PbBs at 24 months were significantly associated with adjusted K-TEA scores. For each 10 µg/dL of increase in 24-month PbB, the battery composite score declined 8.9 points. The results suggested that timing of exposure may be more important than magnitude alone and supported the hypothesis of an age-specific vulnerability. Reanalyses of data, from 48 children whose PbB never exceeded 10 µg/dL at birth or at any of the evaluations throughout the study, showed that an inverse association between IQ and PbB persisted at PbBs below 5 µg/dL and that the inverse slope was greater at lower PbBs than at higher PbBs (Bellinger and Needleman 2003).

The Cincinnati, Ohio, study sample consisted of 305 mothers residing in predesignated lead-hazardous areas of the city (>80% black) (Dietrich et al. 1986, 1987a, 1987b). Maternal PbBs were measured at the

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first prenatal visit; cord PbB was measured at delivery; infant PbB was measured at 10 days and at 3 months of age; and neurobehavioral tests were performed at 3 and 6 months of age. Mean PbBs were as follows: prenatal (maternal), 8.0 µg/dL (range, 1–27 µg/dL); umbilical cord, 6.3 µg/dL (range, 1–28 µg/dL); 10-day-old and 3-month-old infants, 4.6 and 5.9 µg/dL (range, 1–22 µg/dL for each). Multiple regression analyses, with perinatal health factors such as birth weight and gestational age treated as confounders, showed inverse correlations between prenatal or cord PbB and performance on the MDI at 3 months, and between prenatal or 10-day neonatal PbB and performance on the MDI at 6 months. No significant correlation of PbB with PDI was seen. Male infants and low socioeconomic status infants appeared to be more sensitive to the effect on the MDI. Multiple regression analyses for male or low socioeconomic status infants showed covariate-adjusted decrements of 0.84 or 0.73 MDI points per µg/dL of prenatal or 10-day neonatal PbB, respectively (i.e., an approximate 8-point deficit for a 10-µg/dL increase in PbB) (Dietrich et al. 1987a). Cognitive development of 258 children was assessed by the Kaufman Assessment Battery for Children (K-ABC) when the children were 4 years old (Dietrich et al. 1991). Higher neonatal PbBs were associated with poorer performance in all K-ABC subscales; however, there was a significant interaction between neonatal PbB and socioeconomic status, which suggested that children from less advantaged environments express cognitive deficits at lower PbBs than do children from families of relatively higher socioeconomic status. Prenatal (maternal) PbBs were not related to 4-year cognitive status. No statistically significant effects of postnatal PbB on any of the K-ABC subscales was found after covariate adjustment. Evaluation of 253 children at 6.5 years of age showed that when PbB regression coefficients were adjusted for HOME score, maternal IQ, birth weight, birth length, child sex, and cigarette consumption during pregnancy, postnatal PbB continued to be associated with lower Performance IQ (Dietrich et al. 1993a). Also, examination of the PbB concentration for the group from 3 to 60 months of age showed that PbB peaked at approximately 2 years of age and declined thereafter. It was also found that, of the various cofactors, maternal IQ was usually the strongest predictor of a child's Full Scale IQ. Further analysis of the results suggested that average lifetime PbB concentrations in excess of 20 µg/dL were associated with deficits in Performance IQ on the order of about 7 points when compared with children with mean PbB concentrations ≤ 10 µg/dL. At 72 months of age, 245 children were evaluated for motor development status (Dietrich et al. 1993b). The authors hypothesized that measures of motor development may be less confounded with socio-hereditary cofactors in lower socioeconomic status populations than cognitive or other language-based indices. After adjusting for HOME scores, maternal IQ, social class, and child sex and race, both neonatal and postnatal PbB were associated with poorer performance on a measure of upper-limb speed and dexterity and a composite index of fine motor coordination. Prenatal (maternal) PbB was not related to motor proficiency. Further analysis of the results revealed that children having a mean lifetime PbB of ≥ 9 µg/dL

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appeared to experience a deficit on both the Bilateral Coordination subtests and Fine Motor Composite relative to children in the lowest PbB quartile. Information collected at approximately 6.5, 11, and 15 years of age showed that children with the highest PbB at age 15 years (mean, 2.8 $\mu\text{g}/\text{dL}$; range, 1–11.3 $\mu\text{g}/\text{dL}$) had lower verbal comprehension scores over time and greater decline in their rate of vocabulary development at age 15 than children with lower PbB (Coscia et al. 2003). The study also showed that socioeconomic status and maternal intelligence were statistically significantly associated with growth patterns in both tests scores, independent of the effects of lead. The most recent publication in this series provides the results of a neuropsychological evaluation of 195 adolescents age 15–17 years old from this cohort (Ris et al. 2004). The neuropsychological tests yielded five factors labeled Memory, Learning/IQ, Attention, Visual Construction, and Fine-Motor. The results showed a significant effect of PbB at 78 months on the Fine-Motor factor. The results also showed a stronger association between lead exposure and Attention and Visuoconstruction in males than in females. The study also confirmed that adolescents from disadvantaged homes had increased vulnerability toward the effects of lead.

The Cleveland, Ohio, study evaluated neurodevelopmental effects in a sample of urban, disadvantaged, mother-infant pairs (33% black) (Ernhart et al. 1985, 1986, 1987). The mean PbBs at the time of delivery were 6.5 $\mu\text{g}/\text{dL}$ (range, 2.7–11.8 $\mu\text{g}/\text{dL}$) for 185 maternal samples and 5.8 $\mu\text{g}/\text{dL}$ (range, 2.6–14.7 $\mu\text{g}/\text{dL}$) for 162 cord samples. There were 132 mother-infant pairs with complete data. The infants were evaluated for anomalies using a systematic, detailed protocol and for neurobehavioral effects using the NBAS and part of the Graham-Rosenblith Behavioral Examination for Newborns (G-R), including a Neurological Soft Signs scale. Hierarchical regression analysis was performed. No evidence of an association between PbB and morphological anomalies was found. Using the complete set of data, abnormal reflexes and neurological soft signs scales were significantly related to cord PbB and the muscle tonicity scale was significantly related to maternal PbB. Using data from the mother-infant pairs, the only significant association that was found was between the Neurological Soft Signs score and cord PbB, which averaged 5.8 $\mu\text{g}/\text{dL}$ and ranged up to only 14.7 $\mu\text{g}/\text{dL}$; no association with maternal PbBs was seen (Ernhart et al. 1985, 1986). A later analysis related PbBs obtained at delivery (maternal and cord blood) and at 6 months, 2 years, and 3 years of age to developmental tests (MDI, PDI, Kent Infant Development Scale [KID], and Stanford-Binet IQ) administered at 6 months, 1 year, 2 years, and 3 years of age, as appropriate (Ernhart et al. 1987). After controlling for covariates and confounding risk factors, the only significant associations of PbB with concurrent or later development were an inverse association between maternal (but not cord) PbB and MDI, PDI, and KID at 6 months, and a positive association between 6-month PbB and 6-month KID. The investigators concluded that, taken as a whole, the results of the

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21 analyses of correlation between PbB and developmental test scores were "reasonably consistent with what might be expected on the basis of sampling variability," that any association of PbB with measures of development was likely to be due to the dependence of both PbB and development on the caretaking environment, and that if low-level lead exposure has an effect on development, the effect is quite small. Ernhart et al. (1987) also analyzed for reverse causality (i.e., whether developmental deficit or psychomotor superiority in infants at 6 months of age contributes to increases in subsequent blood lead levels). No significant correlations were observed when covariates were controlled. Greene and Ernhart (1991) conducted further analyses of the 132 mother-infant pairs in the Cleveland Prospective Study searching for a potential relationship between prenatal lead exposure and neonatal size measures (weight, height, and head circumference) and gestational age. No such relationship was observed.

Table 3-5 presents a summary of the major prospective studies.

While the majority of the available studies of neurobehavioral effects of lead in children have observed associations between increasing lead burden and measures of cognitive development, a smaller number of studies failed to detect such effects. Harvey et al. (1988) found no significant correlation between PbB (mean 13 µg/dL) and measures of IQ in a study of 201 children 5.5 years of age in England. Similar results were reported by McBride et al. (1982), Smith et al. (1983), Lansdown et al. (1986), Ernhart and Greene (1990), Wolf et al. (1994), Minder et al. (1998), and Prpić-Majić et al. (2000). In the former five studies, the mean PbB was between 10 and 16 µg/dL, whereas in the Minder et al. (1998) and Prpić-Majić et al. (2000) studies, the mean PbBs were 4.4 µg/dL (range, 0.8–16 µg/dL) and 7.1 µg/dL (range, 2.4–14.2 µg/dL), respectively. Finding diverging results in the assessment of such complex parameters is not totally unexpected given the differences in methodology and the statistical issues involved (see Chapter 2 for further discussion).

Meta-analyses. Needleman and Gatsonis (1990) did a meta-analysis of 12 studies, 7 of which used blood lead as a measure of exposure and 5 used tooth lead. Covariates examined by the studies were SES; parental factors (i.e., parent health score); parent IQ; parental rearing measures; perinatal factors (i.e., birth weight, length of hospital stay after birth); physical factors (i.e., age, weight, medical history), and gender. The t-value of the regression coefficient for lead was negative in all but one study, and ranged from -0.36 to 0.48 in the PbB group and from -3 to -0.03 in the tooth lead group. Their analysis also showed that no single study appeared to be responsible for the significance of the final finding. Somewhat unusual in this analysis is the fact that the evaluation is based on accumulated p values rather than accumulated effect sizes. Pocock et al. (1994) analyzed 5 prospective studies, 14 cross-sectional

Table 3-5. Major Prospective Studies of Intellectual Development in Children

Study cohort	Lead biomarker	Outcome measured	Results and main conclusions	Reference
592 Infants born to women living near a smelter in Port Pirie, Australia, followed from birth to age 11–13.	Mean cord PbB was 10 µg/dL; 21.2 µg/dL at age 2; 7.9 µg/dL at age 11–13	MDI, GCI, IQ	Four point difference in MDI score between top and bottom PbB tertiles at age 2; 4.8 point difference in GCI score at age 4; 4.5 IQ points difference at age 11–13. Deficits associated with lead were only partially reversed by decline in blood lead past infancy.	Baghurst et al. 1987, 1992, 1995; McMichael et al. 1988, 1994; Tong et al. 1996, 1998
112 Infants born to women in Mexico City, Mexico, followed at 6 months intervals between ages 6 and 60 months.	Mean PbB at 6–18 months was 10.1 µg/dL; 9.7 µg/dL at 24–63 months; 8.4 µg/dL at 42–54 months	GCI	Increasing PbB at 24–36 months associated with lowered GCI at 48 months; increasing PbB at 42–54 months associated with lower GCI at 54 months. Postnatal, but not prenatal PbB associated with intellectual function.	Rothenberg et al. 1989, 1994a; Schnaas et al. 2000
577 Infants born to women living near a lead smelter, refinery, and battery plant in K. Mitrovica, Yugoslavia, followed from birth to age 12.	Mean PbB at birth was 22.4 µg/dL; 39.9 µg/dL at age 4; 31 µg/dL at age 12; mean tibia lead was 39 ppm at age 12	MDI, GCI, WISC, IQ	PbB was associated with poorer MDI at age 2, GCI at age 4, WISC at age 7. Tibia lead showed stronger association with IQ decrements than PbB at age 12. Both prenatal and postnatal PbB independently associated with small decrements in IQ.	Factor-Litvak et al. 1991, 1999; Wasserman et al. 1992, 1994, 1998, 2000a, 2003
216 Middle- and upper-class Boston, Massachusetts, children followed from birth to age 10.	90% of cord PbB was <16 µg/dL; mean PbB of 7 µg/dL at 24 months	MDI, PDI, GCI, WISC, IQ	Inverse correlation between cord PbB and MDI scores at 6, 12, 18, and 24 months. No correlation between PDI scores and PbB. Lower GCI at age 5 correlated with PbB at age 2, but not prenatal PbB. Full scale IQ at age 10 associated with PbB at 24 months. Timing of exposure more important than magnitude alone.	Bellinger et al. 1984, 1985a, 1986b, 1987a, 1987b, 19889a, 1989b, 1991, 1992

Table 3-5. Major Prospective Studies of Intellectual Development in Children

Study cohort	Lead biomarker	Outcome measured	Results and main conclusions	Reference
305 Children born to women living in pre-designated lead-hazardous areas of Cincinnati, Ohio, followed to age 15–17.	Mean prenatal PbB was 8 µg/dL; cord PbB was 6.3 µg/dL; 5.9 µg/dL at 3 months; 2.8 µg/dL at age 15 years	K-ABC, MDI, PDI	Prenatal PbB inversely correlated with MDI at 3 and 6 months. Lower KABC scores at 4 years associated with higher neonatal PbB. Postnatal PbB associated with lower performance IQ at 6.5 years. Neonatal and postnatal PbB associated with altered motor development at age 6.	Coscia et al. 2003; Dietrich et al. 1986, 1987a, 1987b, 1991, 1993a, 1993b; Ris et al. 2004
389 Children born to urban disadvantaged women in Cleveland, Ohio followed from birth to 7 years old.	Mean PbB in cord was 5.8 µg/dL; mean prenatal PbB was 6.5 µg/dL	MDI, PDI, KID, NBAS, IQ	Neurological soft signs associated with cord PbB. Only maternal PbB at delivery (6.5 µg/dL) associated with MDI, PDI, and KID scores at 6 months. Dentine lead at 5 years associated with decreased verbal and full scale IQ.	Ernhart et al. 1985, 1986, 1987, 1988; Greene and Ernhart 1991

GCI = McCarthy General Cognitive Index; KABC = Kaufman Assessment Battery for Children; KID = Kent Infant Development Scale; MDI = Mental Developmental Index; NBAS = Brazelton Neonatal Behavioral Assessment Scale; PDI = Psychomotor Developmental Index; WISC = Weschler Intelligence Scale for Children

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studies of blood lead, and 7 cross-sectional studies of tooth lead separately and together. Only studies published since 1979 were included in the analysis. Analyses of the prospective studies showed no association of cord blood lead or antenatal maternal blood lead with subsequent IQ. PbB at around age 2 had a small and significant inverse association with IQ, which was greater than that for mean PbB over the preschool years; the estimated mean change was -1.85 IQ points for a change in PbB from 10 to 20 $\mu\text{g}/\text{dL}$. For the cross-sectional studies of PbB, the combined estimate for mean change in IQ for a change in PbB from 10 to 20 $\mu\text{g}/\text{dL}$ was -2.53 IQ points. For the cross-sectional studies of tooth lead, the mean change in IQ for a change in tooth lead from 5 to 10 $\mu\text{g}/\text{g}$ was -1.03 IQ points. Comparison of the association with and without adjustment for covariates showed that, with few exceptions, adjusting reduced the association by <1.5 points. Analysis of the 26 studies simultaneously indicated that a doubling of PbB from 10 to 20 $\mu\text{g}/\text{dL}$ or of tooth lead from 5 to 10 $\mu\text{g}/\text{g}$ is associated with a mean deficit in Full Scale IQ of around 1–2 IQ points. A threshold below which there is negligible influence of lead could not be determined.

An analysis carried out by Schwartz (1994) included a total of eight studies, three longitudinal and five cross-sectional, relating blood lead to Full Scale IQ in school age children. To evaluate potential confounding, the baseline meta-analysis was followed by sensitivity analyses in order to contrast results across studies that differ on key factors that are potential confounders. The analyses showed an estimated decrease of 2.57 IQ points for an increase in PbB from 10 to 20 $\mu\text{g}/\text{dL}$. Analyses that excluded individual studies showed that no single study appeared to dominate the results. For longitudinal studies, the loss was 2.96 IQ points and for cross-sectional studies, the loss was 2.69 IQ points. For studies in disadvantaged populations, the estimated IQ loss was 1.85 IQ points versus 2.89 IQ points in nondisadvantaged populations. Also of interest in Schwartz's analysis was the fact that a trend towards a higher slope at lower blood lead levels was seen. Direct analysis of the Boston prospective study (Bellinger et al. 1992), which had the lowest mean PbB concentration (6.5 $\mu\text{g}/\text{dL}$) showed no evidence of a threshold for the effects of lead on IQ.

The European Multicenter Study (Winneke et al. 1990) combined eight individual cross-sectional studies from eight European countries that shared a common protocol with inherent quality assurance elements. A total of 1,879 children, age 6–11 years, were studied. PbB concentration was used as a measure of exposure, and the range was 5–60 $\mu\text{g}/\text{dL}$. The overall statistical analysis was done using a uniform predetermined regression model with age, gender, occupational status of the father, and maternal education as confounders or covariates. The results of the analyses showed an inverse association between PbB and IQ of only borderline significance ($p < 0.1$), and a decrease of 3 IQ points was estimated

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for a PbB increase from 5 to 20 µg/dL. Much higher and significant associations were found for tests of visual-motor integration and in serial choice reaction performance. Yet, the outcome variance explained by lead never exceeded 0.8% of the total variance. No obvious threshold could be located on the dose-effect curves.

A Task Group on Environmental Health Criteria for Inorganic Lead conducted separate meta-analyses on four prospective studies and four cross-sectional studies (IPCS 1995). The European Multicenter Study was one of the cross-sectional studies included in the analyses. The outcome measured was Full Scale IQ at age 6–10 years old, and the measure of exposure was PbB. In the analyses of prospective studies, when cumulative exposure rather than lead at a specific time was used as measure of exposure, the association between changes in PbB and changes in IQ did not reach statistical significance ($p>0.05$). However, weighing studies according to the inverse of their variance produced a weighed mean decrease in Full Scale IQ of 2 points for a 10 µg/dL increase in PbB. When PbB at specific times were considered, the inverse association varied from significant and very strong to less strong and of borderline significance, depending on the specific time chosen. Analyses of cross-sectional studies showed a significant inverse association between increase in PbB and decrease in IQ in only 2 out 10 studies; however, there was no evidence of statistical heterogeneity. The meta-analysis estimated that Full Scale IQ was reduced by 2.15 IQ points for an increase on PbB from 10 to 20 µg/dL. IPCS (1995) also confirmed the positive association between lead measures and indicators of social disadvantage. When social and other confounding factors are controlled, the effect in most cases was to reduce the strength of the association between lead measures and IQ without, however, changing the direction. IPCS (1995) concluded that their analysis revealed a consistency between studies which pointed towards a “collectively significant” inverse association between PbB and full-scale IQ. IPCS (1995) also noted that below the 10–20 µg/dL PbB range, “uncertainties increased, concerning firstly the existence of an association and secondly estimates of the magnitude of any putative association.”

Thacker et al. (1992) reviewed 35 reports from five prospective studies that examined the relationship between PbB and mental development in children. However, efforts to pool the data with meta-analytic techniques were unsuccessful because the methods used in the studies to analyze and report data were inconsistent. Specific issues mentioned by Thacker et al. (1992) included (a) IQ and PbB were not always measured at comparable times in different studies, (b) there were differences among studies in independent variable, data transformations, and statistical parameters reported, (c) results conflicted when measurement intervals were comparable, (d) patterns of regression and correlation coefficients were inconsistent, and (e) data were insufficient to interconvert the parameters reported.

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Lead and Delinquent Behavior. The possible association between lead and antisocial behavior has been examined in several studies. In 1996, Needleman and coworkers published the results of a study of 301 young males in the Pittsburgh School System. After adjustment for covariates, the investigators found that bone lead levels at 12 years of age were significantly related to parents and teacher's Child Behavior Checklist ratings of aggression, attention, and delinquency. A later study from the same group of investigators reported the results of a case-control study of 194 youths aged 12–18, arrested and adjudicated as delinquent by the Juvenile Court of Allegheny County, Pennsylvania, and 146 non-delinquent controls from high schools in the city of Pittsburgh (Needleman et al. 2002). The association between delinquent status and bone lead concentrations was modeled using logistic regression. Also, separate regression analyses were conducted after stratification by race. Care was taken to insure that unidentified delinquents did not populate the control group. Bone lead was significantly higher in cases than in controls (11.0 vs. 1.5 ppm) and this also applied to both racial categories, white and African American. After adjusting for covariates and interactions, and removal of noninfluential covariates, adjudicated delinquents were 4 times more likely to have bone lead concentrations higher than 25 ppm than controls. Covariates included in the models were child race; parental education and occupation; absence of two parental figures in the home; number of children in the home; and neighborhood crime rate. Limitations of the study include the lack of blood lead data and definition of dose-effect relationships. Also, explicit information on SES factors was not provided and there were large differences in social confounders between cases and controls.

Dietrich et al. (2001) examined the relationships between prenatal and postnatal exposure to lead and antisocial and delinquent behaviors in a cohort study of 195 urban, inner city adolescents recruited from the Cincinnati Prospective Lead Study between 1979 and 1985. At the time of the study, the subjects were between approximately 15 and 17 years of age; 92% were African-American and 53% were male. The mean prenatal (maternal) PbB concentration was 8.9 µg/dL. Blood was sampled shortly after birth and on a quarterly basis thereafter, until the children were 5 years old. From birth to 5 years of age, 35% of the cohort had PbBs in excess of 25 µg/dL, 79% >15 µg/dL, and 99% >10 µg/dL. As adolescents, the mean PbB was 2.8 µg/dL. After adjustment for covariables that were independently associated with delinquent behavior, prenatal blood lead concentration was significantly associated with an increase in the frequency of parent-reported delinquent and antisocial behaviors, while prenatal and postnatal blood lead concentrations (i.e., at 78 months or childhood average) were significantly associated with an increase in the frequency of self-reported delinquent and antisocial behaviors, including marijuana use. Limitations of the study are the inclusion of only four variables in the covariate analysis despite the fact that nine

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were selected, only total scores were reported omitting the results for all delinquency variables, and maternal levels but not cord levels were used in the analysis.

Two ecological investigations correlated leaded gasoline sales or ambient lead levels with crime rates. Stretesky and Lynch (2001) examined the relationship between air lead concentrations and the incidence of homicides across 3,111 counties in the United States. The estimated air lead concentrations across all counties ranged from 0 to $0.17 \mu\text{g}/\text{m}^3$. After adjusting for sociologic confounding and nine measures of air pollution, they reported a 4-fold increase in homicide rate in those counties with the highest air lead levels compared to controls. Nevin (2000) found a statistical association between sales of leaded gasoline and violent crime rates in the United States after adjusting for unemployment and percent of population in the high-crime age group. As with most ecological investigations, the results are difficult to interpret because there are no measurements of individual exposure levels or controls of confounders.

Many of the behavioral deficits observed in children exposed to lead have been reproduced in studies in animals, particularly monkeys, and at similar blood lead levels. Such studies have suggested that the impaired performance on a variety of tasks is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseveration in behavior that are no longer appropriate. Behavioral tests that have been proven useful in this area of research include discrimination reversal, spatial delayed alternation, delayed matching to sample, and intermittent schedules of reinforcement. Representative studies are summarized below. Additional information can be found in reviews about this topic and references therein (Cory-Slechta 1995, 1997, 2003; Rice 1993, 1996a).

Rhesus monkeys treated orally from birth with doses of lead that produced PbBs $\geq 32 \mu\text{g}/\text{dL}$ for 5 months to 1 year showed impairment in a series of discrimination reversal tasks early in life and when they were tested at 33 months of age and at 49–55 months of age (Bushnell and Bowman 1979a, 1979b). The monkeys tested at 49–55 months of age had mean PbBs of 4, 5, and $6 \mu\text{g}/\text{dL}$, for controls, low-dose, and high-dose monkeys, respectively. The corresponding mean PbBs during the year of treatment were 4, 32, and $65 \mu\text{g}/\text{dL}$. Additional experiments were conducted in monkeys exposed to lower levels of lead that peaked at approximately 15 or $25 \mu\text{g}/\text{dL}$, and then decreased to steady state PbBs of about 11 and $13 \mu\text{g}/\text{dL}$, respectively (Rice 1985). At 3 years of age, the monkeys were tested on a series of nonspatial discrimination reversal problems with irrelevant form cues, which provided the opportunity to study distractibility. The results showed that the treated monkeys attended to irrelevant cues in a systematic way. This suggested that the treated monkeys were being distracted by the irrelevant cues to a greater degree than the controls. Similar conclusions were reached when these same monkeys were tested again

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at 9–10 years of age on a series of spatial discrimination reversal tasks without irrelevant cues. Studies in which the dosing periods varied in order to evaluate possible sensitive periods of exposure showed that spatial and nonspatial tasks were affected differentially depending on the developmental period of lead exposure (Rice 1990; Rice and Gilbert 1990a). These studies also suggested that while exposure beginning after infancy produces impairment, continuous exposure during and after infancy magnifies the effects.

Spatial delayed alternation testing has provided evidence of perseverative behavior and inability to inhibit inappropriate responding. For example, Levin and Bowman (1986) dosed monkeys from birth to 1 year of age, a regimen that produced PbBs of approximately 80 µg/dL during most of the treatment period, although peak PbB reached near 300 µg/dL during the initial phase of treatment. Tests conducted when the monkeys were 5–6 years of age, when mean PbB was about 5 µg/dL, indicated that the treated monkeys perseverated on an alternation strategy even when it was not rewarded. Inappropriate responding also was observed in monkeys that had much lower (11–13 µg/dL) steady state PbBs and were tested at 7–8 years of age (Rice and Karpinski 1988). Further studies to determine possible sensitive periods of exposure showed no significant difference in the degree of impairment on a spatial delayed alternation task among three groups of monkeys exposed at different times during development (Rice and Gilbert 1990b). One group of monkeys was dosed with lead from birth onward; another group was dosed from birth to 400 days of age, and a third group began to receive lead at 300 days of age; testing was conducted at that 6–7 years of age. Perseverative behavior has also been put in evidence in studies in monkeys using the delayed matching to sample paradigm (Rice 1984).

Further evidence that lead induces behavior that can be characterized as failure to inhibit inappropriate responding has been obtained using intermittent schedules of reinforcement, particularly, the fixed interval (FI) schedule of reinforcement. For instance, monkeys with a steady-state PbB of approximately 30 µg/dL tended to respond excessively or inappropriately (e.g., with more responses than controls during time-outs) when responses were not rewarded (Rice and Willes 1979). In addition, lead-treated monkeys with a steady-state PbB of 11 or 13 µg/dL were also slower to learn reinforcement schedule, which required a low rate of responding (Rice and Gilbert 1985). Similar observations were made in adult monkeys dosed with lead from birth, having a peak PbB of 115 µg/dL by 100 days of age and a steady state PbB of 33 µg/dL at 270 days of age (Rice 1992). Increases in response rate on FI performance have been seen in rats at comparable PbB to those in monkeys. For example, Cory-Slechta et al. (1985) reported that postweaning exposure of rats having PbBs of 15–20 µg/dL had a significantly higher rate of response and significantly shorter interval bar-press responses on a FI operant schedule of food

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reinforcement than control rats. Similar results were obtained at higher exposure levels in a series of earlier studies (Cory-Slechta and Thompson 1979; Cory-Slechta et al. 1981, 1983). The same group of investigators also showed that rats exposed to lead after weaning and having a PbB of approximately 11 µg/dL showed inappropriate responding in a Fixed-Ratio (FR) waiting-for-reward paradigm (Brockel and Cory-Slechta 1998). Treated rats increased the response rates and decreased the mean longest waiting time than control rats.

Peripheral Neurological Effects in Children. Effects of lead on peripheral nerve function have been documented in children. Frank peripheral neuropathy has been observed in children at PbBs of 60–136 µg/dL (Erenberg et al. 1974). Of a total of 14 cases of childhood lead neuropathy reviewed by Erenberg et al. (1974), 5 also had sickle cell disease (4 were black), a finding that the authors suggested might indicate an increased susceptibility to lead neuropathy among children with sickle cell disease. Seto and Freeman (1964) reported signs of peripheral neuropathy in a child with a PbB of 30 µg/dL, but lead lines in the long bones suggested past exposures leading to peak PbB of ≥40–60 µg/dL and probably in excess of 60 µg/dL (EPA 1986a). NCV studies have indicated an inverse correlation between peroneal NCV and PbB over a PbB range of 13–97 µg/dL in children living near a smelter in Kellogg, Idaho (Landrigan et al. 1976). These data were reanalyzed to determine whether a threshold exists for this effect. Three different methods of analysis revealed evidence of a threshold for NCV at PbBs of 20–30 µg/dL (Schwartz et al. 1988). NCV in the sural and peroneal nerves from young adults exposed to lead during childhood (20 years prior to testing) while living near a lead smelter in the Silver Valley, Idaho, were not significantly different than in a control group. Current PbBs in the exposed and control groups were 2.9 and 1.6 µg/dL, respectively. Data from past blood lead surveillance indicated a mean childhood PbB of approximately 45 µg/dL.

Other Neurological Effects in Children. Several studies of associations between lead exposure and hearing thresholds in children have been reported, with mixed results. A study of 49 children aged 6–12 years revealed an increase in latencies of waves III and V of the BAEP associated with PbB measured 5 years prior to the tests (mean, 28 µg/dL) (Otto et al. 1985). The current mean PbB was 14 µg/dL (range, 6–59 µg/dL). Assessment of a group of children from the Mexico City prospective study revealed significant associations between maternal PbB at 20 weeks of pregnancy (geometric mean, 7.7 µg/dL; range, 1–31 µg/dL) and brainstem auditory evoked responses in 9–39-day-old infants, 3-month-old infants, and children at 67 months of age (Rothenberg et al. 1994b, 2000). In the most recent assessment, I–V and III–V interpeak intervals decreased as PbB increased from 1 to 8 µg/dL and then increased as PbB rose from 8 to 31 µg/dL. Rothenberg et al. (2000) hypothesized that the negative linear term was

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related to lead effect on brainstem auditory pathway length, and that the positive term was related to neurotoxic lead effect on synaptic transmission or conduction velocity.

Robinson et al. (1985) and Schwartz and Otto (1987, 1991) provided suggestive evidence of a lead-related decrease in hearing acuity in 75 asymptomatic black children, 3–7 years old, with a mean PbB of 26.7 µg/dL (range, 6–59 µg/dL). Hearing thresholds at 2,000 Hertz increased linearly with maximum blood lead levels, indicating that lead adversely affects auditory function. These results were confirmed in an examination of a group of 3,545 subjects aged 6–19 years who participated in the Hispanic Health and Nutrition Survey (Schwartz and Otto 1991). An increase in PbB from 6 to 18 µg/dL was associated with a 2-dB loss in hearing at all frequencies, and an additional 15% of the children had hearing thresholds that were below the standard at 2,000 Hz.

Osman et al. (1999) found a significant association between blood lead concentration (2–39 µg/dL) and hearing thresholds in a group of 155 children ages 4–14 years, after adjustment for covariates. The association remained significant when the analysis was confined to 107 children who had blood lead concentrations below 10 µg/dL. Osman et al. (1999) also reported increased latency of wave I of the BAEP in children with PbB above 10 µg/dL compared to children with PbB below 4.6 µg/dL. Covariates included in the regression models were child gender age, Apgar score, absence of ear and nasopharynx pathologies; history of ear diseases, frequent colds, mumps, gentamycin use, or exposure to environmental noise; and maternal smoking during pregnancy. Increased BAEP interpeak latencies was also described in a study of Chinese children with a mean PbB of 8.8 µg/dL (range, 3.2–38 µg/dL) after controlling for age and gender as confounding factors (Zou et al. 2003).

In contrast with results of the studies mentioned above, Counter et al. (1997a) found no difference in hearing threshold between groups of children who had relatively low or higher exposures to lead (mainly from local ceramics glazing and automobile battery disposal). PbBs were 6 µg/dL (range, 4–12 µg/dL, n=14) and 53 µg/dL (10–110 µg/dL, n=62), respectively. In a separate study of the same cohort, Counter et al. (1997b) found normal wave latencies and neural transmission times, and no correlation between PbB and interpeak latencies in children with a median PbB of 40 µg/dL (range, 6.2–128.2 µg/dL). Furthermore, audiological tests showed normal cochlear function and no statistical relation between auditory thresholds and PbB concentration. Subsequent studies of these children showed no evidence that PbB affected the cochlea (Buchanan et al. 1999) or BAEP interpeak conduction (Counter 2002). It is worth noting that Counter and coworkers studied children in small villages in the Andes mountains who may not be very representative of the general population.

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Studies in animals also have provided mixed results regarding exposure to lead and auditory function. Some monkeys dosed with lead from birth through 13 years of age had elevated thresholds for pure tones, particularly at higher frequencies (Rice 1997). These monkeys had a PbB of approximately 30 µg/dL until 10–11 years old and 50–70 µg/dL when they were tested at 13 years of age. Studies by Lasky et al. (1995) and Lilienthal and Winneke et al. (1996) in monkeys chronically exposed to lead and with moderate PbBs suggested that lead might be altering cochlear function. However, a more recent study by Lasky and coworkers showed that continuous exposure of monkeys beginning shortly after birth until 1–2 years old, resulting in PbB 35–40 µg/dL, had no significant effect on middle ear function, cochlear function, or auditory evoked potentials assessed at least 1 year after exposure to lead (Lasky et al. 2001c).

A study of 384 6-year-old German children with a geometric mean PbB concentration of 4.3 µg/dL (range, 1.4–17.4 µg/dL) from three environmentally contaminated areas in East and West Germany found significant lead-related deficits for two out of three visual evoked potentials (VEP) interpeak latencies after adjusting for confounding effects (Altmann et al. 1998). No association was found between PbB concentrations and VEP amplitudes. These results confirmed previous findings from the same group of investigators (Winneke et al. 1994). Altmann et al. (1998) also measured visual contrast sensitivity and found no significant association between this parameter and lead. Alterations in scotopic (rod-mediated) retinal function were reported in a group of 45 children (7–10 years old) participants in the Mexico City Lead Study (Rothenberg et al. 2002a). The association was significant only with lead measures during the first trimester of pregnancy and not with other periods during pregnancy or throughout postnatal development. The threshold for the effect was 10.5 µg/dL. Results from studies in animals are in general agreement with the findings in humans. For example, studies in rats exposed to lead via the mother's milk, which produced PbBs of approximately 19 µg/dL in the pups, reported reductions in retinal sensitivity attributed to selective alterations of the rods (Fox et al. 1991, 1997). Impairment of scotopic visual function was reported in monkeys treated with lead during the first year of life to produce mean PbBs of 55 or 85 µg/dL and tested 18 months later when PbBs had returned near controls levels (14 µg/dL) (Bushnell et al. 1977). Lilienthal et al. (1988) reported alterations in visual evoked potentials and in the ERG in monkeys exposed to lead during gestation and then for life, and tested at approximately 7 years old; at this time, the PbBs in the two treated groups were approximately 40 and 60 µg/dL. Alterations of the ERG under scotopic conditions were still present when the monkeys were tested again more than 2 years after termination of exposure (Lilienthal et al. 1994). Rice (1998) reported that life-time exposure of monkeys to lead producing steady-state PbBs between 25 and 35 µg/dL altered temporal

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visual function, in six out of nine animals; however, there was no evidence of impairment of spatial visual function.

Bhattacharya et al. (1993) examined the effect of lead exposure on postural balance in 109 children from the Cincinnati Lead Program Project. The mean age of the children was 5.8 years and the geometric mean PbB for the first 5 years of life was 11.9 µg/dL (range, 5.1–28.2 µg/dL). Balance was assessed in a system that provided a quantitative description of postural sway by measuring the movement pattern of the body's center of gravity during testing. Sway area was significantly correlated with PbB in tests performed with the eyes closed, but not in a test performed with the eyes open. This led the authors to suggest that lead-induced sway impairment might be related to modifications of the functions of vestibular and proprioception systems, on which close-eye tests rely more. Sway length was significantly correlated with blood lead under all test conditions.

3.2.5 Reproductive Effects

A number of studies have examined the potential association between lead exposure and reproductive parameters in humans. The available evidence suggest that occupational and environmental exposure resulting in moderately high PbBs might result in abortion and pre-term delivery in women, and in alterations in sperm and decreased fertility in men.

Effects in Females. Female workers at a lead smelter in Sweden had an increased frequency of spontaneous miscarriage when employed during pregnancy (294 pregnancies, 13.9% ended in spontaneous abortion) or when employed at the smelter prior to pregnancy and still living within 10 km of the smelter (176 pregnancies, 17% ended in spontaneous abortion) (Nordstrom et al. 1979). The abortion rates in these two groups of pregnant women were significantly higher than in women who were pregnant before they became employed at the smelter and in women who became pregnant after employment but lived >10 km from the smelter. Although no environmental or biological monitoring for lead was available, women who worked in more highly contaminated areas of the smelter were more likely to have aborted than were other women. A nested control-case study of a cohort of 668 pregnant women in Mexico City showed that the risk of spontaneous abortion (defined as loss of pregnancy by gestation week 20) increased with increasing PbB (Borja-Aburto et al. 1999). Notably, there was a 1.13-fold increase in the risk of spontaneous abortion per µg/dL increase in PbB. Mean PbBs in cases and controls were 12.0 and 10.1 µg/dL, respectively.

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Negative associations also have been reported. For instance, no association was found between PbBs and spontaneous abortions in a cohort of women living in Port Pirie, a lead smelter community in South Australia and the surrounding rural area and neighboring towns (Baghurst et al. 1987). Mean, midpregnancy PbBs in women living in Port Pirie or outside of the town were 10.6 µg/dL (n=531) and 7.6 µg/dL (n=171), respectively (Baghurst et al. 1987; McMichael et al. 1986). While no association was found between PbB and spontaneous abortions, 22 of 23 miscarriages and 10 of 11 stillbirths occurred among the Port Pirie residents, with only 1 miscarriage and 1 stillbirth occurring among residents outside Port Pirie. Maternal PbB was lower in the cases of stillbirth than in the cases of live birth, but fetal and placental levels in this and another study (Wibberley et al. 1977) were higher than in cases of normal birth. Davis and Svendsgaard (1987) suggested that these findings may be due to a transfer of lead from mother to fetus, which is toxic to the fetus. Alexander and Delves (1981) showed a reduction in maternal PbB during the progression of pregnancy and concluded that the reduction could not be explained by dilution of PbB in an increasing plasma volume. The authors suggested that lead was being transferred to placental or fetal tissues or eliminated from maternal blood via other pathways. The rates of spontaneous abortions were also compared in a prospective study of females living close to a lead smelter (midpregnancy mean PbB, 15.9 µg/dL; n=304) and females living 25 miles away (midpregnancy mean PbB, 5.2 µg/dL; n=335) (Murphy et al. 1990). Women were recruited at midpregnancy and their past reproductive history (first pregnancy; spontaneous abortion/fetal loss prior to 7th month; stillbirth/fetal loss from 7th month) was examined. The results indicated no difference between the two groups. The spontaneous abortion rates in women living close to the smelter or 25 miles away were 16.4 and 14.0%, respectively, but the differences were not statistically significant.

In the study of Australian women mentioned above, the rate of preterm delivery (delivery before the 37th week) was significantly higher in women living in the smelter town (566 pregnancies, 5.3% preterm deliveries; mean PbB, 11.2 µg/dL at the time of delivery) than in women not living in the town (174 pregnancies, 2.9% preterm deliveries; mean PbB, 7.5 µg/dL at the time of delivery) (McMichael et al. 1986). Similarly, Torres-Sánchez et al. (1999) observed that preterm births were almost 3 times more frequent in women with umbilical PbB ≥ 5.1 µg/dL than in women with PbB < 5.1 µg/dL. In a study of 121 women biologically monitored for exposure to lead at the Finnish Institute of Occupational Health from 1973 to 1983, there was no evidence of alterations in the time-to-pregnancy (TTP) or decreased fecundability (Sallmen et al. 1995). Women were categorized as having very low exposure (PbB, < 10 µg/dL), low exposure (PbB, between 10 and 19 µg/dL), or moderate-to-high exposure (PbB, ≥ 20 µg/dL).

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Stillbirths have been reported in rats exposed to doses of lead that resulted in PbBs much higher than those reported in the studies in women mentioned above. Treatment of Sprague-Dawley rats with lead in the drinking water on gestation days 5–21 resulted in 19% incidence of stillbirth compared to 2% observed in a control group (Ronis et al. 1996). PbBs in the dams and offspring in this experiment were >200 µg/dL. In subsequent studies using a similar experimental protocol, the same group of investigators reported that treatment of rats with lead in the drinking water on gestation days 5–21 resulted in 28% incidence of stillbirth (Ronis et al. 1998b). The mean PbB level in the pups at birth in this exposure group was 197 µg/dL. In studies with female monkeys, exposure to lead in the drinking water for 75 months resulted in reduced circulating concentration of progesterone, suggesting impaired luteal function; however, treatment with lead did not prevent ovulation; the PbB was approximately 70 µg/dL (Franks et al. 1989). The monkeys also exhibited longer and more variable menstrual cycles and shorter menstrual flow. Female Cynomolgus treated daily for up to 10 years with gelatin capsules containing lead acetate had significantly suppressed circulating levels of LH, FSH, and estradiol although progesterone concentrations were not significantly affected (Foster 1992). PbB in these monkeys was approximately 35 µg/dL. Also, a study in rats showed that exposure to lead can enhance some parameters of estrogen stimulation, inhibit other estrogenic responses, and some responses remain unaltered (Tchernitchin et al. 2003). In that study, female rats were administered lead acetate every 3 days from age 7 days and until they were 19 days old; the PbB in these rats was approximately 47 µg/dL. Lead enhanced the estrogen-induced eosinophilia and reduced the estrogen-induced edema deep in the endometrial stroma of treated rats. In addition, lead altered the proportion of eosinophils in the different histological layers in the uterus. A recent study with human granulosa cell *in vitro* showed that incubation with lead reduced aromatase activity as well as P-450 aromatase and estrogen receptor β protein levels (Taupeau et al. 2003). P-450 aromatase converts C19 androgens to C18 estrogenic steroids and is essential for follicular maturation, oogenesis, ovulation, and normal luteal functions in females. Moreover, mice that lack the ability to synthesize endogenous estrogen suffer folliculogenic disruption and fail to ovulate and are thus infertile. Mice that lack the estrogen receptor β also have a poor reproductive capacity attributed to folliculogenesis blockade (Taupeau et al. 2003).

Effects in Males. A study of 2,111 Finnish workers occupationally exposed to inorganic lead showed a significant reduction in fertility relative to 681 unexposed men (Sällmen et al. 2000a). The risk ratio (RR) for infertility in exposed men appeared to increase with increasing PbB; thus, the RRs for the PbB categories 10–20, 21–30, 31–40, 41–50, and ≥ 51 µg/dL were 1.27, 1.35, 1.37, 1.50, and 1.90, respectively; however, there was no evidence of decreased fertility in couples who had achieved at least one pregnancy. Based on the latter finding, the authors suggested that lead exposure was not associated

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with a delay in pregnancy. A significant reduction in fertility was observed in a group of 74 exposed workers (mean exposure period, 10.7 years; mean PbB, 46.3 µg/dL) relative to a control group of 138 men (mean PbB, 10.4 µg/dL) (Gennart et al. 1992b). Duration of exposure was associated with decreased fertility. A study of 4,256 male workers with PbB >40 µg/dL (sampled before 1986) or ≥25 µg/dL (sampled from 1981–1992) showed a reduction in the number of births relative to a control group of 5,148 subjects (Lin et al. 1996). Workers with the highest cumulative exposure to lead had the most marked reduction in fertility. A study of 163 Taiwanese male lead battery workers showed decreased fertility in men with PbB in the range of 30–39 and ≥40 µg/dL, but there was no significant reduction in fertility in men with PbB of ≤9 µg/dL (Shiau et al. 2004). There was no effect on fertility among men (n=229) employed in a French battery factory (Coste et al. 1991) or among Danish men (n=1,349) exposed to lead (mean PbB of a subset of 400 workers, 39.2 µg/dL) during the manufacture of batteries (Bonde and Kolstad 1997). There was weak evidence of increased time-to-pregnancy (TTP) in the wives of 251 occupationally-exposed men in Finland with PbB ranging from 10 to 40 µg/dL or higher (Sällmen et al. 2000b). The study included only couples who had at least one pregnancy and the association was limited to men whose wives were <30 years old. A study with similar exposure levels in 251 Italian men did not find an association between lead exposure in men and delayed TTP in their wives (Apostoli et al. 2000). There was no association between occupational exposure to lead and low fertility in a multi-country (Belgium, Finland, Italy, and England) study of 638 men exposed occupationally to lead (Joffe et al. 2003). Mean PbB in exposed men ranged from 29.3 to 37.5 µg/dL, but most were below 50 µg/dL. Although the evidence for reduced fertility is not conclusive, it appears that a threshold for fertility effects in men could be in the PbB range of 30–40 µg/dL.

Studies have shown that sperm quality is affected by occupational exposure to lead. Although there is some variation in the results, most of the available studies suggest that reductions in sperm concentration, indications of adverse effects on sperm chromatin, and evidence of sperm abnormalities may occur in men with mean PbB > 40 µg/dL but not in men with lower PbBs. A study of 81 lead smelter workers showed an association between PbB and sperm concentration (Alexander et al. 1998a). In addition, although PbB concentrations were not related to serum testosterone, a reduction in serum testosterone with increasing semen lead concentration was observed. In a study of 150 male workers with long-term lead exposure, men with a mean PbB of 52.8 µg/dL showed asthenospermia, hypospermia, and teratospermia (Lancranjan et al. 1975). These effects were not evident in two groups of men with mean PbBs of 41 or 23 µg/dL. The effect of lead was thought to be directly on the testes because tests for changes in gonadotropin secretion were negative. Secretion of androgens by the testes was not affected. A cross-sectional study of 149 industrial workers in Zagreb, Croatia, found that 98 men who had

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moderate occupational exposure to lead (mean PbB, 36.7 µg/dL) had significantly lower sperm density, and lower counts of total motile and viable sperm; lower percentage and count of progressively motile sperm; higher prevalence of morphologically abnormal sperm head; and lower level of indicators of prostate secretory function compared with 51 referents (mean PbB, 10.3 µg/dL) (Telisman et al. 2000). No significant differences were found for semen volume or percentages of motile, viable, and pathologic sperm. Workers also had significantly higher serum estradiol than the reference group, but there were differences in serum FSH, LH, prolactin, and testosterone levels (Telisman et al. 2000). A study of workers in a Swedish battery factory showed decreased seminal plasma constituents, low semen volumes, and reduced functional maturity of sperm in men with mean PbB of approximately 45 µg/dL during the study period (Wildt et al. 1983). The unexposed (control) group of men had a mean PbB of about 21 µg/dL. A study of men employed in a lead smelter showed that workers with current PbB of ≥ 40 µg/dL had an increased risk of below normal sperm and total sperm count relative to those with PbBs < 15 µg/dL (Alexander et al. 1996). A cross-sectional survey of 503 European workers showed a 49% reduction in the median sperm concentration in men with PbB ≥ 50 µg/dL, whereas there was no significant difference in sperm concentration between the reference group of men (mean PbB, ≤ 10 µg/dL) and men with mean PbB of 10–50 µg/dL (Bonde et al. 2002). Although there was no association between PbBs and abnormal sperm chromatin, there were indications of deterioration of the sperm chromatin in men with the highest lead concentrations in spermatozoa (Bonde et al. 2002). Changes in sperm chromatin also have been reported in monkeys exposed to lead for life and with a mean PbB of 56 µg/dL (Foster et al. 1996). In mammalian spermatozoa, DNA is tightly packaged with protamines in the nucleus. Since lead binds tightly to free thiols, it might compete or replace the zinc atoms that are normally bound with nuclear protamines. These changes could affect normal disulfide bond formation, alter DNA-protamine binding, or impair chromatin decondensation during fertilization (Quintanilla-Vega et al. 2000; Silbergeld et al. 2003). Sperm protamine plays an important role in the condensation-decondensation events that are critical to fertilization, and cases of male infertility have been associated with deficiencies in human protamine (Quintanilla-Vega et al. 2000). A recent study from the latter group supported their earlier hypothesis that lead affects sperm chromatin condensation (Hernández-Ochoa et al. 2005). In a group of 68 urban men with a geometric mean PbB of 9.3 µg/dL (range, 1.9–24.4 µg/dL) 54% of semen samples showed values for sperm chromatin condensation outside the normal range. In addition, evaluation of semen quality parameters and sperm chromatin showed that sperm concentration, motility, morphology, and viability were negatively associated with lead in spermatozoa, whereas semen volume was negatively associated with lead seminal fluid. PbB did not associate with either semen quality parameters or nuclear chromatin decondensation, and PbB did not correlate with lead levels in any semen compartment (Hernández-Ochoa et al. 2005). Smaller studies (< 40 men/study) of men exposed to

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lead have also shown detrimental changes in sperm quality (Assennato et al. 1987; Chowdhury et al. 1986; Lerda 1992).

Direct toxic effects of lead on the testicle might mediate the adverse reproductive effects of lead in occupationally exposed men. A study of 122 workers (mean PbB, 35.1 µg/dL; mean exposure duration, 6 years) employed in three lead battery factories in Singapore showed higher serum LH and FSH concentrations in the exposed workers than in 49 unexposed individuals (mean PbB, 8.3 µg/dL) (Ng et al. 1991). However, there was no difference in testosterone levels between these two groups. Raised LH and FSH levels are an indication of Leydig and Sertoli cell failure (Ng et al. 1991). These results are in general agreement with those of earlier studies of lead workers with high PbBs (≥ 66 µg/dL). These findings indicate that lead can act directly on the testes to cause depression of sperm count and peritubular testicular fibrosis, reduced testosterone synthesis, and disruption of regulation of LH (Braunstein et al. 1978; Cullen et al. 1984; Rodamilans et al. 1988).

The question of whether lead poisoning as a child can have adverse reproductive effects later in life was examined in a group of 35 survivors of childhood plumbism who had been admitted to the Boston Children's Hospital for treatment from 1930 to 1944 (Hu 1991b). Plumbism was diagnosed in children who showed repeated ingestion of lead-containing material or x-ray or clinical evidence of lead poisoning. Although the rates of spontaneous abortions or stillbirths in this group of survivors appeared to be higher than in unexposed matched subjects, the differences were not statistically significant (RR, 1.60; 95% CI, 0.6–4.0).

Sperm parameters also have been examined in animals exposed to lead. Evaluation of 15–20-year-old Cynomolgus monkeys administered lead acetate for their lifetime and having a mean PbB of 56 µg/dL showed no significant alterations in parameters of semen quality such as sperm count, viability, motility, and morphology, or in circulating levels of testosterone (Foster et al. 1996). Adverse sperm effects have been observed in rats, but at relatively high PbBs (Barratt et al. 1989; Hsu et al. 1998a, 1998b). A significant reduction in the number of spermatozoa within the epididymis was observed in mice administered lead acetate in drinking water for 6 weeks, but PbBs were not provided (Wadi and Ahmad 1999). In male rats exposed maternally to lead during gestation and lactation and administered lead for an additional 9 months after weaning, there were no significant effects on sperm count or sperm morphology (Fowler et al. 1980). The PbB in these animals ranged from 4.5 to 67 µg/dL.

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Numerous studies in animals have reported testicular effects following exposure to lead. For example, Foster et al. (1998) evaluated changes in testis ultrastructure, semen characteristics, and hormone levels in monkeys exposed to lead from postnatal day 300 to 10 years of age (postinfancy), from postnatal day 0 to 400 (infancy), or for their lifetime. PbBs in lifetime and postinfancy exposed monkeys were approximately 35 µg/dL compared to <1.0 µg/dL in controls and infancy exposed animals. Electron microscopic analysis revealed disruption of the general architecture of the seminiferous epithelium that involved Sertoli cells, basal lamina, and spermatids in the groups exposed for lifetime and during infancy, with equal severity. No such alterations were seen controls or in the postinfancy exposure group. The results showed that lead exposure in monkeys during infancy can induce testicular alterations that persist in later life when blood lead concentrations had decreased considerably. Circulating concentrations of FSH, LH, and testosterone were not altered by treatment with lead, and semen characteristics were not affected by treatment with lead. Other effects reported in recent studies in rats following oral dosing with lead include disorganization and disruption of spermatogenesis and reduction in the activities of the enzymes alkaline phosphatase and Na⁺-K⁺-ATPase (Batra et al. 2001), and an increase in the percentage of seminiferous tubules showing apoptotic germ cells (Adhikari et al. 2001). No PbBs were reported in these two studies. Also, male rats administered lead acetate in water for 1 week (PbB, 12–28 µg/dL) showed a dose-related increase in gonadotropin-releasing hormone (GnRH) mRNA (Sokol et al. 2002). However, lead did not have an effect on the serum concentrations of hypothalamic gonadotropin-releasing hormone (GnRH) or LH, suggesting a compensatory mechanism in the hypothalamic-pituitary axis. In the only study of exposure by the inhalation route, CD-1 male mice exposed to 0.01 M lead acetate intermittently for 4 weeks showed a time-related increase in the fraction of damaged mitochondria in Sertoli cells, which according to the investigators could lead to a transformation process that may interfere with spermatogenesis (Bizarro et al. 2003).

3.2.6 Developmental Effects

This section summarizes studies of the effects of lead exposure on end points other than neurological in developing organisms exposed during the period from conception to maturity. Neurodevelopmental effects are summarized in Section 3.2.4.

No reports were found indicating low levels of lead as a cause of major congenital anomalies. However, in a study of 5,183 consecutive deliveries of at least 20 weeks of gestation, cord blood lead was associated with the incidence of minor anomalies (hemangiomas and lymphangiomas, hydrocele, skin anomalies, undescended testicles), but not with multiple or major malformations (Needleman et al. 1984). In

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addition, no particular type of malformation was associated with lead. According to the investigators, the results suggested that lead may interact with other teratogenic risk factors to enhance the probability of abnormal outcome.

Anthropometric Indices. Since the report by Nye (1929) of runting in overtly lead-poisoned children, a number of epidemiological studies have reported an association between PbB and anthropometric dimensions. For example, a study of 1-month-old Mexican infants found that infant PbB (measured at birth in umbilical cord and at 1 month of age) was inversely associated with weight gain, with an estimated decline of 15.1 grams per $\mu\text{g/dL}$ of blood lead (Sanín et al. 2001). The mean infant (at 1 month) and maternal PbBs (1 month postpartum) were 5.6 and 9.7 $\mu\text{g/dL}$, respectively; mean umbilical cord lead was 6.8 $\mu\text{g/dL}$. They also found that children who were exclusively breastfed had significantly higher weight gains, but this gain decreased significantly with increasing levels of maternal patella lead. An additional study from the same groups of investigators reported that birth length of newborns decreased as maternal patella lead increased, and also that patella lead was significantly related to the risk of a low head circumference score (Hernandez-Avila et al. 2002). In the Mexico City Prospective Study, an increase in PbB at 12 months of age from 6 to 12.5 $\mu\text{g/dL}$ was associated with a decrease in head circumference of 0.34 cm (Rothenberg et al. 1999c). Also, a study by Stanek et al. (1998) reported that in children aged 18–36 months, with a mean PbB of 6.4 $\mu\text{g/dL}$, PbB was inversely related with head circumference.

In the Cincinnati Prospective Study, higher prenatal PbB was associated with reduced birth weight and reduced gestational age (Dietrich et al. 1987a). Analyses of the data indicated that for each natural log unit increase in PbB, the decrease in birth weight averaged 114 g, but ranged from 58 to 601 g depending on the age of the mother (Bornschein et al. 1989). The investigators reported that the threshold for this effect could be approximately 12–13 $\mu\text{g/dL}$ PbB. In addition, a decrease in birth length of 2.5 cm per natural log unit of maternal PbB was seen, but only in white infants. In a later report, the prenatal PbB (mean, 8.2 $\mu\text{g/dL}$; range, 1–27 $\mu\text{g/dL}$) was related to lower birth weight (Dietrich et al. 1989). PbBs ≥ 10 $\mu\text{g/dL}$ also were significantly associated ($p < 0.05$) with a decrease in total days of gestation and an increase risk of preterm and small-for-gestational-age birth in a sample of 262 mother-infant pairs from the general population in California (Jelliffe-Pawlowski et al. 2006). Lower mean birth weight and In a study of 705 women from Camden, New Jersey, with PbBs throughout pregnancy below 1.5 $\mu\text{g/dL}$, PbB showed no significant association with low birth weight, preterm delivery, Apgar scores, or small-for-gestational age (Sowers et al. 2002a). In contrast, in a study of 148 Russian mothers and 114 Norwegian mothers with maternal and cord PbBs as low as 1.2 $\mu\text{g/dL}$, PbBs had a negative impact on birth weight

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and child's body mass index (BMI, weight in kg divided by the square of the height in meters) with or without adjusting for gestational age (Odland et al. 1999). In a study of 89 mother-infant pairs from Spain, higher placental lead levels were unrelated to smaller birth weight, head and abdominal circumference, or shorter length at birth (Falcón et al. 2003).

Analyses of data for 2,695 children ≤ 7 years old from the NHANES II study indicated that PbB (range, 4–35 $\mu\text{g/dL}$) was a statistically significant predictor of children's height, weight, and chest circumference, after controlling for age, race, sex, and nutritional covariates (Schwartz et al. 1986). The mean PbB of the children at the average age of 59 months appeared to be associated with a reduction of approximately 1.5% in the height that would be expected if the PbB had been zero. An analysis of data on PbB for 4,391 U.S. children, ages 1–7 years, recorded in the NHANES III (1988–1994) showed that increasing PbB (1–72 $\mu\text{g/dL}$) was significantly associated with decreasing body stature (length or height) and head circumference, after adjusting for covariates (Ballew et al. 1999). An increase in PbB of 10 $\mu\text{g/dL}$ was associated with a 1.57 cm decrease in stature and a 0.52 cm decrease in head circumference. A study of 1,454 Mexican-American children aged 5–12 who were participants in the Hispanic Health and Nutrition Examination Survey (HHANES) conducted in 1982–1984 found that PbBs in the range of 2.8–40 $\mu\text{g/dL}$ were related with decreased stature (Frisancho and Ryan 1991). The mean PbB in males and females was 10.6 and 9.3 $\mu\text{g/dL}$, respectively. Eighty-two percent of the variance in height in males was accounted by hematocrit and PbB; in females, the same 82% was accounted by age, poverty index, and PbB. After adjusting for these covariates, children whose PbB was above the median for their age and sex (9–10 $\mu\text{g/dL}$ range) were 1.2 cm shorter than children with PbBs below the median. Angle and Kuntzleman (1989) also reported reduced rates of height and weight from birth to 36 months in children with PbB of ≥ 30 $\mu\text{g/dL}$.

Evaluation of 260 infants from the Cincinnati Prospective Study revealed that postnatal growth rate (stature) from 3 to 15 months of age was inversely correlated with increases in PbB during the same period, but this effect was significant only for infants whose mothers had prenatal PbB > 7.7 $\mu\text{g/dL}$ (Shukla et al. 1989). Reevaluation of 235 infants during the second and third years of life revealed that mean PbB during the second and third years was negatively associated ($p=0.002$) with attained height at 33 months of age (Shukla et al. 1991). However, this association was observed only among children who had mean PbBs greater than the cohort median (10.8 $\mu\text{g/dL}$) during the 3–15-month interval. It also appeared that the effect of lead exposure (both prenatal and during the 3–15-month interval) was transient as long as subsequent exposure was not excessive.

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An absence of significant associations between lead exposure and anthropomorphic measures has also been reported. Evaluation of 359 mother-infant pairs from the Cleveland Prospective Study found no statistically significant effect of PbBs on growth from birth through age 4 years 10 months after controlling for a variety of possible confounding factors (Greene and Ernhart 1991). Also, a study of 104 children who suffered lead poisoning (PbB up to 470 µg/dL) between the ages of 16 and 55 months and underwent chelation therapy showed normal height when they were evaluated at 8 and 18 years of age (Sachs and Moel 1989). At age 18, all patients had PbBs <27 µg/dL. A study by Kim et al. (1995) found that bone lead was not associated with physical growth in a cohort of children followed longitudinally for 13 years. The children were first assessed in 1975–1978 and then in 1989–1990. However, the study found that dentin lead was positively associated with BMI as of 1975–1978 and increased BMI between 1975–1978 and 1989–1990. Confounders controlled for included age, sex, baseline body size, and mother's socioeconomic status. According to the investigators, the results suggested that chronic lead exposure during childhood may result in obesity that persists into adulthood.

As previously mentioned under *Musculoskeletal Effects*, studies in animals, mostly rats, indicate that oral lead exposure may impair normal bone growth and remodeling as indicated by decreased bone density and bone calcium content, decreased trabecular bone volume, increased bone resorption activity, and altered growth plate morphology (Escribano et al. 1997; Gonzalez-Riola et al. 1997; Gruber et al. 1997; Hamilton and O'Flaherty 1994, 1995; Ronis et al. 2001). Ronis et al. (2001) showed that in rats, exposure to lead reduced somatic longitudinal bone growth and bone strength during the pubertal period. These effects could not be reversed by a growth hormone axis stimulator or by sex appropriate hormone, suggesting that the lead effects are not secondary to growth hormone axis disruption. It should be mentioned that the blood lead levels achieved in the pups were in the range of 67–192 µg/dL.

Sexual Maturation. Two studies provide information on the effect of lead exposure on sexual maturation in girls. Selevan et al. (2003) performed an analysis of data on blood lead concentrations and various indices of sexual maturation in a group of 2,741 U.S. female children and adolescents, ages 8–18 years, recorded in the NHANES III (1988–1994). Increasing PbB was significantly associated with decreasing stature (height) and delayed sexual development (lower Tanner stage, a numerical categorization of female sexual maturity based on breast and pubic hair development), after adjusting for covariates. The geometric mean PbB among the three major race/ethnicity categories recorded in the NHANES III was 1.4 µg/dL (95% CI, 1.2–1.5) in non-Hispanic whites, 2.1 µg/dL (95% CI, 1.9–2.3) in African Americans, and 1.7 µg/dL (95% CI, 1.6–1.9) in Mexican Americans. ORs for differences in breast and pubic hair development, and age at menarche were significant in comparisons made at PbBs of 1 and 3 µg/dL in the

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African American group. Delays in sexual development, estimated for Tanner stages 2–5, ranged from 4 to 6 months. ORs were significant for breast and pubic hair development, but not for age at menarche in the Mexican American group. Covariates included in the models were age, height, body mass index; history of tobacco smoking or anemia; dietary intakes of iron, vitamin C and calcium; and family income. Selevan et al. (2003) acknowledged that other factors associated with body lead burden and pubertal development that they did not assess may be responsible for the observed associations. In addition, they noted that reporting of past events, such as age at menarche and dietary history, could have been subject to errors in recall. Finally, potential confounders that were measured at the time of the study may have differed during periods critical for pubertal development or other unmeasured confounders may have affected the results.

An additional study of the same cohort also found a significant and negative association between PbB and delayed sexual maturation (Wu et al. 2003a). The study included 1,706 girls 8–16 years old with PbB ranging from 0.7 to 21.7 µg/dL. PbBs were categorized in three levels: 0.7–2, 2.1–4.9, and 5.0–21.7 µg/dL. Covariates included in the models were race/ethnicity, age, family size, residence in a metropolitan area, poverty income ratio, and body mass index. Girls who had not reached menarche or stage 2 pubic hair had higher PbBs than did girls who had. Among girls in the three levels of PbB mentioned above, the unweighted percentages of 10-year-old girls who had attained Tanner stage 2 pubic hair were 60, 51, and 44%, respectively, and for 12-year-old girls who reported reaching menarche, the values were 68, 44, and 39%, respectively. These negative relationships remained significant in logistic regression even after adjustment for the covariates mentioned above. Interestingly, no significant association was found between PbB and breast development, in contrast to the findings of Selevan et al. (2003) who used the same database. Wu et al. (2003b) concluded that although they found a significant negative association between low PbB and some markers of sexual maturation, judicious interpretation of the results is needed given the cross-sectional study sample and limited attention to other nutritional or genetic factors that may impact the findings.

Some studies have reported delays in sexual maturation in animals exposed to lead, although associated with PbBs much higher than those measured in girls in the Selevan et al. (2003) and Wu et al. (2003b) studies. For example, Grant et al. (1980) reported delayed vaginal opening in female rats exposed *in utero* and via lactation and then directly. PbBs in these female offspring ranged between 20 and 40 µg/dL. Exposure of male and female Sprague-Dawley rats prepubertally (age 24–74 days) to lead acetate in the drinking water resulted in significant reduction in testis weight and in the weight of secondary sex organs in males and in delayed vaginal opening and disruption of estrus cycle in females

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(Ronis et al. 1996). However, these effects were not observed in rats exposed postpubertally (day 60–74 in males, 60–85 in females). Mean PbBs in rats exposed prepubertally and postpubertally were 57 and 31 $\mu\text{g/dL}$, respectively. In the same study, an additional group of rats was exposed during gestation and continuing through lactation and postpubertally. In this group, the effects were much more severe than in the rats exposed only pre- or postpubertally, and were consistent with the much higher PbB achieved in the offspring, approximately 316 $\mu\text{g/dL}$. In follow-up studies, it was found that prenatal lead exposure that continued until adulthood (85 days old) delayed sexual maturation in male and female pups in a dose-related manner (Ronis et al. 1998a, 1998b, 1998c). PbBs in the pups between the ages of 21 and 85 days were >100 $\mu\text{g/dL}$ and reached up to 388 $\mu\text{g/dL}$. Effects at much lower PbBs were reported by Dearth et al. (2002), who treated Fisher 344 rats with lead by gavage from 30 days before mating until weaning the pups at 21 days of age. A cross-fostering design allowed the female pups to be exposed during gestation and lactation or during only one of those periods. PbB in the dams was about 38 $\mu\text{g/dL}$ at breeding, peaked at about 46 $\mu\text{g/dL}$ on lactation day 1, and decreased thereafter. Pups exposed during gestation and lactation had the highest PbB of 38.5 $\mu\text{g/dL}$ on day 10; at this time, the PbBs in pups exposed during gestation only and lactation only were 13.7 and 27.6 $\mu\text{g/dL}$, respectively. By day 30, all three groups had PbBs ≤ 3 $\mu\text{g/dL}$. Vaginal opening as well as first diestrus was significantly delayed to similar extents in all treated groups. This delay was associated with decreased serum levels of insulin-like growth factor-1 (IGF-1), LH, and estradiol. Since liver IGF-1 mRNA was not affected, it appeared that lead altered translation and/or secretion of IGF-1, which in turn decreased LH-releasing hormone at the hypothalamic level. A subsequent study in both Sprague-Dawley and Fisher 344 rats (Dearth et al. 2004) showed that the latter strain is more sensitive to maternal lead exposure than Sprague-Dawley rats regarding puberty-related effects, which could, in part, explain the discrepancy with the effect levels reported by Ronis and coworkers. Results similar to those of Dearth et al. (2002) were reported in Swiss mice by Iavicoli et al. (2004). Female offspring of mice treated with various levels of lead in the diet during pregnancy, lactation, and then directly showed dose-related delay in sexual maturation. Blood lead levels of the dams were not determined; blood lead levels of the female offspring determined once at estrus (day 24–44) ranged from 0.7 to 13.2 $\mu\text{g/dL}$. Removing lead from the control diet (0.2 ppm Pb) reduced PbB in the offspring from 2–3 to 0.7 $\mu\text{g/dL}$ and accelerated puberty from age 33–37 days to age 21 days.

Hematological Effects. The hypothesis that PbB might be associated with depressed erythropoietin (EPO) in children was examined in subjects from the Yugoslavia Prospective Study (Factor-Litvak et al. 1998; Graziano et al. 2004) (see Section 3.2.4 for a detailed description of the Yugoslavia Prospective Study). EPO is a glycoprotein hormone that regulates both steady-state and accelerated erythrocyte

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production. Nearly all of the EPO is produced in the proximal tubule of the kidney. PbB, EPO, and hemoglobin were measured at ages 4.5, 6.5, 9.5, and 12. In addition, tibial lead concentration was measured at age 12. Mean PbBs in the exposed children at the age of 4.5 and 9 years were 39 and 28 µg/dL, respectively, and mean hemoglobin concentration throughout the study period was within normal limits. The results of the analyses, after adjusting for hemoglobin, showed that serum EPO was positively associated with PbB at ages 4.5 and 6.5 years, but the magnitude of the association gradually declined from 4.5 to 12 years. This suggested that in children with moderate PbB, hyperproduction of EPO is necessary to maintain normal hemoglobin concentrations. The decline in slope with age suggested that the compensatory mechanism gradually begins to fail due to lead-induced loss of renal endocrine function. No association was found between tibia lead and EPO. Different results were reported by Liebelt et al. (1999) in a pilot study of 86 children between 1 and 6 years of age with a median PbB of 18 µg/dL (range, 2–84 µg/dL) recruited from a university-based lead clinic and primary care clinic. The investigators in that study found an inverse relationship between PbB and serum EPO concentration. Confounding by age in the Liebelt et al. (1999) study may have contributed to the discrepancy in results. A study of 88 children (2–15 years old) living in a highly lead-contaminated area in the Equatorial Andes reported a significant inverse correlation between PbB and hemoglobin concentration (Counter et al. 2000). The mean PbB was 43.2 µg/dL and the range was 6.2–128.2 µg/dL.

3.2.7 Genotoxic Effects

The potential genotoxic effects of lead have been studied in lead workers and members of the general population, as well as in *in vitro* cultures of mammalian cells and microorganisms. Although not always consistent, the results suggest that lead is a clastogenic agent, as judged by the induction of chromosomal aberrations, micronuclei, and sister chromatid exchanges (SCE) in peripheral blood cells (Table 3-6).

Nordenson et al. (1978) reported a significant increase in chromosomal aberrations in peripheral lymphocytes from a group of 26 lead workers with a mean PbB of approximately 65 µg/dL, and so did Schwanitz et al. (1970), Forni et al. (1976), Al-Hakkak et al. (1986), and Huang et al. (1988b) in workers with mean PbBs of 60–80 µg/dL (n=8), 40–50 µg/dL (n=11), 64 µg/dL (n=19), and 50 µg/dL (n=21), respectively. Schwanitz et al. (1975) reported a small, but not statistically significant increase in chromosomal aberrations in lead workers with a mean PbB of 38 µg/dL. Negative results were reported by Mäki-Paakkanen et al. (1981) among a group of 13 workers with a mean PbB of 49 µg/dL, by Bulsma and De France (1976) in 11 volunteers who ingested lead acetate for 49 days and had a PbB of 40 µg/dL, and by O’Riordan and Evans (1974) in 70 workers with PbBs ranging from <40 µg/dL to 120 µg/dL. A

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Table 3-6. Genotoxicity of Lead *In Vivo*

Species (test system)	End point	Results	Reference
<i>Drosophila melanogaster</i>	Chromosome loss or nondisjunction	–	Ramel and Magnusson 1979
Mouse bone marrow, rat	Structural chromosomal aberrations or gaps, micronucleus formation; unscheduled DNA synthesis, sister chromatid exchange	±	Bruce and Heddle 1979; Deknuds and Gerber 1979
bone marrow, mouse		+	Deknuds et al. 1977
leukocyte, monkey		+	Jacquet and Tachon 1981
lymphocyte, rabbit		–	Jacquet et al. 1977
		–	Muro and Goyer 1969
		+	Tachi et al. 1985
		–	Willems et al. 1982
		+	Jagetia and Aruna 1998
Lead workers, peripheral lymphocytes		+	Vaglenov et al. 2001
		+	Vaglenov et al. 1998
Lead workers, peripheral lymphocytes	DNA damage	+	Danadevi et al. 2003
		+	Fracasso et al. 2002
Lead workers, peripheral lymphocytes	Chromosomal aberration	+	Al-Hakkak et al. 1986
		+	Forni et al. 1976
		–	Mäki-Paakkanen et al. 1981
		+	Nordenson et al. 1978
		–	O'Riordan and Evans 1974
		+	Schwanitz et al. 1975
		+	Huang et al. 1988b
		–	Bauchinger et al. 1977
Children, general population	Chromosomal aberration	–	
Adults, general population	Chromosomal aberration	–	Bulsma and De France 1976
Lead workers, peripheral lymphocytes	Sister chromatid exchange	±	Grandjean et al. 1983
		–	Mäki-Paakkanen et al. 1981
		+	Huang et al. 1988b
		+	Duydu et al. 2001
		+	Wu et al. 2002
Children, general population	Sister chromatid exchange	–	Dalpra et al. 1983
Adults, general population	Altered cell division	+	Bulsma and De France 1976
Lead workers, peripheral lymphocytes	Altered cell division	+	Sarto et al. 1978
		+	Schwanitz et al. 1970

– = negative result; + = positive result; ± = inconclusive result; DNA = deoxyribonucleic acid

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study of 30 children living in a town with a lead plant also found no evidence for lead-induced chromosomal aberrations; PbBs among the children ranged from 12 to 33 $\mu\text{g/dL}$ (Bauchinger et al. 1977). Exposure concentrations were not reported in any of the studies mentioned above.

A significant increase in sister chromatid exchanges was reported in 23 lead workers whose mean PbB was approximately 32 $\mu\text{g/dL}$ (Wu et al. 2002). In this study, the TWA exposure concentration, measured for 11 lead workers, ranged from 0.19 to 10.32 mg/m^3 . Similar results were obtained in a study of 31 workers with a mean PbB of 36 $\mu\text{g/dL}$ (Duydu et al. 2001). In the latter study, the urinary concentration of ALA exhibited a stronger correlation with SCE frequencies than PbB, which led the authors to suggest a possible ALA-mediated mechanism in the genotoxic effects of lead. An increase in SCE frequencies also was reported in workers with a PbB $\geq 80 \mu\text{g/dL}$, but not less (Huang et al. 1988b). In contrast, in a group of 18 workers with a mean PbB of 49 $\mu\text{g/dL}$, there was no detectable increase in SCE frequency relative to controls (PbB $< 10 \mu\text{g/dL}$) (Mäki-Paakkanen et al. 1981); the concentration of lead in air ranged from 0.05 to 0.5 mg/m^3 . Grandjean et al. (1983) observed that PbB and SCE rates decreased in lead workers after summer vacation. They also noticed that newly employed workers failed to show any increase in SCE rates during the first 4 months of employment despite increases in both ZPP and PbB, suggesting that genotoxic effects may occur after long exposure to lead. This could also suggest that current PbB is not a good biomarker of genotoxic effects. A study of 19 children living in a widely contaminated area reported no significant differences in SCE rates between the exposed children (PbB, 30–60 $\mu\text{g/dL}$) and 12 controls (PbB, 10–21 $\mu\text{g/dL}$) (Dalpra et al. 1983).

An increased incidence of micronuclei in peripheral lymphocytes was observed in a group of 22 lead workers whose mean PbB was 61 $\mu\text{g/dL}$ relative to control groups with mean PbBs of 18 or 28 $\mu\text{g/dL}$ (Vaglenov et al. 1998). The concentration of lead in the air ranged from 0.13 to 0.71 mg/m^3 (mean, 0.45 mg/m^3). After the workers consumed a polyvitamin-rich diet for 4 months, the micronuclei frequency showed a significant reduction, which led the authors to suggest that oxidative damage might be involved in the genotoxicity of lead. However, since concurrent controls were not administered vitamins, and the exposed workers were not divided into vitamin-treated and untreated groups, the possibility that the reduction in micronuclei was unrelated to the treatment with vitamins could not be ruled out. In a subsequent study from the same investigators in which lead workers were stratified into four exposure levels, PbBs $> 25 \mu\text{g/dL}$ were associated with significant increases in micronuclei frequency (Vaglenov et al. 2001).

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Lead exposure also has been shown to be associated with DNA damage. For example, battery plant workers (n=37) had significantly elevated levels of DNA breaks in lymphocytes compared to unexposed subjects (n=29) (Fracasso et al. 2002). Moreover, the authors found significant correlations between DNA breaks and increased production of reactive oxygen species (ROS) and decreased glutathione levels in the lymphocytes, pointing to oxidative stress as a possible cause for the specific responses. Similar results were reported in a study in which workers were exposed to an air lead concentration of 0.004 mg/m^3 and had a mean PbB of $25 \text{ } \mu\text{g/dL}$ (Danadevi et al. 2003). DNA damage also was observed in a mice model of lead inhalation (Valverde et al. 2002). A single 60-minute exposure to $6.8 \text{ } \mu\text{g/m}^3$ lead acetate induced DNA damage in the liver and lung, but subsequent inhalation induced DNA damage also in the nasal epithelium, whole blood, kidney, bone marrow, and brain; no DNA damage was seen in the testicles. In general, DNA damage in the lung, liver, and kidney was correlated with length of exposure and lead concentration in the tissue.

For the most part, mutagenicity tests in microorganisms have yielded negative results (Table 3-7).

3.2.8 Cancer

Almost all of the information regarding lead exposure and cancer in humans is derived from studies of lead workers and involves exposure to inorganic lead. Several reviews on this topic have been published recently (Landrigan et al. 2000; Silbergeld 2003; Silbergeld et al. 2000; Steenland and Boffetta 2000).

Malcolm and Barnett (1982) studied the causes of death of 754 subjects from a cohort of 1,898 retired lead acid battery workers during the period 1925–1976 in the United Kingdom. The only significant finding regarding cancer was a small but significant excess of malignant neoplasms of the digestive tract (observed/expected, 21/12.6) among men dying in service and who were classified as having the highest lead exposure; the excess was confined to the period 1963–1966, when lead levels were presumably higher than in later years. A subsequent study of workers from the same manufacturing facilities found no association between lead exposure and deaths from malignant neoplasms, either in general or for specific sites (Fanning 1988). Cooper et al. (1985) followed mortality rates among cohorts of 4,519 battery-plant workers and 2,300 lead production workers during 34 years. An increased SMR was found for total malignancies in both groups of workers (statistically significant only in the battery workers) attributed to digestive and respiratory cancers. These small excesses of cancer deaths could not be correlated with onset or duration of exposure. In addition, no adjustments could be made for other concomitant industrial exposures or for smoking. Smoking could easily explain the small increase in

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Table 3-7. Genotoxicity of Lead *In Vitro*

End point	Species (test system)	Results ^a		Reference
		With activation	Without activation	
<i>Salmonella typhimurium</i> (reverse mutation); <i>Escherichia coli</i> (forward mutation, DNA modification); <i>Saccharomyces cerevisia</i> (reverse mutation); <i>Bacillus subtilis</i> (rec assay)	Gene mutation or DNA modification	–	–	Bruce and Heddle 1979; Dunkel et al. 1984; Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979b
<i>S. cerevisiae</i>	Gene conversion or mitotic recombination	–	–	Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Simmon 1979a
<i>E. coli</i> RNA polymerase or Avian myetoblastosis DNA polymerase	RNA or DNA synthesis	NA	+	Hoffman and Niyogi 1977; Sirover and Loeb 1976
Chinese hamster ovary cells; Syrian hamster embryo cells	Chromosomal aberration, DNA repair, mitotic disturbance	NA	+	Ariza et al. 1998; Bauchinger and Schmid 1972; Costa et al. 1982; Robison et al. 1984; Zelikoff et al. 1988
Chinese hamster fibroblasts	Micronuclei	NA	+	Thier et al. 2003
Human melanoma cells	Micronuclei	NA	+	Poma et al. 2003
Human lymphocytes	Structural chromosomal aberration	NA	+	Beek and Obe 1974
			–	Deknudt and Deminatti 1978
			–	Gasiorek and Bauchinger 1981
			–	Schmid et al. 1972
Human lymphocytes	DNA double-strand breaks, DNA-protein cross-links	NA	+	Woźniak and Blasiak 2003
Human lymphocytes	Sister chromatid exchange	NA	–	Beek and Obe 1975
			+	Niebuhr and Wulf 1984
Human melanoma cells	Sister chromatid exchange	NA	+	Poma et al. 2003

C = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid

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respiratory cancer in an industrial cohort that contained an excess of heavy smokers. Cocco et al. (1998b) found a 60% increased risk of cancer of the gastric cardia for subjects with high-level exposure to lead. However, cross-tabulation of gastric cardiac cancer risk by probability and levels of exposure to lead did not show consistent trends. No association was found between lead exposure and stomach cancer in a nested case-control study at a battery plant that had 30 stomach cancer deaths (Wong and Harris 2000); the 30 cases represented half of 60 stomach cancers in the total cohort of about 6,800 workers. No dose-response was found using a variety of exposure indices.

A study of 437 Swedish smelter workers with verified high lead exposure for at least 3 years from 1950 to 1974 reported an increased SMR only for lung cancer, which did not achieve statistical significance when compared with national and county mortality rates specified for cause, sex, and calendar periods (Gerhardsson et al. 1986b). Environmental lead levels and PbBs were available for all workers since 1950. Mean PbB for the workers was 58 $\mu\text{g/dL}$ in 1950 and 34 $\mu\text{g/dL}$ in 1974. A follow-up study of 1,992 workers at this smelter found an increased SMR (1.5, 95% CI, 0.8–2.4) for all malignancies among a group with the highest exposure, and a considerably higher SMR (4.1, 95% CI, 1.5–9.0) for lung cancer (Lundstrom et al. 1997). However, since the workers may have been exposed to other carcinogens, including arsenic, the specific role of lead cannot be ascertained. A third study of 664 Swedish workers found an increase in deaths due to malignant neoplasms, but no dose-response pattern could be discerned, and the risk estimates did not increase when a latency period of 15 years was applied (Gerhardsson et al. 1995a). The study also found an increased incidence of gastrointestinal malignancies among the workers exposed to lead, a tendency that was related to employment before 1970 and not to lead dose or to latency time. Data regarding dietary and smoking habits were not available.

A study of 20,700 Finnish workers exposed to lead during 1973–1983 found a 1.4-fold increase in the overall cancer incidence and a 1.8-fold increase in the incidence of lung cancer among workers who had ever had a PbB ≥ 21 $\mu\text{g/dL}$ (Anttila et al. 1995). The overall mortality for the whole cohort, however, was less than expected, and there was no clear excess mortality for specific causes of death. In a subsequent study of this same cohort, an excess risk of nervous system cancer, specifically gliomas, was found in workers with a PbB ≥ 29 $\mu\text{g/dL}$ compared with those whose PbB had not exceeded 14.4 $\mu\text{g/dL}$ (Anttila et al. 1996). However, the authors stated that no firm conclusions could be drawn because of the small number of cases, the rather short follow-up time, and the low response rate. Data from Cocco et al. (1998a) also suggested that exposure to lead may be associated with an increase in brain cancer risk. The authors analyzed 27,060 cases of brain cancer and 108,240 controls that died of nonmalignant diseases in

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24 U.S. states in 1984–1992. The risk was observed mainly among men likely to have been heavily exposed to lead, which comprised 0.3–1.9% of the study population.

Cocco et al. (1997) evaluated cause-specific mortality among workers of a lead-smelting plant in Italy. The cohort consisted of 1,388 men whose vital status was followed from January 1950, or 12 months after the date of hiring, whichever was later, through December 1992. Compared with the national mortality rates, stomach cancer and lung cancer were significantly decreased, while deaths from cancer of the liver and biliary tract, bladder cancer, and kidney cancer were increased nonsignificantly above expectation. Compared to regional mortality rates, bladder cancer, kidney cancer, and brain cancer were increased. Cocco et al. (1997) noted that as kidney cancer accounts for about 0.4% of the total deaths both at the national and regional level, the small size of the cohort may not have allowed detection of small increases over the very low background rate. Selevan et al. (1985) and a follow-up by Steenland et al. (1992) also reported an excess in kidney cancer among workers employed at a lead smelter in Kellogg, Idaho.

Finally, in a study of cancer incidence in workers exposed to tetraethyl lead, a statistically significant association was found between exposure to this compound and rectal cancer (OR, 3.7; 90% CI, 1.3–10.2) (Fayerweather et al. 1997). The OR increased 4 times at the high-to-very high cumulative exposure level, demonstrating a dose-response relationship. When a latency period of 10 years was assumed, the association became even more pronounced. No increases in the incidence of cancer at other sites (i.e., brain, kidney, lung, spleen, and bone) were observed in the exposed workers.

Fu and Boffetta (1995) conducted a meta-analysis of lead-worker studies focusing on overall cancer, stomach cancer, lung cancer, kidney cancer, and bladder cancer. They found a significant excess risk of overall cancer, stomach cancer, lung cancer, and bladder cancer. More recently, Steenland and Boffetta (2000) did a meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure. The results provided some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer. The results also showed a weak evidence for an association with kidney cancer and gliomas.

In the only available study of the general population, Jemal et al. (2002) examined the relationship of PbB and all cancer mortality using data from the NHANES II Mortality Study. The study consisted of 203 deaths (117 men, 86 women) among 3,992 whites (1,702 men, 1,890 women) with an average of 13.3 years of follow-up. Log-transformed PbB was either categorized into quartiles or treated as a

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continuous variable in a cubic regression spline. After adjusting for confounding covariates, the analyses of the association of quartiles of PbB with all cancer mortality revealed that the risk of cancer mortality was not significantly associated with PbB among men and women combined and among separate analyses of men and women. In addition, none of the site-specific cancer relative risks were significant. Spline analyses found no dose-response for men and women combined or for men alone. However, for women, there appeared to be a threshold at about the 94th percentile of lead, corresponding to a PbB of 24 µg/dL. The authors noted that the results of the spline analysis in women need to be replicated before they can be considered believable and concluded that individuals with PbB in the range of the NHANES II (weighted median, 13 µg/dL) do not appear to have increased risk of cancer mortality.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead is carcinogenic, and that the most common tumors that develop are renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). Administration of lead compounds by the parenteral route produced similar results. Subcutaneous administration of lead phosphate to rats was associated with high incidence of renal tumors (Balo et al. 1965; Zollinger 1953). A study in mice provided suggestive evidence of carcinogenicity of lead following perinatal exposure (Waalkes et al. 1995). In that study, mice were exposed to one of three doses of lead acetate in the drinking water from gestation day 12 until 4 weeks postpartum, such that offspring were exposed *in utero* and via lactation. Offspring were not exposed directly and were sacrificed at 112 weeks postpartum. Renal tubular cell adenomas occurred in high-dose male offspring at a rate of 20% (5/25), whereas renal tubular cell carcinomas occurred in low-dose males (1/25) and in mid-dose males (1/25); no carcinomas were seen in low- or mid-dose males. In exposed male offspring, the incidence of renal tubular cell atypical hyperplasia was increased in a dose-related manner. In female offspring, lesions occurred at a lower rate.

The mechanism of lead-induced carcinogenicity in animals is not known, but some nongenotoxic mechanisms that have been proposed include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage (Silbergeld et al. 2000). Based on inadequate evidence in humans and sufficient evidence in animals, EPA has classified inorganic lead in Group B2, probable human carcinogen (IRIS 2005). The Department of Health and Human Services has determined that lead and lead compounds are reasonably anticipated to be human carcinogens (NTP 2005). The International Agency for Research on Cancer has determined that inorganic lead is probably carcinogenic to humans and that organic lead compounds are not classifiable as to their carcinogenicity to humans (IARC 2004).

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3.3 TOXICOKINETICS

Overview. Inorganic lead can be absorbed following inhalation, oral, and dermal exposure, but the latter route is much less efficient than the former two. Studies in animals have shown that organic lead is well absorbed through the skin. Inorganic lead in submicron size particles can be almost completely absorbed through the respiratory tract, whereas larger particles may be swallowed. The extent and rate of absorption of lead through the gastrointestinal tract depend on characteristics of the individual and on physicochemical characteristics of the medium ingested. Children can absorb 40–50% of an oral dose of water-soluble lead compared to 3–10% for adults. Gastrointestinal absorption of inorganic lead occurs primarily in the duodenum by saturable mechanisms. The distribution of lead in the body is route-independent and, in adults, approximately 94% of the total body burden of lead is in the bones compared to approximately 73% in children. Lead in blood is primarily in red blood cells. Conditions such as pregnancy, lactation, menopause, and osteoporosis increase bone resorption and consequently also increase lead in blood. Lead can be transferred from the mother to the fetus and also from the mother to infants via maternal milk. Metabolism of inorganic lead consists of formation of complexes with a variety of protein and nonprotein ligands. Organic lead compounds are actively metabolized in the liver by oxidative dealkylation by P-450 enzymes. Lead is excreted primarily in urine and feces regardless of the route of exposure. Minor routes of excretion include sweat, saliva, hair, nails, and breast milk. The elimination half-lives for inorganic lead in blood and bone are approximately 30 days and 27 years, respectively. Several models of lead pharmacokinetics have been proposed to characterize such parameters as intercompartmental lead exchange rates, retention of lead in various tissues, and relative rates of distribution among the tissue groups. Some models are currently being used or are being considered for broad application in lead risk assessment.

3.3.1 Absorption**3.3.1.1 Inhalation Exposure**

Inorganic Lead. Inorganic lead in ambient air consists of aerosols of particulates that can be deposited in the respiratory tract when the aerosols are inhaled. Amounts and patterns of deposition of particulate aerosols in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose breathing vs. mouth breathing), airway geometry, and air-stream velocity within the respiratory tract (James et al. 1994). Absorption of deposited lead is influenced by particle size and solubility as well as the pattern of regional deposition within the respiratory tract. Larger particles ($>2.5\ \mu\text{m}$) that are deposited in the ciliated airways (nasopharyngeal and tracheobronchial

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regions) can be transferred by mucociliary transport into the esophagus and swallowed. Smaller particles ($<1\ \mu\text{m}$), which can be deposited in the alveolar region, can be absorbed after extracellular dissolution or ingestion by phagocytic cells (see Section 3.4.1 for further discussion).

The respiratory tract deposition and clearance from the respiratory tract have been measured in adult humans (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). In these studies, exposures were to lead-bearing particles having mass median aerodynamic diameters (MMAD) below $1\ \mu\text{m}$ and, therefore, deposition of the inhaled lead particles can be assumed to have been primarily in the bronchiolar and alveolar regions of the respiratory tract (James et al. 1994) where transport of deposited lead to the gastrointestinal tract is likely to have been only a minor component of particle clearance (Hursh et al. 1969). Approximately 25% of inhaled lead chloride or lead hydroxide (MMAD 0.26 and $0.24\ \mu\text{m}$, respectively) was deposited in the respiratory tract in adult subjects who inhaled an inorganic lead aerosol through a standard respiratory mouthpiece for 5 minutes (Morrow et al. 1980). Approximately 95% of deposited inorganic lead that is inhaled as submicron particles is absorbed (Hursh et al. 1969; Wells et al. 1975). Rates of clearance from the respiratory tract of inorganic lead inhaled as submicron particles of lead oxide, or lead nitrate, were described with half-times of 0.8 hours (22%), 2.5 hours (34%), 9 hours (33%), and 44 hours (12%) (Chamberlain et al. 1978). These rates are thought to represent, primarily, absorption from the bronchiolar and alveolar regions of the respiratory tract.

Rates and amounts of absorption of inhaled lead particles $>2.5\ \mu\text{m}$ will be determined, primarily, by rates of transport to and absorption from the gastrointestinal tract. Absorption of lead from the gastrointestinal tract varies with the chemical form ingested, age, meal status (e.g., fed vs. fasted), and a variety of nutritional factors (see Section 3.3.1.2 for further discussion).

Organic Lead. Following a single exposure to vapors of radioactive (^{203}Pb) tetraethyl lead (approximately $1\ \text{mg}/\text{m}^3$ breathed through a mouthpiece for 1–2 minutes) in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). One hour after the exposure, approximately 50% of the ^{203}Pb burden was associated with liver, 5% with kidney, and the remaining burden widely distributed throughout the body (determined by external gamma counting), suggesting near complete absorption of the lead that was not exhaled. In a similar experiment conducted with (^{203}Pb) tetramethyl lead, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was

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exhaled in 48 hours. The distribution of ^{203}Pb 1 hour after the exposure was similar to that observed following exposure to tetraethyl lead.

The relatively rapid and near complete absorption of tetraalkyl lead that is inhaled and deposited in the respiratory tract is also supported by studies conducted in animal models (Boudene et al. 1977; Morgan and Holmes 1978).

3.3.1.2 Oral Exposure

Inorganic Lead. The extent and rate of gastrointestinal absorption of ingested inorganic lead are influenced by physiological states of the exposed individual (e.g., age, fasting, nutritional calcium and iron status, pregnancy) and physicochemical characteristics of the medium ingested (e.g., particle size, mineralogy, solubility, and lead species). Lead absorption may also vary with the amount of lead ingested.

Effect of Age. Gastrointestinal absorption of water-soluble lead appears to be higher in children than in adults. Estimates derived from dietary balance studies conducted in infants and children (ages 2 weeks to 8 years) indicate that approximately 40–50% of ingested lead is absorbed (Alexander et al. 1974; Ziegler et al. 1978). In adults, estimates of absorption of ingested water-soluble lead compounds (e.g., lead chloride, lead nitrate, lead acetate) ranged from 3 to 10% in fed subjects (Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980; Watson et al. 1986). Data available on lead absorption between childhood and adulthood ages are very limited. While no absorption studies have been conducted on subjects in this age group, the kinetics of the change in stable isotope signatures of blood lead in mothers and their children as both come into equilibrium with a novel environmental lead isotope profile, suggest that children ages 6–11 years and their mothers may absorb a similar percentage of ingested lead (Gulson et al. 1997b).

Studies in experimental animals provide additional evidence for an age-dependency of gastrointestinal absorption of lead. Absorption of lead, administered as lead acetate (6.37 mg lead /kg, oral gavage), was higher in juvenile Rhesus monkeys (38% of dose) compared to adult female monkeys (26% of the dose) (Pounds et al. 1978). Rat pups absorb approximately 40–50 times more lead via the diet than do adult rats (Aungst et al. 1981; Forbes and Reina 1972; Kostial et al. 1978). This age difference in absorption may be due, in part, to the shift from the neonatal to adult diet, and to postnatal physiological development of intestine (Weis and LaVelle 1991).

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Effect of Fasting. The presence of food in the gastrointestinal tract decreases absorption of water-soluble lead (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Maddaloni et al. 1998; Rabinowitz et al. 1980). In adults, absorption of a tracer dose of lead acetate in water was approximately 63% when ingested by fasted subjects and 3% when ingested with a meal (James et al. 1985). Heard and Chamberlain (1982) reported nearly identical results. The arithmetic mean of reported estimates of absorption in fasted adults was 57% (calculated by ATSDR based on Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980). Reported fed/fasted ratios for absorption in adults range from 0.04 to 0.2 (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Mineral content is one contributing factor to the lower absorption of lead when lead is ingested with a meal; in particular, the presence of calcium and phosphate in a meal will depress the absorption of ingested lead (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982).

Effect of Nutrition. Lead absorption in children is affected by nutritional iron status. Children who are iron deficient have higher blood lead concentrations than similarly exposed children who are iron replete, which would suggest that iron deficiency may result in higher absorption of lead or, possibly, other changes in lead biokinetics that would contribute to lower PbB (Mahaffey and Annest 1986; Marcus and Schwartz 1987). Evidence for the effect for iron deficiency on lead absorption has been provided from animal studies. In rats, iron deficiency increases the gastrointestinal absorption of lead, possibly by enhancing binding of lead to iron binding proteins in the intestine (Bannon et al. 2003; Barton et al. 1978b; Morrison and Quaterman 1987) (see Section 3.4.1 for further discussion).

Dietary calcium intake appears to affect lead absorption. An inverse relationship has been observed between dietary calcium intake and blood lead concentration in children, suggesting that children who are calcium-deficient may absorb more lead than calcium-replete children (Mahaffey et al. 1986; Ziegler et al. 1978). An effect of calcium on lead absorption is also evident in adults. In experimental studies of adults, absorption of a single dose of lead (100–300 µg lead chloride) was lower when the lead was ingested together with calcium carbonate (0.2–1 g calcium carbonate) than when the lead was ingested without additional calcium (Blake and Mann 1983; Heard and Chamberlain 1982). A similar effect of calcium occurs in rats (Barton et al. 1978a). In other experimental animal models, absorption of lead from the gastrointestinal tract has been shown to be enhanced by dietary calcium depletion or administration of vitamin D (Mykkänen and Wasserman 1981, 1982) (see Section 3.4.1 for further discussion).

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Effect of Pregnancy. Absorption of lead may increase during pregnancy. Although there is no direct evidence for this in humans, an increase in lead absorption may contribute, along with other mechanisms (e.g., increased mobilization of bone lead), to the increase in PbB that has been observed during the later half of pregnancy (Gulson et al. 1997b, 1998b, 2004; Lagerkvist et al. 1996; Rothenberg et al. 1994b; Schuhmacher et al. 1996).

Effect of Dose. Lead absorption in humans may be a capacity limited process, in which case, the percentage of ingested lead that is absorbed may decrease with increasing rate of lead intake. Studies, to date, do not provide a firm basis for discerning if the gastrointestinal absorption of lead is limited by dose. Numerous observations of nonlinear relationships between blood lead concentration and lead intake in humans provide support for the existence of a saturable absorption mechanism or some other capacity limited process in the distribution of lead in humans (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984) (see Section 3.4.1 for discussion of saturable uptake of lead in red blood cells). However, in immature swine that received oral doses of lead in soil, lead dose-blood lead relationships were curvilinear, whereas dose-tissue lead relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for blood lead concentration and linearity for tissues) was observed in swine administered lead acetate intravenously (Casteel et al. 1997). These results suggest that the nonlinearity in the lead dose-blood lead concentration relationship may derive from an effect of lead dose on some aspect of the biokinetics of lead other than absorption. In fasted rats, absorption was estimated at 42 and 2% following single oral administration of 1 and 100 mg lead/kg, respectively, as lead acetate, suggesting a limitation on absorption imposed by dose (Aungst et al. 1981). Evidence for capacity-limited processes at the level of the intestinal epithelium is compelling, which would suggest that the intake-uptake relationship for lead is likely to be nonlinear (see Section 3.4.1 for further discussion); however, the dose at which absorption becomes appreciably limited in humans is not known.

Effect of Particle Size. Particle size influences the degree of gastrointestinal absorption (Ruby et al. 1999). In rats, an inverse relationship was found between absorption and particle size of lead in diets containing metallic lead particles that were ≤ 250 μm in diameter (Barltrop and Meek 1979). Tissue lead concentration was a 2.3-fold higher when rats ingested an acute dose (37.5 mg Pb/kg) of lead particles that were < 38 μm in diameter, than when rats ingested particles having diameters in the range of 150–250 μm (Barltrop and Meek 1979). Dissolution kinetics experiments with lead-bearing mine waste soil suggest that surface area effects control dissolution rates for particles sizes of < 90 μm diameter; however, dissolution of 90–250 μm particle size fractions appeared to be controlled more by surface morphology

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(Davis et al. 1994). Similarly, Healy et al. (1982) found that the solubility of lead sulfide in gastric acid *in vitro* was much greater for particles that were 30 μm in diameter than for particles that were 100 μm in diameter.

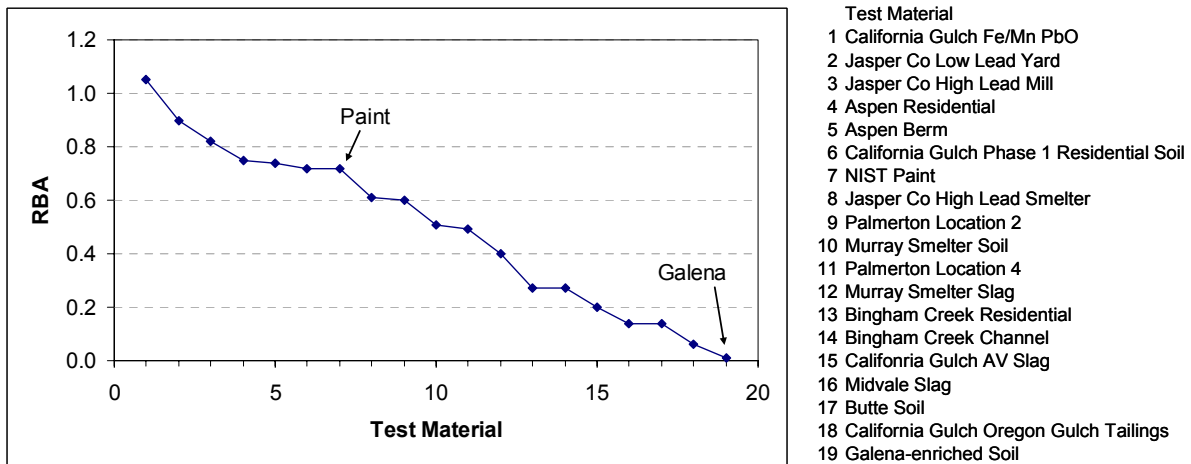
Absorption from Soil. Absorption of lead in soil is less than that of dissolved lead, but is similarly depressed by meals. Adult subjects who ingested soil (particle size $<250\ \mu\text{m}$) collected from the Bunker Hill NPL site absorbed 26% of the resulting 250 $\mu\text{g}/70\ \text{kg}$ body weight lead dose when the soil was ingested in the fasted state, and 2.5% when the same soil lead dose was ingested with a meal (Maddaloni et al. 1998). The value reported for fasted subjects (26%) was approximately half that reported for soluble lead ingested by fasting adults, approximately 60% (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Measurements of the absorption of soil lead in infants or children have not been reported.

Additional evidence for a lower absorption of soil lead compared to dissolved lead is provided from studies in laboratory animal models. In immature swine that received oral doses of soil-like materials from various mine waste sites (75 or 225 $\mu\text{g Pb/kg}$ body weight), relative bioavailability of soil-borne lead ranged from 6 to 100%, compared to that of a similar dose of highly water-soluble lead acetate (Casteel et al. 1997; EPA 2004b; Figure 3-4). Electron microprobe analyses of lead-bearing grains in the various test materials revealed that the grains ranged from as small as 1–2 μm up to a maximum of 250 μm (the sieve size used in preparation of the samples), and that the lead was present in a wide range of different mineral associations (phases), including various oxides, sulfides, sulfates, and phosphates (Table 3-8). These variations in size and mineral content of the lead-bearing grains are the suspected cause of variations in the rate and extent of gastrointestinal absorption of lead from different samples of soil. Based on these very limited data, the relative bioavailability of lead mineral phases were rank-ordered (Table 3-9).

Studies conducted in rats provide additional evidence for a lower absorption of soil-borne lead compared to water-soluble lead. Fed rats were administered lead in soil from mine waste over a 30-day period, and relative bioavailability compared to that of lead acetate was estimated from measurements of PbB (Freeman et al. 1992). For one test soil, relative bioavailability estimates for samples having lead concentrations of 1.62 and 4.05 ppm were 18.1 and 12.1% in males and 25.7 and 13.8% in females for average lead dosages of 1.13 and 3.23 mg Pb/kg/day in males, and 1.82 and 4.28 mg Pb/kg/day in females (1.62 and 4.05 ppm Pb), respectively. For a second test soil, relative bioavailability estimates for samples having lead concentrations of 78.2 and 19.5 ppm were 19.6 and 21.5% in males and 26.8 and 22.1% in

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Figure 3-4. Relative Bioavailability (RBA) of Ingested Lead from Soil and Soil-like Test Materials as Assessed in an Immature Swine Model*



*RBA is the bioavailability (BA) of the lead in the test material compared to that of lead acetate relative to lead acetate ($BA_{\text{test}}/BA_{\text{acetate}}$). See Table 3-8 for mineral composition of test materials.

Source: EPA 2004c

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Table 3-8. Percent Relative Lead Mass of Mineral Phases Observed in Test Materials Assessed for Relative Bioavailability in Immature Swine^a

Test material	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Cal. Gulch Fe/Mn PbO																			
Jasper County low lead yard																			
Jasper County high lead mill																			
Aspen residential																			
Aspen Berm																			
Cal. Gulch Phase I residential soil																			
NIST paint																			
Jasper County high lead smelter																			
Palmerton location 2																			
Murray smelter soil																			
Palmerton location 4																			
Murray smelter slag																			
Bingham Creek residential																			
Bingham Creek channel soil																			
Cal. Gulch AV slag																			
Midvale slag																			
Butte soil																			
Cal. Gulch Oregon Gulch tailings																			
Galena-enriched soil																			
Mineral phase																			
Anglesite	0.5		2	1	7	10	1	1	6		4	1.0		28	2		36		
As(M)O										0.003									
Calcite			0.1					0.2											
Cerussite	81		57	64	62	20	5	32		14		1.1	2	0.3	1	4	0.3		
Clay	0.01	0.003	0.017		0.1		5										0.1		
Fe-Pb oxide	8	2	10	7	9	6	14		2	0.13	2	2	6	3	51	0.3	7		
Fe-Pb sulfate	3	1	1	5	5	6	3		1	0.6		0.3	22	30	0.3	0.1	20		
Galena	8		3	17	12	2				20		9		9	3	6	12	100	100
Lead barite	0.14		0.01		0.06	0.15			1		0.1			0.04			0.007		
Lead organic	0.11			0.03	0.03	0.11								0.3	1				
Lead oxide			7				4	0.09		27		69							
Lead phosphate	15	6	7	1	1	30	21		24		1		50	26			3.6		
Lead silicate	0.8	0.04	0.5			1.9					1.4								
Lead vanadate	0.4					0.1					18								
Mn-Pb oxide	72	2	9	5	4	22	2		66		66	0.8	18	2			20.2		
Native lead			2				22					0.7			15				
Pb(M)O										3	7	4			26				
Pb-As oxide	0.15				0.1					29		6	2	1	31	33			

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Table 3-8. Percent Relative Lead Mass of Mineral Phases Observed in Test Materials Assessed for Relative Bioavailability in Immature Swine^a

Test material	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	Cal. Gulch Fe/Mn PbO	Jasper County low lead yard	Jasper County high lead mill	Aspen residential	Aspen Berm	Cal. Gulch Phase I residential soil	NIST paint	Jasper County high lead smelter	Palmerton location 2	Murray smelter soil	Palmerton location 4	Murray smelter slag	Bingham Creek residential	Bingham Creek channel soil	Cal. Gulch AV slag	Midvale slag	Butte soil	Cal. Gulch Oregon Gulch tailings	Galena-enriched soil
PbO-cerussite						1													
Slag			1			1	4		6		7				10	16			
Sulfosalts																0.4			
Zn-Pb silicate											2	0.03							

^aTest material numbers refer to Figure 3-4.

Source: EPA 2004c

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Table 3-9. Ranking of Relative Bioavailability of Lead Mineral Phases in Soil^a

Low bioavailability (RBA<0.25)	Medium bioavailability (RBA=0.25–0.75)	High bioavailability (RBA>0.75)
Angelsite Fe(M) oxide Fe(m) sulfate Galena Pb(m) oxide	Lead oxide Lead phosphate	Cerussite Mn(M) oxide

^aEstimates are based on studies of immature swine (see Figure 3-4, Table 3-8).

M = metal; RBA = relative bioavailability (compared to lead acetate)

Source: EPA 2004c

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females for average lead dosages of 5.13 and 12.1 mg Pb/kg/day in males and 7.39 and 23.2 mg Pb/kg/day in females, respectively. In a subsequent follow-up study, absolute bioavailability of ingested lead acetate in rats was estimated to be 15% based on measurements of blood lead concentrations after oral or intravenous administration of lead acetate (Freeman et al. 1994). Based on this estimate, the absolute bioavailability of lead in the soils from the Freeman et al. (1992) study was estimated to be 2.7% (Freeman et al. 1994). In rats that received diets containing 17–127 mg lead/kg for 44 days in the form of lead acetate, lead sulfide, or lead-contaminated soil, bone and tissue lead levels increased in a dose-dependent manner (Freeman et al. 1996). Estimated bioavailability of lead sulfide was approximately 10% that of lead acetate. Bioavailability of lead in soil from the California Gulch NPL site (Freeman et al. 1996), a former mining site, decreased with increasing soil lead concentration in the diet and ranged from 7 to 28% of that of lead acetate. The predominant forms of lead in the NPL site soil were identified as: iron-lead oxide (40%), manganese-lead oxide (16%), lead phosphate (13%), "slag" (12%), and iron-lead sulfate (10%). The addition of "uncontaminated soil" (having a lead concentration of 54 ± 3 mg lead/kg soil) to diets containing lead acetate decreased the bioavailability of lead acetate by approximately 76%.

3.3.1.3 Dermal Exposure

Inorganic Lead. Dermal absorption of inorganic lead compounds is generally considered to be much less than absorption by inhalation or oral routes of exposure; however, few studies have provided quantitative estimates of dermal absorption of inorganic lead in humans, and the quantitative significance of the dermal absorption pathway as a contributor to lead body burden in humans remains an uncertainty. Lead was detected in the upper layers of the stratum corneum of lead-battery workers, prior to their shifts and after cleaning of the skin surface (Sun et al. 2002), suggesting adherence and/or possible dermal penetration of lead. Following skin application of ^{203}Pb -labeled lead acetate in cosmetic preparations (0.12 mg Pb in 0.1 mL or 0.18 mg Pb in 0.1 g of a cream) to eight male volunteers for 12 hours, absorption was $\leq 0.3\%$, based on whole-body, urine and blood ^{203}Pb measurements, and was predicted to be 0.06% during normal use of such preparations (Moore et al. 1980). Most of the absorption took place within 12 hours of exposure. Lead also appears to be absorbed across human skin when applied to the skin as lead nitrate; however, quantitative estimates of absorption have not been reported. Lead (4.4 mg, as lead nitrate) was applied (vehicle or solvent not reported) to an occluded filter placed on the forearm of an adult subject for 24 hours, after which, the patch was removed, the site cover and the forearm were rinsed with water, and total lead was quantified in the cover material and rinse (Stauber et al. 1994). The amount of lead recovered from the cover material and rinse was 3.1 mg (70% of the applied dose). Based

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on this recovery measurement, 1.3 mg (30%) of the applied dose remained either in the skin or had been absorbed in 24 hours; the amount that remained in or on the skin and the fate of this lead (e.g., exfoliation) was not determined. Exfoliation has been implicated as an important pathway of elimination of other metals from skin (e.g., inorganic mercury; Hursh et al. 1989). Lead concentrations in sweat collected from the right arm increased 4-fold following the application of lead to the left arm, indicating that some lead had been absorbed (amounts of sweat collected or total lead recovered in sweat were not reported). In similar experiments with three subjects, measurements of ^{203}Pb in blood, sweat and urine, made over a 24-hour period following dermal exposures to 5 mg Pb as ^{203}Pb nitrate or acetate, accounted for <1% of the applied (or adsorbed) dose. This study also reported that absorption of lead could not be detected from measurements of lead in sweat following dermal exposure to lead as lead carbonate.

Information on relative dermal permeability of inorganic and organic lead salts of lead comes from studies of *in vitro* preparations of excised skin; the rank ordering of penetration rates through excised human skin were: lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

Studies conducted in animals provide additional evidence that dermal absorption of inorganic lead is substantially lower than absorption from the inhalation or oral route. In a comparative study of dermal absorption of inorganic and organic salts of lead conducted in rats, approximately 100 mg of lead was applied in an occluded patch to the shaved backs of rats. Based on urinary lead measurements made prior to and for 12 days following exposure, lead compounds could be ranked according to the relative amounts absorbed (i.e., percent of dose recovered in urine; calculated by ATSDR): lead naphthalene (0.17%), lead nitrate (0.03%), lead stearate (0.006%), lead sulfate (0.006%), lead oxide (0.005%), and metal lead powder (0.002%). This rank order (i.e., lead naphthalene > lead oxide) is consistent with a rank ordering of penetration rates of inorganic and organic lead salts through excised skin from humans and guinea pigs: lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

Following application of lead acetate to the shaved clipped skin of rats, the concentration of lead in the kidneys was found to be higher relative to controls, suggesting that absorption of lead had occurred (Laug and Kunze 1948). This study also observed that dermal absorption of lead from lead arsenate was significantly less than from lead acetate, and that mechanical injury to the skin significantly increased the dermal penetration of lead.

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Organic Lead. Relative to inorganic lead and organic lead salts, tetraalkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). A 0.75-mL amount of tetraethyl lead, which was allowed to spread uniformly over an area of 25 cm² on the abdominal skin of rabbits, resulted in 10.6 mg of lead in the carcass at 0.5 hours and 4.41 mg at 6 hours (Kehoe and Thamann 1931). Tetraethyl lead was reported to be absorbed by the skin of rats to a much greater extent than lead acetate, lead oleate, and lead arsenate (Laug and Kunze 1948). Evidence for higher dermal permeability of organic lead compounds compared to inorganic organic salts of lead also comes from *in vitro* studies conducted with excised skin. The rank order of absorption rates through excised skin from humans and guinea pigs was as follows: tetrabutyl lead > lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

3.3.2 Distribution

Inorganic Lead. Absorbed inorganic lead appears to be distributed in essentially the same manner regardless of the route of absorption (Chamberlain et al. 1978; Kehoe 1987); therefore, the distribution of absorbed lead (i.e., by any route) is discussed in this section, rather than in separate sections devoted to specific routes of exposure. The expression, body burden is used here to refer to the total amount of lead in the body. Most of the available information about the distribution of lead to major organ systems (e.g., bone, soft tissues) derives from autopsy studies conducted in the 1960s and 1970s and reflect body burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). In general, these studies indicate that the distribution of lead appears to be similar in children and adults, although a larger fraction of the lead body burden of adults resides in bone (see Section 3.3.3 for further discussion). Several models of lead pharmacokinetics have been proposed to characterize such parameters as intercompartmental lead exchange rates, retention of lead in various tissues, and relative rates of distribution among the tissue groups (see Section 3.3.5 for further discussion of the classical compartmental models and physiologically based pharmacokinetic (PBPK) models developed for lead risk assessments).

Lead in Blood. Concentrations of lead in blood vary considerably with age, physiological state (e.g., pregnancy, lactation, menopause) and numerous factors that affect exposure to lead. The NHANES provide estimates for average blood lead concentrations in various demographic strata of the U.S. population. Samples for the most recent NHANES III were collected during the period 1999–2002. Geometric mean PbB of U.S. adults, ages 20–59 years, estimated from the NHANES III 1999–2002, were

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1.5 µg/dL (95% CI, 1.5–1.6) (CDC 2005a). Among adults, blood lead concentrations were highest in the strata that included ages 60 years and older (2.2 µg/dL; 95% CI, 2.1–2.3). Geometric mean PbB of children, ages 1–5 years, was 1.9 (95% CI, 1.8–2.1) for the 1999–2002 survey period; however, the geometric mean PbB for non-Hispanic black children is higher than that for Mexican-American and non-Hispanic white children, showing that differences in risk for exposure still exist (CDC 2005a). Central estimates from NHANES 1999–2002 when compared to those from NHANES III Phase 2 (1991–1994), and from Phase 1 of the NHANES III (1988–1991) and NHANES II (1976–1980), indicate a downward temporal trend in blood lead concentrations in the United States, over this period.

The excretory half-life of lead in blood, in adult humans, is approximately 30 days (Chamberlain et al. 1978; Griffin et al. 1975; Rabinowitz et al. 1976). Lead in blood is primarily in the red blood cells (99%) (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002). Most of the lead found in red blood cells is bound to proteins within the cell rather than the erythrocyte membrane. Approximately 40–75% of lead in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980a). Lead may also bind to γ -globulins (Ong and Lee 1980a). Lead in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine) and other ligands (Al-Modhefer et al. 1991).

Lead in Bone. In human adults, approximately 94% of the total body burden of lead is found in the bones. In contrast, bone lead accounts for 73% of the body burden in children (Barry 1975). Lead concentrations in bone increase with age throughout the lifetime, indicative of a relatively slow turnover of lead in adult bone (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). This large pool of lead in adult bone can serve to maintain blood lead levels long after exposure has ended (Fleming et al. 1997; Inskip et al. 1996; Kehoe 1987; O'Flaherty et al. 1982; Smith et al. 1996). It can also serve as a source of lead transfer to the fetus when maternal bone is resorbed for the production of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003).

Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Two physiological compartments appear to exist for lead in cortical and trabecular bone, to

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varying degrees. In one compartment, bone lead is essentially inert, having a half-life of several decades. A labile compartment exists as well that allows for maintenance of an equilibrium of lead between bone and soft tissue or blood (Rabinowitz et al. 1976). Although a high bone formation rate in early childhood results in the rapid uptake of circulating lead into mineralizing bone, bone lead is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate (O'Flaherty 1995a). Thus, most of the lead acquired early in life is not permanently fixed in the bone (O'Flaherty 1995a). In general, bone turnover rates decrease as a function of age, resulting in slowly increasing bone lead levels among adults (Barry 1975; Gross et al. 1975; Schroeder and Tipton 1968). An x-ray fluorescence study of tibial lead concentrations in individuals older than 10 years showed a gradual increase in bone lead after age 20 (Kosnett et al. 1994). In 60–70-year-old men, the total bone lead burden may be ≥ 200 mg, while children <16 years old have been shown to have a total bone lead burden of 8 mg (Barry 1975). However, in some bones (i.e., mid femur and pelvic bone), the increase in lead content plateaus at middle age and then decreases at higher ages (Drasch et al. 1987). This decrease is most pronounced in females and may be due to osteoporosis and release of lead from resorbed bone to blood (Gulson et al. 2002). Bone lead burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b).

Evidence for the exchange of bone lead and soft tissue lead stores comes from analyses of stable lead isotope signatures of lead in bone and blood. A comparison of blood and bone lead stable isotope signatures in five adults indicated that bone lead stores contributed to approximately 40–70% of the lead in blood (Smith et al. 1996). During pregnancy, the mobilization of bone lead increases, apparently as the bone is catabolized to produce the fetal skeleton. Analysis for kinetics of changes in the stable isotope signatures of blood lead in pregnant women as they came into equilibrium with a novel environmental lead isotope signature indicated that 10–88% of the lead in blood may derive from the mobilization of bone lead stores and approximately 80% of cord blood may be contributed from maternal bone lead (Gulson 2000; Gulson et al. 1997b, 1999c, 2003). The mobilization of bone lead during pregnancy may contribute, along with other mechanisms (e.g., increased absorption), to the increase in lead concentration that has been observed during the later stages of pregnancy (Gulson et al. 1997b; Lagerkvist et al. 1996; Schuhmacher et al. 1996). Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). Additional evidence for increased mobilization of bone lead into blood during pregnancy is provided from studies in nonhuman primates and rats (Franklin et al. 1997; Maldonado-Vega et al. 1996). Direct evidence for transfer of maternal bone lead to the fetus has been provided from stable lead isotope studies in *Cynomolgus* monkeys (*Macaca fascicularis*) that were dosed with lead having a different stable isotope ratio than the lead to which the monkeys were exposed at an

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earlier age; approximately 7–39% of the maternal lead burden that was transferred to the fetus appeared to have been derived from the maternal skeleton (Franklin et al. 1997).

In addition to pregnancy, other states of increased bone resorption appear to result in release of bone lead to blood; these include lactation and osteoporosis. Analysis for kinetics of changes in the stable isotope signatures of blood lead in postpartum women as they came into equilibrium with a novel environmental lead isotope signature indicated that the release of maternal bone lead to blood appears to accelerate during lactation (Gulson et al. 2003, 2004). Similar approaches have detected increased release of bone lead to blood in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowitz et al. 2004; Hernandez-Avila et al. 2000; Nash et al. 2004; Symanski and Hertz-Picciotto 1995).

Lead in Soft Tissues. Several studies have compared soft tissue concentrations of lead in autopsy samples of soft tissues (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). These studies were conducted in the 1960s and 1970s and, therefore, reflect burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels. Average PbBs reported in the adult subjects were approximately 20 µg/dL in the Barry (1975) and Gross et al. (1975) studies, whereas more current estimates of the average for adults in the United States are below 5 µg/dL (Pirkle et al. 1998). Levels in other soft tissues also appear to have decreased substantially since these studies were reported. For example, average lead concentrations in kidney cortex of male adults were 0.78 µg/g wet tissue and 0.79 µg/g, as reported by Barry (1975) and Gross et al. (1975), respectively (samples in the Barry study were from subjects who had no known occupational exposures). In a more recent analysis of kidney biopsy samples collected in Sweden, the mean level of lead in kidney cortex among subjects not occupationally exposed to lead was 0.18 µg/g (maximum, 0.56 µg/g) (Barregård et al. 1999). In spite of the downward trends in soft tissue lead levels, the autopsy studies provide a basis for describing the relative soft tissue distribution of lead in adults and children. Most of the lead in soft tissue is in liver. Relative amounts of lead in soft tissues as reported by Schroeder and Tipton (1968), expressed as percent of total soft tissue lead, were: liver, 33%; skeletal muscle, 18%; skin, 16%; dense connective tissue, 11%; fat, 6.4%; kidney, 4%; lung, 4%; aorta, 2%; and brain, 2% (other tissues were <1%). The highest soft tissue concentrations in adults also occur in liver and kidney cortex (Barry 1975; Gerhardsson et al. 1986a, 1995b; Gross et al. 1975; Oldereid et al. 1993). The relative distribution of lead in soft tissues, in males and females, expressed in terms of tissue:liver concentration ratios, were: liver, 1.0 (approximately 1 µg/g wet weight); kidney cortex, 0.8; kidney medulla, 0.5; pancreas, 0.4; ovary, 0.4; spleen, 0.3;

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prostate, 0.2; adrenal gland, 0.2; brain, 0.1; fat, 0.1; testis, 0.08; heart, 0.07; and skeletal muscle, 0.05 (Barry 1975; Gross et al. 1975). In contrast to lead in bone, which accumulates lead with continued exposure in adulthood, concentrations in soft tissues (e.g., liver and kidney) are relatively constant in adults (Barry 1975; Treble and Thompson 1997), reflecting a faster turnover of lead in soft tissue, relative to bone.

Maternal-Fetal-Infant Transfer. The maternal/fetal blood lead concentration ratio, indicated from cord blood lead measurements, is approximately 0.9 (Carbone et al. 1998; Goyer 1990; Graziano et al. 1990). In one of the larger studies of fetal blood lead concentration, maternal and cord blood lead concentration were measured at delivery in 888 mother-infant pairs; the cord/maternal ratio was relatively constant, 0.93, over a PbB range of approximately 3–40 µg/dL (Graziano et al. 1990). A study of 159 mother-infant pairs also found a relatively constant cord/maternal ratio (0.84) over a maternal blood lead range of approximately 1–12 µg/dL (Carbone et al. 1998). As noted in the discussion of the distribution of lead in bone, measurements of stable lead isotope ratios in pregnant women and cord blood, as they came into equilibrium with a novel environmental lead isotope signature, indicated that approximately 80% of lead in fetal cord blood appears to derive from maternal bone stores (Gulson et al. 2003). A recent study looked at factors that might influence the amount of lead that infants receive (Harville et al. 2005). The analysis, conducted on 159 mother-infant pairs, revealed that higher blood pressure and alcohol consumption late in pregnancy were associated with more lead in cord blood relative to maternal PbB. In addition, higher hemoglobin and sickle cell trait were associated with reduced cord blood lead relative to maternal PbB. No associations were found for calcium intake, physical activity, or smoking.

Maternal lead can also be transferred to infants during breastfeeding. Numerous studies have reported lead concentrations in maternal blood and breast milk. In general, these studies indicate that breast milk/maternal blood concentration ratios are <0.1, although values of 0.9 have been reported (Ettinger et al. 2006; Gulson et al. 1998a). Ettinger et al. (2006) assessed factors influencing breast milk lead concentration in a group of 367 women and found that PbB (mean, 8–9 µg/dL; range, 2–30) was a stronger predictor of breast milk lead (mean, 0.9–1.4 µg/L; range, 0.2–8 µg/dL) than bone lead, and that tibia lead (mean, 9.5 µg/g; range, <1–76.5 µg/dL) was a stronger predictor of breast milk lead than patella bone lead (mean, 14.6 µg/dL; range, <1–67.2 µg/dL). Stable lead isotope dilution measurements in infant-mother pairs, measured as they came into equilibrium with a novel environmental lead isotope signature, suggested that lead in breast milk can contribute substantially to isotope profile of infant blood (approximately 40–80%; Gulson et al. 1998b).

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Organic Lead. Information on the distribution of lead in humans following exposures to organic lead is extremely limited. One hour following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl or tetramethyl lead (1 mg/m^3), approximately 50% of the ^{203}Pb body burden was associated with liver and 5% with kidney; the remaining ^{203}Pb was widely distributed throughout the body (Heard et al. 1979). The kinetics of ^{203}Pb in blood of these subjects showed an initial declining phase during the first 4 hours (tetramethyl lead) or 10 hours (tetraethyl lead) after the exposure, followed by a phase of gradual increase in PbB that lasted for up to 500 hours after the exposure. Radioactive lead in blood was highly volatile immediately after the exposure and transitioned to a nonvolatile state thereafter. These observations may reflect an early distribution of organic lead from the respiratory tract, followed by a redistribution of de-alkylated lead compounds (see Section 3.3.3 for further discussion of alkyl lead metabolism).

In a man and woman who accidentally inhaled a solvent containing 31% tetraethyl lead (17.6% lead by weight), lead concentrations in the tissues, from highest to lowest, were liver, kidney, brain, pancreas, muscle, and heart (Bolanowska et al. 1967). In another incident, a man ingested a chemical containing 59% tetraethyl lead (38% lead w/w); lead concentration was highest in the liver followed by kidney, pancreas, brain, and heart (Bolanowska et al. 1967).

3.3.3 Metabolism

Inorganic Lead. Metabolism of inorganic lead consists of formation of complexes with a variety of protein and nonprotein ligands. Major extracellular ligands include albumen and nonprotein sulfhydryls (see Section 3.3.2 for further discussion). The major intracellular ligand in red blood cells is ALAD (see Section 3.3.2 for further discussion). Lead also forms complexes with proteins in the cell nucleus and cytosol (see Section 3.4.2 for further discussion).

Organic Lead. Alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450. Relatively few studies that address the metabolism of alkyl lead compounds in humans have been reported. Occupational monitoring studies of workers who were exposed to tetraethyl lead have shown that tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead, and inorganic lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994). Trialkyl lead metabolites were found in the liver, kidney, and brain following exposure to the tetraalkyl compounds in workers; these metabolites have also been detected in brain tissue of nonoccupational subjects (Bolanowska et al. 1967; Nielsen et al. 1978). In volunteers exposed by inhalation to 0.64 and 0.78 mg lead/m^3 of ^{203}Pb -labeled tetraethyl and tetramethyl lead, respectively, lead was cleared from the

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blood within 10 hours, followed by a re-appearance of radioactivity back into the blood after approximately 20 hours (Heard et al. 1979). The high level of radioactivity initially in the plasma indicates the presence of tetraalkyl/trialkyl lead. The subsequent rise in blood radioactivity, however, probably represents water-soluble inorganic lead and trialkyl and dialkyl lead compounds that were formed from the metabolic conversion of the volatile parent compounds (Heard et al. 1979).

3.3.4 Excretion

Independent of the route of exposure, absorbed lead is excreted primarily in urine and feces; sweat, saliva, hair and nails, and breast milk are minor routes of excretion (Chamberlain et al. 1978; Griffin et al. 1975; Hursh and Suomela 1968; Hursh et al. 1969; Kehoe 1987; Rabinowitz et al. 1976; Stauber et al. 1994). Fecal excretion accounts for approximately one-third of total excretion of absorbed lead (fecal/urinary excretion ratio of approximately 0.5), based on intravenous injection studies conducted in humans (Chamberlain et al. 1978). A similar value for fecal/urinary excretion ratio, approximately 0.5, has been observed following inhalation of submicron lead particles (Chamberlain et al. 1978; Hursh et al. 1969).

3.3.4.1 Inhalation Exposure

Inorganic Lead. Inorganic lead inhaled as submicron particles is deposited primarily in the bronchiolar and alveolar regions of the respiratory tract, from where it is absorbed and excreted primarily in urine and feces (Chamberlain et al. 1978; Hursh et al. 1969; Kehoe 1987). Fecal/urinary excretion ratios were approximately 0.5 following inhalation of submicron lead-bearing particles (Chamberlain et al. 1978; Hursh et al. 1969). Higher fecal-urinary ratios would be expected following inhalation of larger particle sizes (e.g., $>1\ \mu\text{m}$) as these particles would be cleared to the gastrointestinal tract from where a smaller percentage would be absorbed (Kehoe 1987; see Section 3.3.1.2).

Organic Lead. Lead derived from inhaled tetraethyl and tetramethyl lead is excreted in exhaled air, urine, and feces (Heard et al. 1979). Following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl ($1\ \text{mg}/\text{m}^3$), in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). In a similar experiment conducted with (^{203}Pb) tetramethyl lead, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was exhaled in 48 hours. Lead that was not exhaled was excreted in urine and feces. Fecal/urinary excretion ratios were 1.8 following exposure to tetraethyl lead and 1.0 following exposure to tetramethyl lead (Heard et al. 1979). Occupational monitoring studies of workers who were exposed to tetraethyl lead have shown that tetraethyl lead is excreted in the urine as

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diethyl lead, ethyl lead, and inorganic lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

3.3.4.2 Oral Exposure

Inorganic Lead. Much of the available information on the excretion of ingested lead in adults derives from studies conducted on five male adults who received daily doses of ^{207}Pb nitrate for periods up to 210 days (Rabinowitz et al. 1976). The dietary intakes of the subjects were reduced to accommodate the tracer doses of ^{207}Pb without increasing daily intake, thus preserving a steady state with respect to total lead intake and excretion. Total lead intakes (diet plus tracer) ranged from approximately 210 to 360 $\mu\text{g}/\text{day}$. Urinary excretion accounted for approximately 12% of the daily intake (range for five subjects: 7–17%) and fecal excretion, approximately 90% of the daily intake (range, 87–94%). Based on measurements of tracer and total lead in saliva, gastric secretions, bile, and pancreatic secretions (samples collected from three subjects by intubation), gastrointestinal secretion of lead was estimated to be approximately 2.4% of intake (range, 1.9–3.3%). In studies conducted at higher ingestion intakes, 1–3 mg/day for up to 208 weeks, urinary lead excretion accounted for approximately 5% of the ingested dose (Kehoe 1987).

3.3.4.3 Dermal Exposure

Inorganic lead is excreted in sweat and urine following dermal exposure to lead nitrate or lead acetate (Moore et al. 1980; Stauber et al. 1994).

3.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewett and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

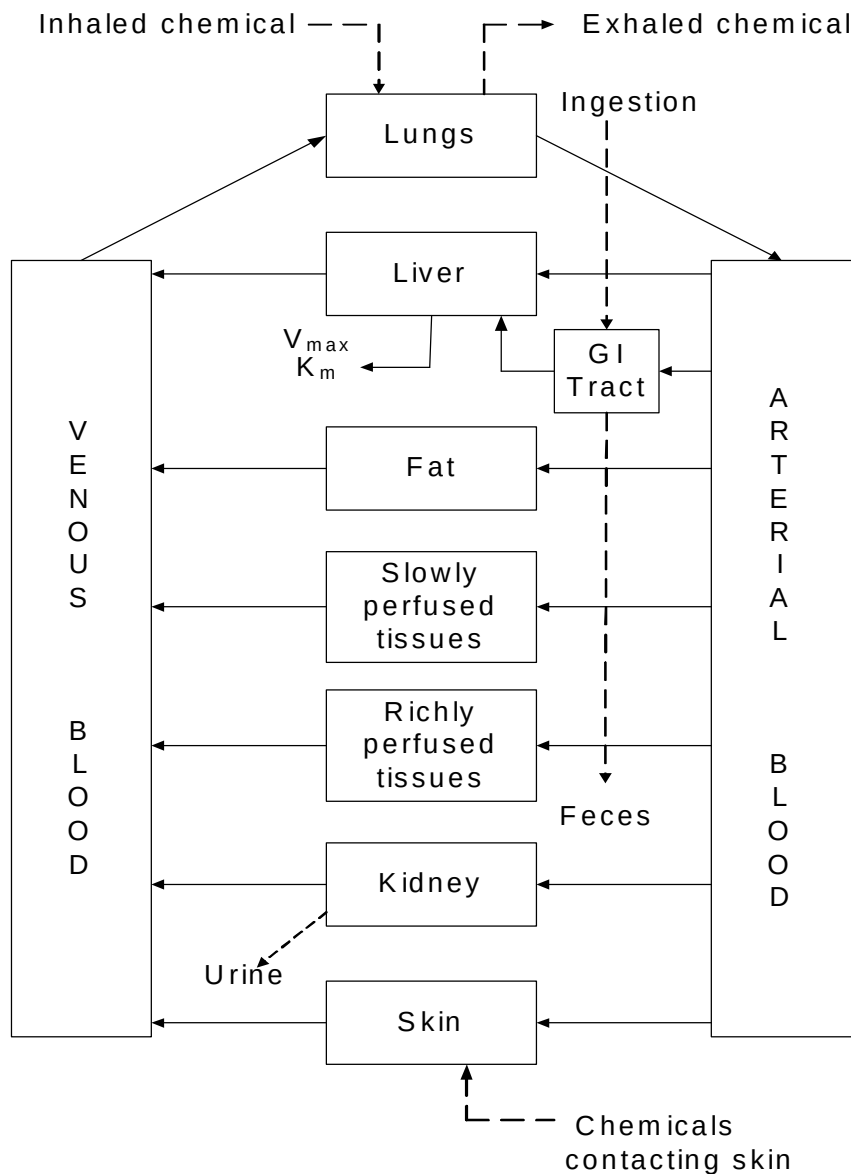
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

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Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan et al. 1994

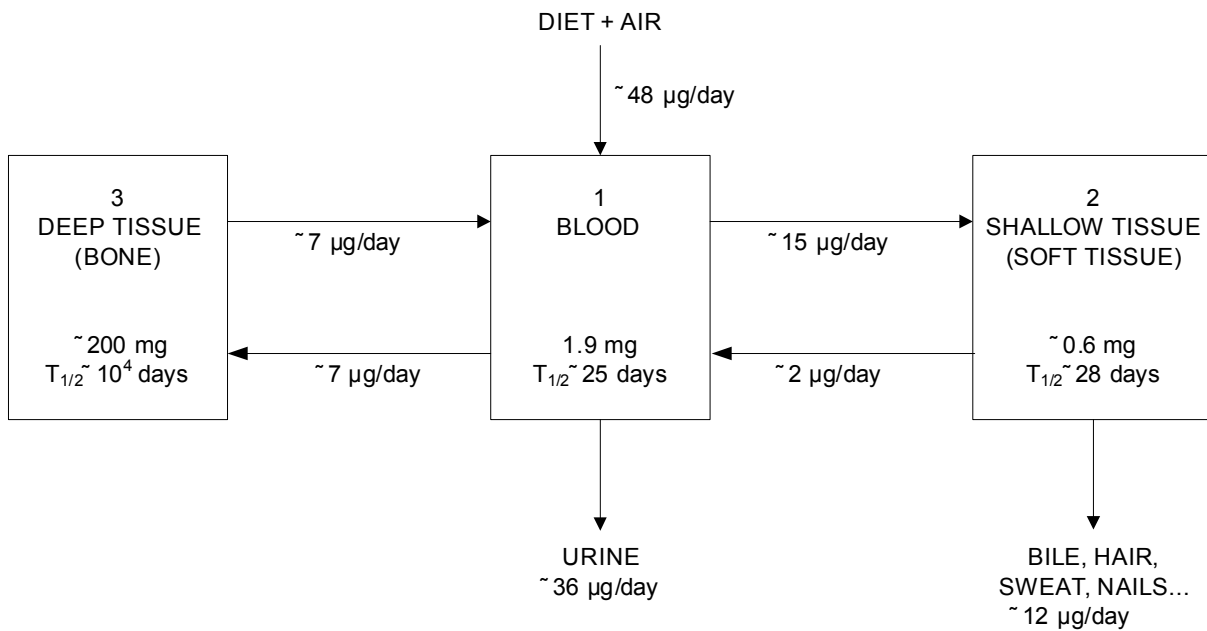
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If PBPK models for lead exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Early lead modeling applications relied on classical pharmacokinetics. Compartments representing individual organs or groups of organs that share a common characteristic were defined as volumes, or pools, that are kinetically homogeneous. For example, the body could be represented by a central compartment (e.g., blood plasma), and one or two peripheral compartments, which might be “shallow” or “deep” (i.e., they may exchange relatively rapidly or relatively slowly with blood plasma) (O’Flaherty 1987). One of the first of such models was proposed by Rabinowitz et al. (1976) based on a study of the kinetics of ingested stable lead isotope tracers and lead balance data in five healthy adult males. The Rabinowitz model includes three compartments: a central compartment representing blood and other tissues and spaces in rapid equilibrium with blood (e.g., interstitial fluid); a shallow tissue compartment, representing soft tissues and rapidly exchanging pools within the skeleton; and a deep tissue compartment, representing, primarily, slowly exchanging pools of lead within bone. Excretion pathways represented in the model included urinary, from the central compartment, and bile, sweat, hair, and nails, from the shallow tissue compartment. A diagram of the model is shown in Figure 3-6, along with the lead content and reported mean residence times and the rates of lead movement between compartments (residence times are the reciprocal of the sum of the individual elimination rate constants). The model predicts pseudo-first order half-times for lead of approximately 25, 28, and 10^4 days in the central, shallow tissue, and deep compartments, respectively. The slow kinetics of the deep tissue compartment leads to the prediction that it would contain most of the lead burden after lengthy exposures (e.g., years), consistent with lead measurements made in human autopsy samples (see Section 3.3.2 Distribution). Note that this model did not simulate the distribution of lead within blood (e.g., erythrocytes and plasma), nor did it simulate subcompartments within bone or physiological processes of bone turnover that might affect kinetics of the deep tissue compartment.

Marcus (1985b) reanalyzed the data from stable isotope tracer studies of Rabinowitz et al. (1976) and derived an expanded multicompartment kinetic model for lead (Figure 3-7). The model included separate compartments for cortical (slow, $t_{1/2}$ 1.2×10^4 – 3.5×10^4 days) and trabecular (fast, $t_{1/2}$ 100–700 days), an approach subsequently adopted in several models (Bert et al. 1989; EPA 1994a, 1994b; Leggett 1993; O’Flaherty 1993, 1995a). A more complex representation of the lead disposition in bone included explicit simulation of diffusion of lead within the bone volume of the osteon and exchange with blood at the canaliculus (Marcus 1985a; Figure 3-8). The bone diffusion model was based on lead kinetics data from studies conducted in dogs. Marcus (1985c) also introduced nonlinear kinetics of exchange of lead

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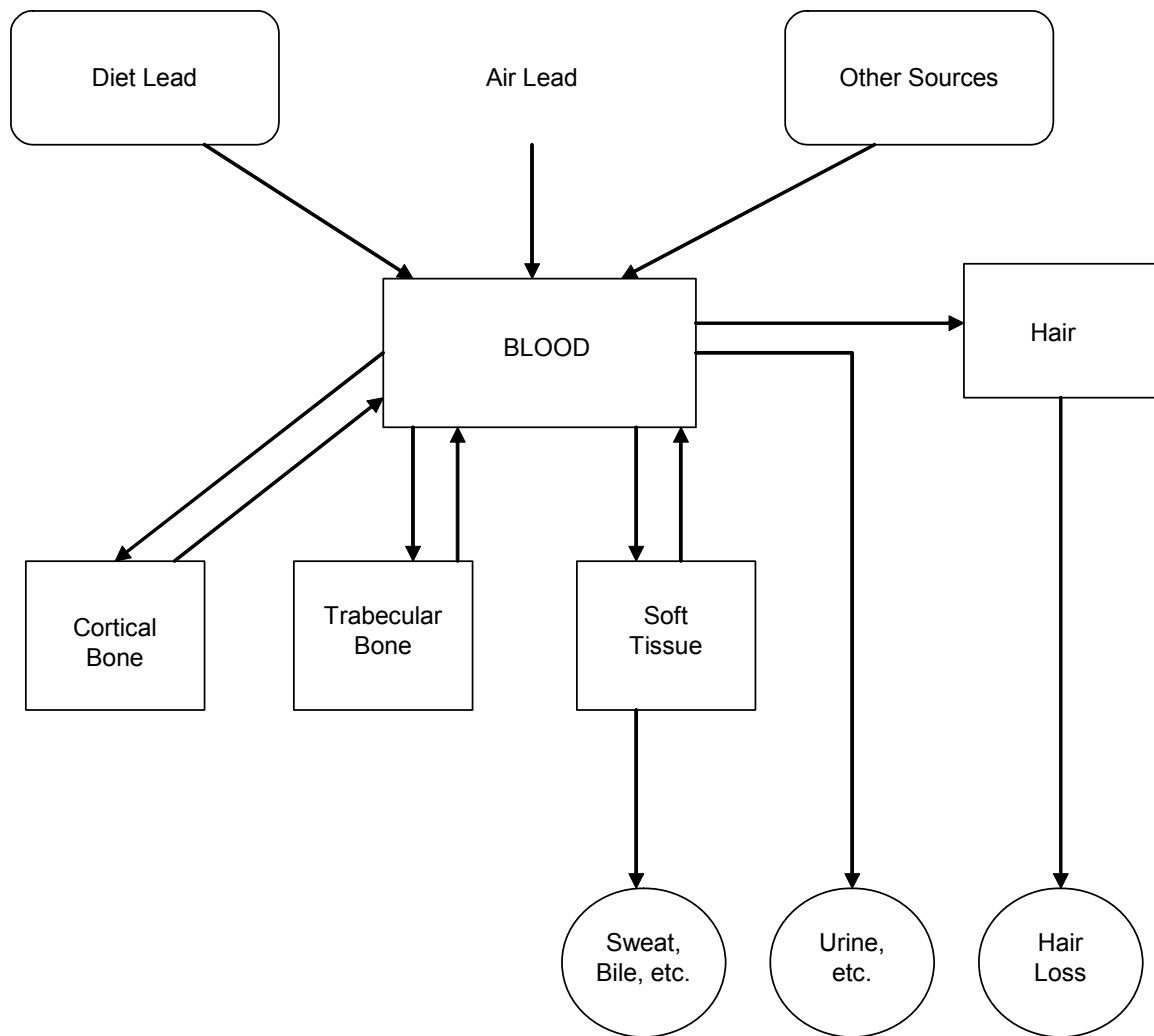
Figure 3-6. Lead Metabolism Model*

*Schematic model for lead kinetics, in which distribution is represented as a central (blood) compartment and peripheral soft-tissue (fast = $t_{1/2}$ 28 days) and deep tissue (slow = $t_{1/2}$ 10,000 days) compartments.

Source: Rabinowitz et al. 1976

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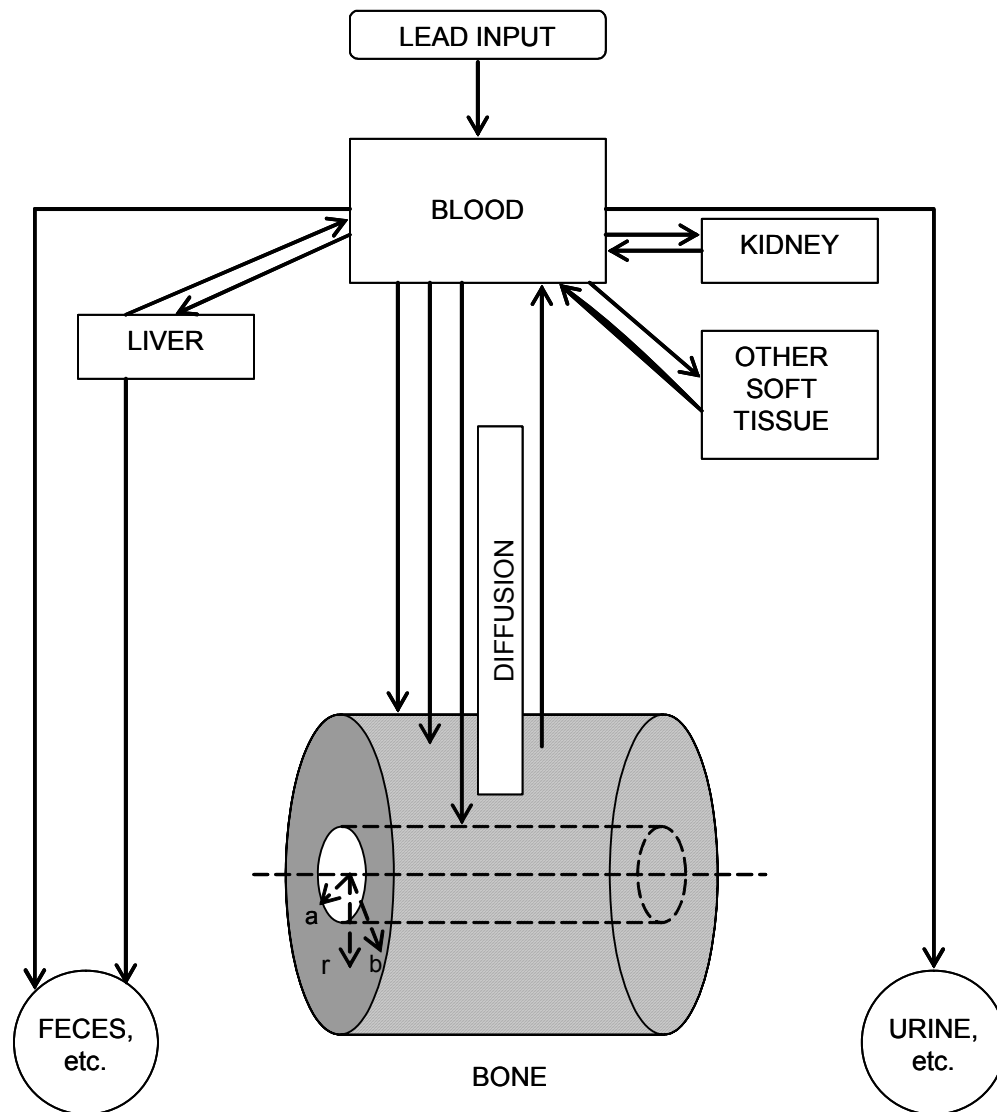
Figure 3-7. Compartments and Pathways of Lead Exchange in the Marcus (1985b) Model*



*Schematic model for lead kinetics, in which bone is represented as a cortical (slow= $t_{1/2}$ 1.2×10^4 – 3.5×10^4 days) and trabecular (fast= $t_{1/2}$ 100–700 days) compartments.

Source: Marcus 1985b

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Figure 3-8. Schematic Model for Lead Kinetics in Marcus (1985a) Bone Model*

*Schematic model for lead kinetics, in which bone is represented as an extended cylindrical *canalicular territory*. The canalicular territory has a radius b , and surrounds the canaliculus of radius a . Lead diffuses across radius r , between the fluid in the canaliculus (which is in communication with blood in the Haversian canal, not shown) and the bone volume of the canalicular territory.

Source: Marcus 1985a

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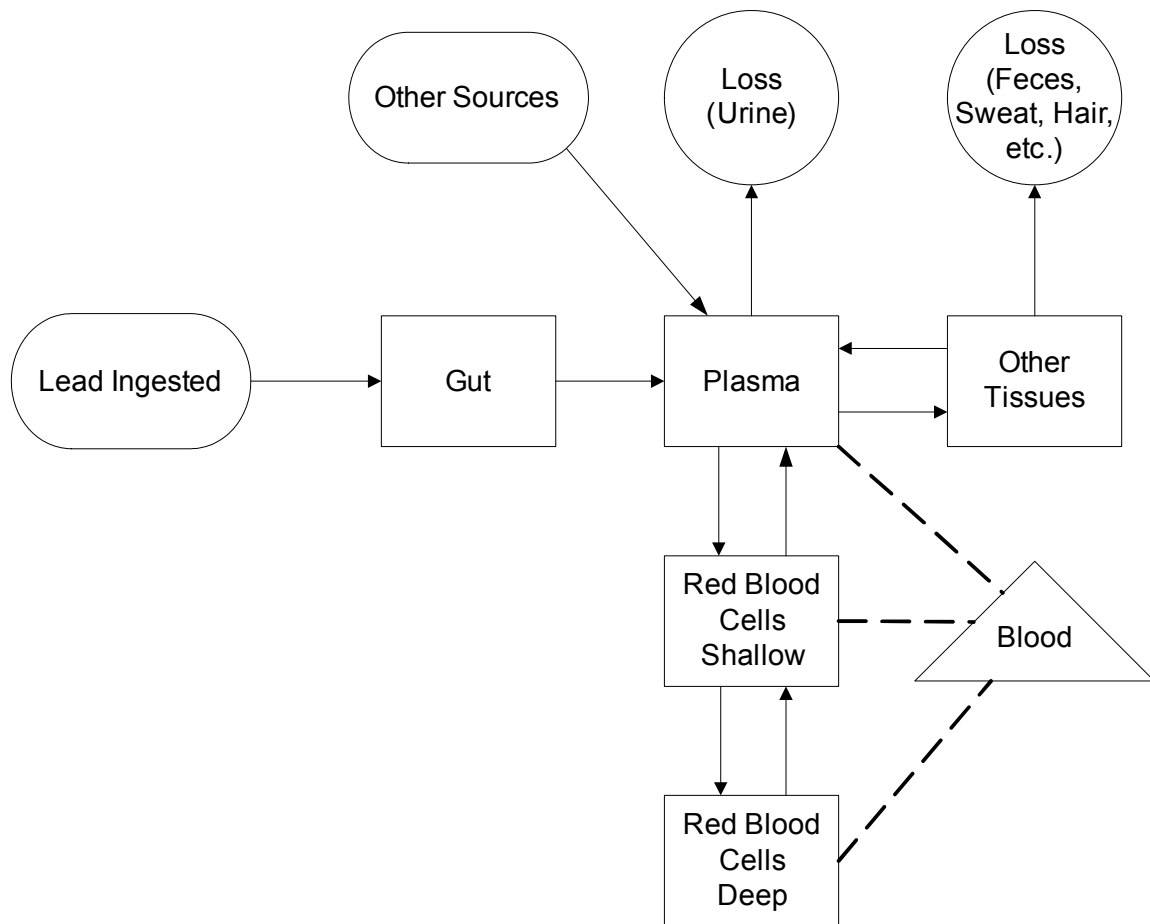
between plasma and erythrocytes. The blood model included four blood subcompartments: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool (see Figure 3-9). This model predicted the curvilinear relationship between plasma and blood lead concentrations observed in humans (see Section 3.3.2 Distribution for further discussion of plasma-erythrocyte lead concentrations).

Additional information on lead biokinetics, bone mineral metabolism, and lead exposures has led to further refinements and expansions of these earlier modeling efforts. Three pharmacokinetic models, in particular, are currently being used or are being considered for broad application in lead risk assessment: (1) the O'Flaherty Model, which simulates lead kinetics from birth through adulthood (O'Flaherty 1993, 1995a); (2) the Integrated Exposure Uptake BioKinetic (IEUBK) Model for Lead in Children developed by EPA (1994a, 1994b); and (3) the Leggett Model, which simulates lead kinetics from birth through adulthood (Leggett 1993). Of the three approaches, the O'Flaherty Model has the fewest lead-specific parameters and relies more extensively on physiologically based parameters to describe volumes, flows, composition, and metabolic activity of blood and bone that determine the disposition of lead in the human body. Both the IEUBK Model and the Leggett Model are classic multicompartmental models; the values of the age-specific transfer rate constants for lead are based on kinetics data obtained from studies conducted in animals and humans, and may not have precise physiological correlates. Thus, the structure and parameterization of the O'Flaherty Model is distinct from both the IEUBK Model and Leggett Model. All three models represent the rate of uptake of lead (i.e., amount of lead absorbed per unit of time) as relatively simple functions (f) of lead intake (e.g., $\text{uptake} = \text{intake} \times A$, or $\text{uptake} = \text{intake} \times f[\text{intake}]$). The values assigned to A or other variables in $f(\text{intake})$ are, in general, age-specific and, in some models, environmental medium-specific. However, the models do not modify the representation of uptake as functions of the many other physiologic variables that may affect lead absorption (e.g., nutritional status). While one can view this approach as a limitation of the models, it also represents a limitation of the data available to support more complex representations of lead absorption.

The IEUBK Model simulates multimedia exposures, uptake, and kinetics of lead in children ages 0–7 years; the model is not intended for use in predicting lead pharmacokinetics in adults. The O'Flaherty and Leggett models are lifetime models, and include parameters that simulate uptake and kinetics of lead during infancy, childhood, adolescence, and adulthood. Lead exposure (e.g., residence-specific environmental lead concentrations, childhood activity patterns) is not readily described by current versions of these models. By contrast, the IEUBK Model includes parameters for simulating exposures and uptake to estimate average daily uptake of lead ($\mu\text{g}/\text{day}$) among populations of children potentially

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Figure 3-9. Compartmental Model for Lead in Plasma and Red Blood Cells in the Marcus (1985c) Model*



*Schematic model for lead kinetics in which blood is represented as plasma (central exchange compartment) and red blood cells, the latter having shallow and deep pools.

Source: Marcus 1985c

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exposed via soil and dust ingestion, air inhalation, lead-based paint chip ingestion, tap water ingestion, and diet.

All three models have been calibrated, to varying degrees, against empirical physiological data on animals and humans, and data on blood lead concentrations in individuals and/or populations (EPA 1994a, 1994c; Leggett 1993; O'Flaherty 1993). However, applications in risk assessment require that the models accurately predict blood lead distributions in real populations, in particular the “upper tails” (e.g., 95th percentile), when input to the models consists of data that describe site-specific exposure conditions (e.g., environmental lead concentrations, physicochemical properties of soil and dust) (Beck et al. 2001; Griffin et al. 1999). In evaluating models for use in risk assessment, exposure data collected at hazardous waste sites have been used to drive model simulations (Bowers and Mattuck 2001; Hogan et al. 1998). The exposure module in the IEUBK Model makes this type of evaluation feasible.

The focus on relying on blood lead concentrations for model evaluation and calibration derives from several concerns. The empirical basis for a relationship between low levels of lead exposure and behavioral dysfunction largely consists of prospective epidemiological studies relating various indices of dysfunction with blood lead concentration (see Section 3.2.2). In this context, blood lead concentration has been related to health effects of lead, and this is the main reason that the focus of interest in the models has been on estimating blood lead concentrations. Also, the most available data with which to calibrate and validate the models has been data relating exposure and/or lead intake to blood concentration. Thus, there is greater confidence in the validity of the models for estimating blood concentrations, rather than lead levels in other physiologic compartments. Although the principal adverse health effects of lead have been related to concentrations of lead in blood, other biomarkers of lead exposure, such as bone lead concentrations, are also of value in assessing associations between lead exposure and health; hence, there is a need for models that predict concentrations of lead in tissues other than blood (see Section 3.2.2).

The following three pharmacokinetic models are discussed in great detail below: (1) the O'Flaherty Model (O'Flaherty 1993, 1995a); (2) the IEUBK Model for Lead in Children (EPA 1994a, 1994b); and (3) the Leggett Model (Leggett 1993).

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3.3.5.1 O'Flaherty Model

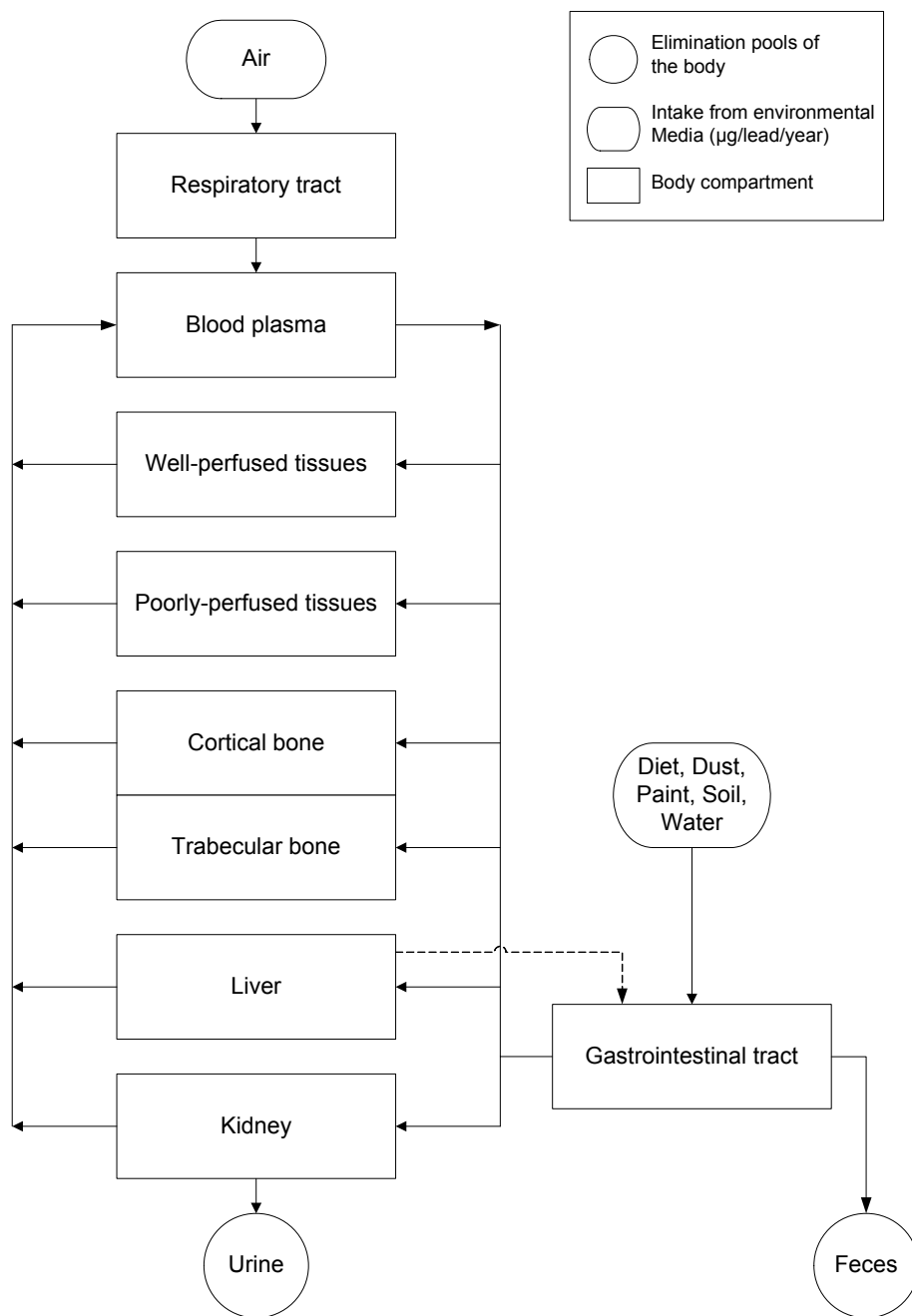
The O'Flaherty Model simulates lead exposure, uptake, and disposition in humans, from birth through adulthood (O'Flaherty 1993, 1995a). Figure 3-10 shows a conceptualized representation of the O'Flaherty Model, including the movement of lead from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between blood plasma, liver, kidney, richly-perfused tissues, poorly-perfused tissues, bone compartments, and excretion from liver and/or kidney. The model simulates both age- and media-specific absorption. Because many of the pharmacokinetic functions are based on body weight and age, the model can be used to estimate blood lead concentrations across a broad age range, including infants, children, adolescents, and adults. The model uses physiologically based parameters to describe the volume, composition, and metabolic activity of blood, soft tissues, and bone that determine the disposition of lead in the human body.

Description of the model. The O'Flaherty Model simulates lead absorption and disposition from birth through adulthood. A central feature of the model is the growth curve, a logistic expression relating body weight to age. The full expression relating weight to age has five parameters (constants), so that it can readily be adapted to fit a range of standardized growth curves for men and women. Tissue growth and volumes are linked to body weight; this provides explicit modeling of concentrations of lead in tissues. Other physiologic functions (e.g., bone formation) are linked to body weight, to age, or to both.

Lead exchange between blood plasma and bone is simulated as parallel processes occurring in cortical (80% of bone volume) and trabecular bone (20% of bone volume). Uptake and release of lead from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively. Rates of bone formation and resorption are simulated as age-dependent functions, which gives rise to an age-dependence of lead kinetics in bone. The model simulates an age-related transition from immature bone, in which bone turn-over (formation and resorption) rates are relatively high, to mature bone, in which turn-over is relatively slow. Changes in bone mineral turnover associated with senescence (e.g., postmenopausal osteoporosis) are not represented in the model. In addition to metabolically active regions of bone, in which lead uptake and loss is dominated by bone formation and loss, a region of slow kinetics in mature cortical bone is also simulated, in which lead uptake and release to blood occur by heteroionic exchange with other minerals (e.g., calcium). Heteroionic exchange is simulated as a radial diffusion in bone volume of the osteon. All three processes are linked to body weight, or the rate of change of weight with age. This approach allows for explicit simulation of the effects of bone formation (e.g., growth) and loss, changes in bone volume, and bone maturation on lead

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Figure 3-10. Compartments and Pathways of Lead Exchange in the O'Flaherty Model*



*Schematic model for lead kinetics in which lead distribution is represented by flows from blood plasma to liver, kidney, richly-perfused tissues, poorly-perfused tissues, and cortical and trabecular bone. The model simulates tissue growth with age, including growth and resorption of bone mineral.

Sources: O'Flaherty 1991b, 1993, 1995a

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uptake and release from bone. Exchanges of lead between blood plasma and soft tissues (e.g., kidney and liver) are represented as flow-limited processes. The model simulates saturable binding of lead in erythrocytes; this replicates the curvilinear relationship between plasma and erythrocyte lead concentrations observed in humans (see Sections 3.3.2 and 3.4.1). Excretory routes include kidney to urine and liver to bile. Total excretion (clearance from plasma attributable to bile and urine) is simulated as a function of glomerular filtration rate. Biliary and urinary excretory rates are proportioned as 70 and 30% of the total plasma clearance, respectively.

The O'Flaherty Model simulates lead intake from inhalation and ingestion. Inhalation rates are age-dependent. Absorption of inhaled lead is simulated as a fraction (0.5) of the amount inhaled, and is independent of age. The model simulates ingestion exposures from infant formula, soil and dust ingestion, and drinking water ingestion. Rates of soil and dust ingestion are age-dependent, increasing to approximately 130 mg/day at age 2 years, and declining to <1 mg/day after age 10 years. Gastrointestinal absorption of lead in diet and drinking water is simulated as an age-dependent fraction, declining from 0.58 of the ingestion rate at birth to 0.08 after age 8 years. These values can be factored to account for relative bioavailability when applied to absorption of lead ingested in dust or soil.

Risk assessment. The O'Flaherty Model has several potential applications to risk assessments at hazardous waste sites. The model can be used to predict the blood lead concentrations in a broad age range, including infants, children, and adults. The model may be modified to simulate the pharmacokinetics of lead in potential sensitive subpopulations, including pregnant women and fetuses, as well as older adults. The model does not contain a detailed exposure module; however, model simulations have been run holding physiological variables fixed and allowing soil and dust lead concentrations to vary in order to estimate the range of environmental lead concentrations that would be expected to yield close correspondence between predicted and observed blood lead concentrations (O'Flaherty 1993, 1995a).

The O'Flaherty Model, as described in O'Flaherty (1993, 1995a), utilizes point estimates for parameter values and yields point estimates as output; however, a subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability in exposure, absorption, and erythrocyte lead binding capacity (Beck et al. 2001). This extension of the model can be used to predict the probability that children exposed to lead in environmental media will have blood lead concentrations exceeding a health-based level of concern (e.g., 10 µg/dL).

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The model was designed to operate with an exposure time step on 1 year (the smallest time interval for a single exposure event). However, the implementation code allows constructions of simulations with an exposure time step as small as 1 day, which would allow simulation of rapidly changing intermittent exposures (e.g., an acute exposure event).

Validation of the model. The O'Flaherty Model was initially calibrated to predict blood, bone, and tissue lead concentrations in rats (O'Flaherty 1991a), and subsequently modified to reflect anatomical and physiological characteristics in children (O'Flaherty 1995a), adults (O'Flaherty 1993), and *Cynomolgus* monkeys (*M. fascicularis*) (O'Flaherty et al. 1998). Model parameters were modified to correspond with available information on species- and age-specific anatomy and physiological processes described above. In general, the model has been shown to reproduce blood lead observations in children and adults well, except in instances where lead is ingested at very high concentrations (O'Flaherty 1993, 1995a).

Target tissues. Output from the O'Flaherty Model is an estimate of age-specific blood lead concentrations. The O'Flaherty Model has also been used to predict lead concentrations in bone and other tissue compartments (O'Flaherty 1995a), in order to evaluate correspondence between predicted tissue concentrations and observed concentrations in different populations of children and adults.

Species extrapolation. The mathematical structure of the O'Flaherty Model for humans is designed to accept parameter values that reflect the physiology and metabolism of different species (O'Flaherty 1993). Although the model has been calibrated to predict compartmental lead masses for human children and adults; the model for humans was derived from a model for rats (O'Flaherty 1991a), and has been successfully extrapolated, with modification, to nonhuman primates (O'Flaherty et al. 1998). Crucial to the extrapolation of the model across species are the parameters describing bone formation, resorptions, and volume. Certain parameter values describing bone physiology and metabolism are likely to be relatively independent of species; for example, volume fractions of cortical bone and trabecular bone appear to be similar across species (i.e., 80% cortical, 20% trabecular) (Gong et al. 1964). However, while the potential for bone resorption and accretion of new bone is present in all species, the magnitude and age dependence of these processes are variable with species (O'Flaherty 1995a). These factors would have to be evaluated in extrapolating the model to other species.

Interroute extrapolation. The O'Flaherty Model simulates intakes and uptake of ingested and inhaled lead and includes media-specific estimates of absorption from the gastrointestinal tract.

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3.3.5.2 IEUBK Model

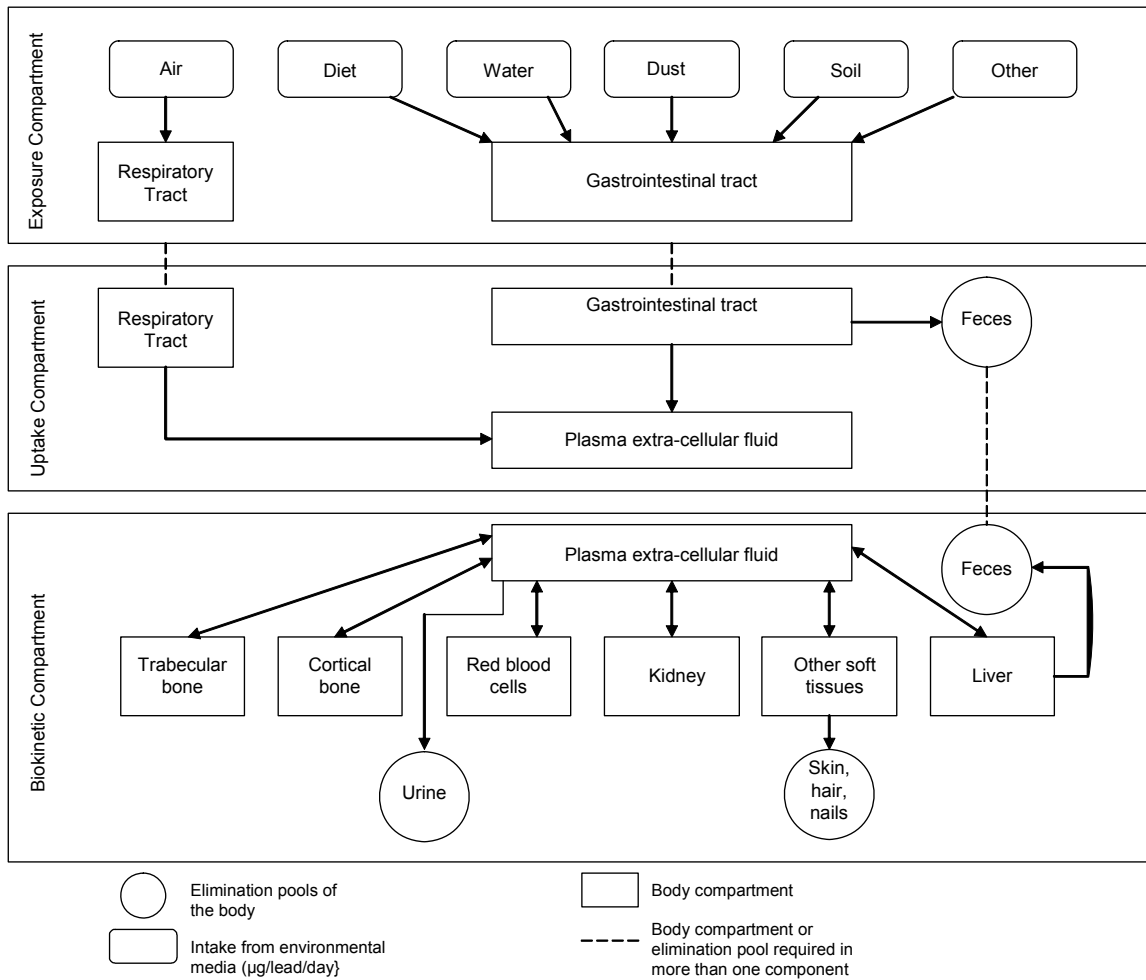
The IEUBK Model for Lead in Children is a classical multicompartamental pharmacokinetics model linked to an exposure and probabilistic model of blood lead concentration distributions in populations of children ages 0–7 years (EPA 1994a, 1994b; White et al. 1998). Figure 3-11 shows a conceptualized representation of the IEUBK Model. The model has four major submodels: (1) exposure model, in which average daily intakes of lead ($\mu\text{g}/\text{day}$) are calculated for each inputted exposure concentration (or rates) of lead in air, diet, dust, soil, and water; (2) uptake model, which converts environmental media-specific lead intake rates calculated from the exposure model into a media-specific time-averaged uptake rate ($\mu\text{g}/\text{day}$) of lead to the central compartment (blood plasma); (3) biokinetic model, which simulates the transfer of absorbed lead between blood and other body tissues, elimination of lead from the body (via urine, feces, skin, hair, and nails), and predicts an average blood lead concentration for the exposure time period of interest; and (4) blood lead probability model, which applies a log-normal distribution (with parameters geometric mean and geometric standard deviation) to predict probabilities for the occurrence of a specified given blood lead concentration in a population of similarly exposed children.

Description of the Model

Exposure Model. The exposure model simulates intake of lead ($\mu\text{g}/\text{day}$) for inputted exposures to lead in air ($\mu\text{g}/\text{m}^3$), drinking water ($\mu\text{g}/\text{L}$), soil-derived dust ($\mu\text{g}/\text{g}$), or diet ($\mu\text{g}/\text{day}$). The exposure model operates on a 1-year time step, the smallest time interval for a single exposure event. The model accepts inputs for media intake rates (e.g., air volumes breathing rates, drinking water consumption rate, soil and dust ingestion rate). The air exposure pathway is partitioned in exposures to outdoor air and indoor air; with age-dependent values for time spent outdoors and indoors (hours/day). Exposure to lead to soil-derived dust is also partitioned into outdoor and indoor contributions. The intakes from all ingested exposure media (diet, drinking water, soil-derived dust) are summed to calculate a total intake to the gastrointestinal tract, for estimating capacity-limited absorption (see description of the uptake model).

Uptake Model. The uptake model simulates lead absorption for the gastrointestinal tract as the sum of a capacity-limited (represented by a Michaelis-Menten type relationship) and unlimited processes (represented by a first-order, linear, relationship). These two terms are intended to represent two different mechanisms of lead absorption, an approach that is in accord with limited available data in humans and animals that suggest a capacity limitation to lead absorption (see Sections 3.3.2 and 3.4.1). One of the parameters for the capacity-limited absorption process (that represents that maximum rate of absorption)

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Figure 3-11. Structure of the IEUBK Model for Lead in Children*

*Schematic for integrated lead exposure-kinetics model in which simulated multi-media exposures are linked to simulations of lead uptake (i.e., absorption into the plasma-ECF) tissue distribution, and excretion.

Sources: EPA 1994a, 1994b

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is age-dependent. The above representation gives rise to a decrease in the fractional absorption of ingested lead as a function of total lead intake as well as an age-dependence of fractional lead absorption. Absorption fractions are also medium-specific. At 30 months of age, at low intakes ($<200 \mu\text{g/day}$), below the rates at which capacity-limitation has a significant impact on absorption, the fraction of ingested lead in food or drinking water that is absorbed is 0.5 and decreases to approximately 0.11 (intake, $>5,000 \mu\text{g/day}$). For lead ingested in soil or dust, fractional absorption is 0.35 at low intakes ($<200 \mu\text{g/day}$) and decreases to 0.09 (intake, $>5,000 \mu\text{g/day}$).

The uptake model assumes that 32% of inhaled lead is absorbed. This value was originally assigned based on a scenario of exposure to active smelter emissions, which assumed the particle size distribution in the vicinity of an active lead smelter ($<1 \mu\text{m}$, 12.5%; $1\text{--}2.5 \mu\text{m}$, 12.5%; $2\text{--}15 \mu\text{m}$, 20%; $15\text{--}30 \mu\text{m}$, 40%; $>30 \mu\text{m}$, 15%); size-specific deposition fractions for the nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract; and region-specific absorption fractions. Lead deposited in the alveolar region is assumed to be completely absorbed from the respiratory tract, whereas lead deposited in the nasopharyngeal and tracheobronchial regions (30–80% of the lead particles in the size range $1\text{--}15 \mu\text{m}$) is assumed to be transported to the gastrointestinal tract.

Biokinetics Model. The biokinetics model includes a central compartment, six peripheral body compartments, and three elimination pools. The body compartments include plasma and extra cellular fluid (central compartment), kidney, liver, trabecular bone, cortical bone, and other soft tissue (EPA 1994a). The model simulates growth of the body and tissues, compartment volumes, and lead masses and concentrations in each compartment. Blood lead concentration at birth (neonatal) is assumed to be 0.85 of the maternal blood lead. Neonatal lead masses and concentrations are assigned to other compartments based on a weighted distribution of the neonatal blood lead concentration. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate constants. Bone is simulated as two compartments: a relatively fast trabecular bone compartment (representing 20% of bone volume) and a relatively slow cortical bone compartment (representing 80% of the bone volume). Saturable uptake of lead into erythrocytes is simulated, with a maximum erythrocyte lead concentration of $120 \mu\text{g/L}$. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway represented losses from skin, hair and nail, from the other soft tissue compartment.

Blood Lead Probability Model. Inputs to the IEUBK Model are exposure point estimates that are intended to represent time-averaged central tendency exposures. The output of the model is a central

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tendency estimate of blood lead concentration for children who might experience the inputted exposures. However, within a group of similarly exposed children, blood lead concentrations would be expected to vary among children as a result of inter-individual variability in media intakes, absorption, and biokinetics. The model simulates the combined impact of these sources of variability as a lognormal distribution of blood lead concentration for which the geometric mean (GM) is given by the central tendency blood lead concentration outputted from the biokinetics model and the GSD is an input parameter. The resulting lognormal distribution also provides the basis for predicting the probability of occurrence of given blood lead concentration within a population of similarly exposed children. The model can be iterated for varying exposure concentrations (e.g., a series of increasing soil lead concentration) to predict the media concentration that would be associated with a probability of 0.05 for the occurrence of a blood lead concentration exceeding 10 µg/dL. A subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability and uncertainty in exposure and absorption (Goodrum et al. 1996; Griffin et al. 1999). This extension of the model provides an alternative to the blood lead probability model for incorporating, explicitly, estimates of variability (and uncertainty in variability) in exposure and absorption into predictions of an expected probability distribution of blood lead concentrations.

Risk assessment. The IEUBK Model was developed to predict the probability of elevated blood lead concentrations in children. The model addresses three components of human health risk assessment: (1) the multimedia nature of exposures to lead; (2) lead pharmacokinetics; and (3) significant variability in exposure and risk. Thus, the IEUBK Model can be used to predict the probability that children of ages up to 7 years who are exposed to lead in multiple environmental media would have blood lead concentrations exceeding a given health-based level of concern (e.g., 10 µg/dL). These risk estimates can be useful in assessing the possible consequences of alternative lead exposure scenarios following intervention, abatement, or other remedial actions. The IEUBK Model was not developed to assess lead risks for age groups older than 7 years. The model operates with an exposure time step on 1 year (the smallest time interval for a single exposure event) and, therefore, is more suited to applications in which long-term (i.e., >1 year) average exposures and blood lead concentrations are to be simulated (Lorenzana et al. 2005).

Validation of the model. An evaluation of the IEUBK Model has been conducted in which model predictions of blood lead concentrations in children were compared to observations from epidemiologic studies of hazardous waste sites (Hogan et al. 1998). Data characterizing residential lead exposures and blood lead concentrations in children living at four Superfund NPL sites were collected in a study

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designed by ATSDR and EPA. The residential exposure data were used as inputs to the IEUBK Model and the resulting predicted blood lead concentration distributions were compared to the observed distributions in children living at the same residences. The IEUBK Model predictions agreed reasonably well with observations for children whose exposures were predominantly from their residence (e.g., who spent no more than 10 hours/week away from home). The predicted geometric mean blood lead concentrations were within 0.7 µg/dL of the observed geometric means at each site. The prediction of the percentage of children expected to have blood lead concentrations exceeding 10 µg/dL were within 4% of the observed percentage at each site. This evaluation provides support for the validity of the IEUBK Model for estimating blood lead concentrations in children at sites where their residential exposures can be adequately characterized. Similar empirical comparisons of the IEUBK Model have shown that agreement between model predictions and observed blood lead concentrations at specific locations is influenced by numerous factors, including the extent to which the exposure and blood lead measurements are adequately matched, and site-specific factors (e.g., soil characteristics, behavior patterns, bioavailability) that may affect lead intake or uptake in children (Bowers and Mattuck 2001; EPA 2001c). In addition to the above empirical comparisons, the computer code used to implement the IEUBK Model (IEUBK version 0.99d) has undergone an independent validation and verification and has been shown to accurately implement the conceptual IEUBK Model (Zaragoza and Hogan 1998).

Target tissues. The output from the IEUBK Model is an estimate of age-specific blood lead concentrations. The current version of the IEUBK Model does not save as output the interim parameter values determined for lead in other tissues or tissue compartments.

Species extrapolation. Data in both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the IEUBK Model. The model is calibrated to predict compartmental lead masses for human children ages 6 months to 7 years, and is not intended to be applied to other species or age groups.

Interroute extrapolation. The IEUBK Model includes an exposure module that simulates age-specific lead exposures via inhalation and ingestion of lead in diet, dust, lead-based paint, soil, and water. The total exposure from each route is defined as the total lead uptake (µg/day) over a 1-month period. Other routes of exposure may be simulated by the IEUBK Model pending available information from which to characterize both the exposure and media-specific absorption variables. Values for variables in the biokinetic component of the IEUBK Model are independent of the route of exposure.

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3.3.5.3 Leggett Model

The Leggett Model is a classical multicompartmental pharmacokinetic model of lead uptake and disposition in children and adults (Leggett 1993). Figure 3-12 shows a conceptualized representation of the model, including the movement of lead from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between diffusible blood plasma, soft tissues, bone compartments, and excretion from liver, kidneys, and sweat. A detailed exposure module is not linked to the Leggett Model; rather, lead exposure estimates are incorporated into the model as age-specific point estimates of average daily intake ($\mu\text{g/day}$) from inhalation and ingestion. A detailed description of the model and its potential application to risk assessment are provided below.

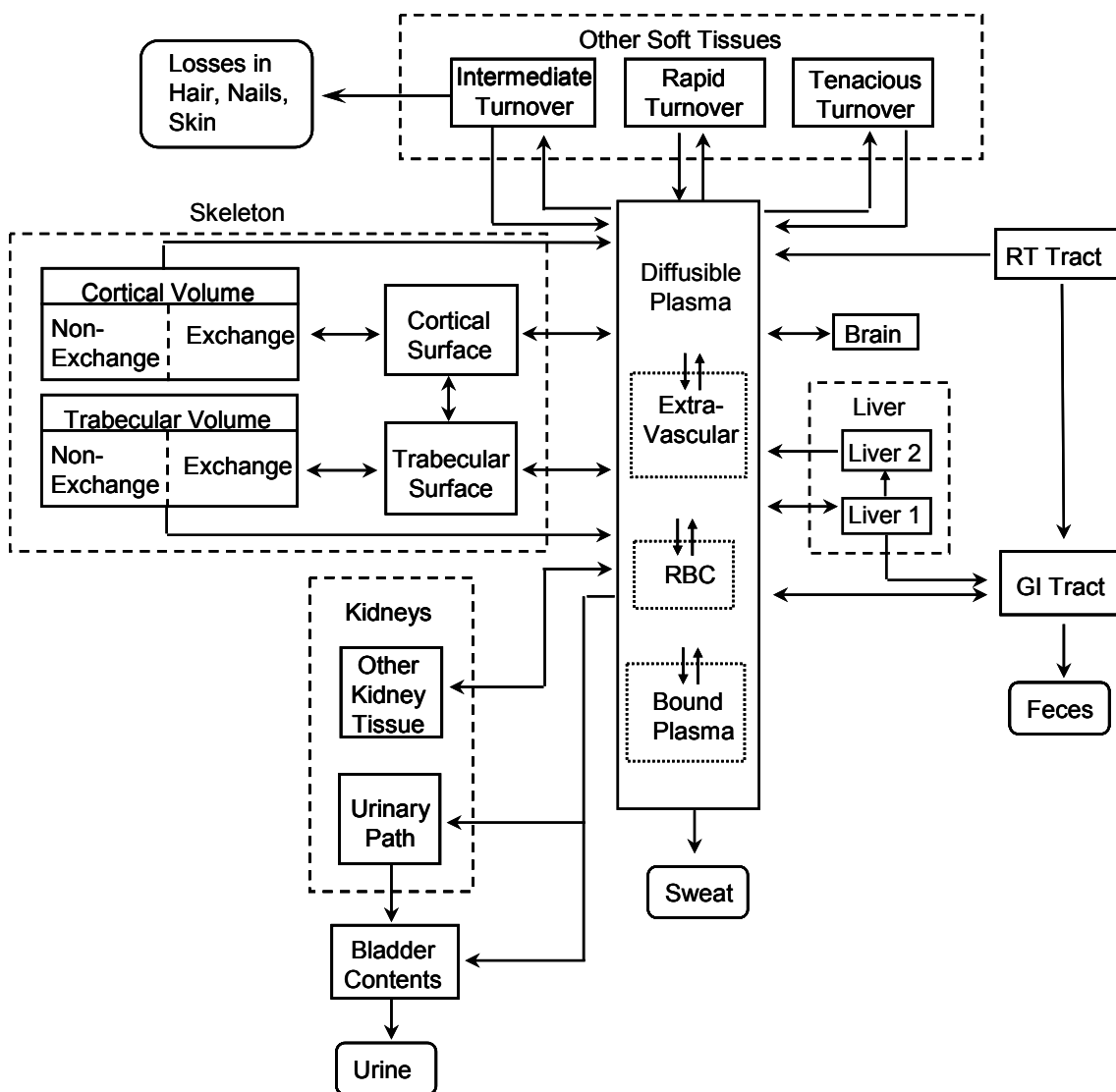
Description of the model. The Leggett Model includes a central compartment, 15 peripheral body compartments, and 3 elimination pools, as illustrated in Figure 3-12. Transport of lead from blood plasma to tissues is assumed to follow first-order kinetics. Transfer rate constants vary with age and blood lead concentration. Above a nonlinear threshold concentration in red blood cells (assumed to be $60 \mu\text{g/dL}$), the rate constant for transfer to red blood cells declines and constants to all other tissues increase proportionally (Leggett 1993). This replicates the nonlinear relationship between plasma and red blood observed in humans (see Section 3.4.1). The model simulates blood volume as an age-dependent function, which allows simulation of plasma and blood lead concentrations. Lead masses are simulated in all other tissues (tissue volumes are not simulated).

Unidirectional, first-order transfer rates (day^{-1}) between compartments were developed for six age groups, and intermediate age-specific values are obtained by linear interpolation. The total transfer rate from diffusible plasma to all destinations combined is assumed to be $2,000 \text{ day}^{-1}$, based on isotope tracer studies in humans receiving lead via injection or inhalation. Values for transfer rates in various tissues and tissue compartments are based on measured deposition fractions or instantaneous fractional outflows of lead between tissue compartments (Leggett 1993).

The Leggett Model was developed from a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP) for calculating radiation doses from environmentally important radionuclides, including radioisotopes of lead (Leggett 1993). The Leggett Model simulates age-dependent bone physiology using a model structure developed for application to the alkaline earth elements, but parameterized using data specific to lead where possible. The model simulates both rapid

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Figure 3-12. Compartments and Pathways of Lead Exchange in the Leggett Model*



*Schematic model for lead kinetics in which lead distribution is represented by exchanges between the central plasma-ECF and tissue compartments. Bone is represented as having surface (which rapidly exchanges with plasma-ECF), and volume compartments; the latter simulates slow exchange with the surface and slow return of lead to the plasma-ECF from bone resorption.

Source: Leggett 1993

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exchange of lead with plasma via bone surface and slow loss by bone resorption. Cortical bone volume (80% of bone volume) and trabecular bone volume (20% of bone volume) are simulated as bone surface compartments, which rapidly exchange with lead the blood plasma, and bone volume, within which are *exchangeable* and *nonexchangeable* pools. Lead enters the exchangeable pool of bone volume via the bone surface and can return to the bone surface, or move to the nonexchangeable pool, from where it can return to the blood only when bone is resorbed. Rate constants for transfer of lead from the nonexchangeable pools and blood plasma vary with age to reflect the age-dependence of bone turnover.

The liver is simulated as two compartments; one compartment has a relatively rapid uptake of lead from plasma and a relatively short removal half-life (days) for transfers to plasma and to the small intestine by biliary secretion; a second compartment simulates a more gradual transfer to plasma of approximately 10% of lead uptake in liver. The kidney is simulated as two compartments, one that exchanges slowly with blood plasma and accounts for lead accumulation kidney tissue and a second compartment that receives lead from blood plasma and rapidly transfers lead to urine, with essentially no accumulation (urinary pathway). Other soft tissues are simulated as three compartments representing rapid, intermediate, and slow turnover rates (without specific physiologic correlates). Other excretory pathways (hair nails and skin) are represented as a lumped pathway from the intermediate turnover rate soft tissue compartment.

The Leggett Model simulates lead intakes from inhalation, ingestion, or intravenous injection. The latter was included to accommodate model evaluations based on intravenous injection studies in humans and animal models. The respiratory tract is simulated as four compartments into which inhaled lead is deposited and absorbed with half-times of 1, 3, 10, and 48 hours. Four percent of the inhaled lead is assumed to be transferred to the gastrointestinal tract. These parameter values reflect the data on which the model was based, which were derived from studies in which human subjects inhaled submicron lead-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). These assumptions would not necessarily apply to exposures to large airborne particles (see Section 3.3.1.1). Absorption of ingested lead simulated as an age-dependent fraction of the ingestion rate, declining from 0.45 at birth to 0.3 at age 1 year (to age 15 years), and to 0.15 after age 25 years.

Risk assessment. The Leggett Model has several potential applications to risk assessment at hazardous waste sites. The model can be used to predict blood lead concentrations in both children and adults. The model allows the simulation of lifetime exposures, including assumptions of blood lead

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concentrations at birth (from which levels in other tissue in the first time step after birth are calculated). Thus, exposures and absorption of lead prior to any given period of time during the lifetime can be simulated with the Leggett Model. The model operates with an exposure time step on 1 day (the smallest time interval for a single exposure event), which allows simulation of rapidly changing intermittent exposures (Khoury and Diamond 2003; Lorenzana et al. 2005). The model does not contain a detailed exposure module and, therefore, requires assumptions regarding total lead intake from multiple exposure media. In addition, the model utilizes point estimates for intakes and yields point estimates as output (e.g., blood lead concentration) and predicted blood lead distributions in exposed populations.

Validation of the model. Output from the Leggett Model has been compared with data in children and adult subjects exposed to lead in order to calibrate model parameters. The model appears to predict blood lead concentrations in adults exposed to relatively low levels of lead; however, no information could be found describing efforts to compare predicted blood lead concentrations with observations in children.

Target tissues. The output from the Leggett Model is an estimate of age-specific PbB concentrations. The current version of the Leggett Model does not save as output the interim parameter values determined for lead in other tissues or tissue compartments.

Species extrapolation. Data on both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the Leggett Model. The model is calibrated to predict compartmental lead masses only for humans, both children and adults.

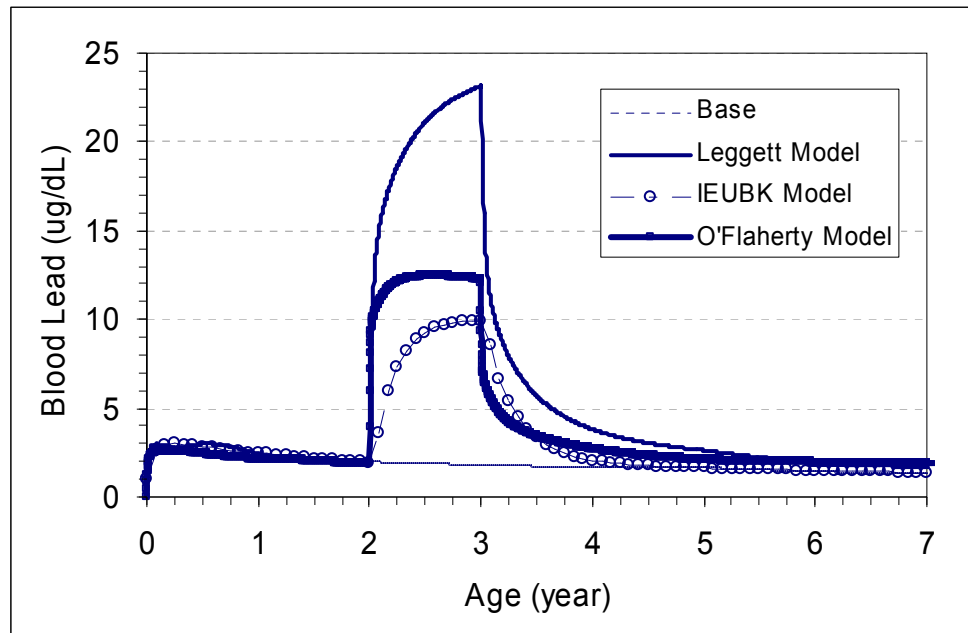
Interroute extrapolation. The values for pharmacokinetic variables in the Leggett Model are independent of the route of exposure. Based on the description of the inputs to the model provided by Leggett (1993), lead intake from different exposure routes is defined as a total lead intake from all routes of exposure.

3.3.5.4 Model Comparisons

The O'Flaherty, IEUBK, and Leggett Models differ considerably in the way each represents tissues, exchanges of lead between tissues, and lead exposure. Figure 3-13 compares the PbBs predicted by each model for a hypothetical child who ingests 100 µg lead/day in soil for a period of 1 year beginning at the

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Figure 3-13. Blood Lead Concentrations in Children Predicted by the O'Flaherty, IEUBK, and Leggett Models*



*The simulations are of a hypothetical child who has a PbB of 2 µg/dL at age 2 years, and then experiences a 1-year exposure to 100 µg Pb/day. The 100 µg/day exposure was simulated as an exposure to lead in soil in the IEUBK Model. Default bioavailability assumptions were applied in all three models.

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age of 2 years (e.g., equivalent to ingestion of 100 µg soil/day at a soil lead concentration of 1,000 mg lead/g soil). The 100-µg/day exposure is superimposed on a baseline exposure that yields a PbB of approximately 2 µg/dL at 2 years of age. All three models predict an increase in PbB towards a quasi-steady state during the exposure period, followed by a decline towards the pre-exposure baseline PbB with a half-time of approximately 1 month. Predicted PbBs at the end of the 12-month soil exposure period were 6, 10, and 23 µg/dL for the IEUBK, O'Flaherty, and Leggett Models, respectively.

Differences in the magnitude of the predicted impact of the soil exposure on PbB reflect differences in assumptions about lead biokinetics and cannot be attributed solely to different assumptions about lead bioavailability. Bioavailability assumptions in the three models for the age range 2–3 years are:

O'Flaherty Model, 45% (50% at age 2 years, decreasing to 40% at age 3 years); IEUBK Model, 30% (soil lead at low intakes); and Leggett Model, 30%. A comparison of model predictions for a similar exposure during adulthood (100 µg Pb/day for 1 year, beginning at age 25) is shown in Figure 3-14. Predicted PbBs at the end of the 12-month soil exposure period were: 3 and 8 µg/dL for the O'Flaherty and Leggett Models, respectively. Both the O'Flaherty and Leggett Models predict a smaller change in PbB in adults, compared to children, for a similar increment in exposure. This is attributed, in part, to assumptions of lower lead bioavailability in adults (i.e., O'Flaherty, 8%; Leggett, 15%).

3.3.5.5 Slope Factor Models

Slope factor models have been used as simpler alternatives to compartmental models for predicting PbBs, or the change in PbB, associated with a given exposure (Abadin et al. 1997a; Bowers et al. 1994; Carlisle and Wade 1992; EPA 2003b, Stern 1994, 1996). In slope factor models, lead biokinetics is represented with a simple linear relationship between the PbB and either lead uptake (biokinetic slope factor, BSF) or lead intake (intake slope factor, ISF). The models take the general mathematical forms:

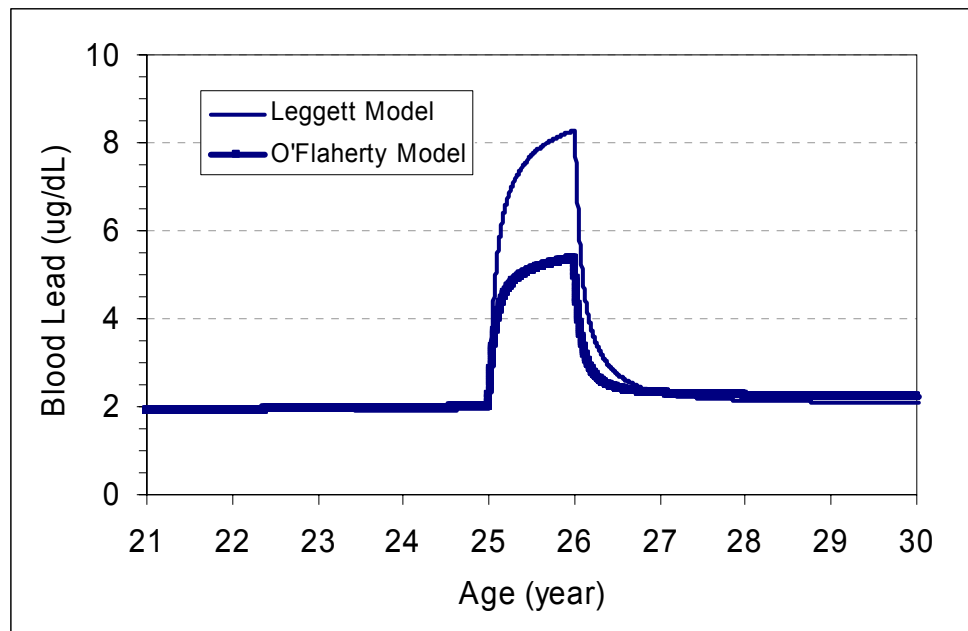
$$PbB = E \cdot ISF$$

$$PbB = E \cdot AF \cdot BSF$$

where E is an expression for exposure (e.g., soil intake x soil lead concentration) and AF is the absorption fraction for lead in the specific exposure medium of interest. Intake slope factors are based on ingested rather than absorbed lead and, therefore, integrate both absorption and biokinetics into a single slope factor, whereas models that utilize a biokinetic slope factor to account for absorption in the relationship include an absorption parameter. Slope factors used in various models are presented in Table 3-10. Of

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Figure 3-14. Blood Lead Concentrations in Adults Predicted by the O'Flaherty and Leggett Models*



*The simulations are of a hypothetical adult who has a PbB of 2 $\mu\text{g/dL}$ at age 25 years, and then experiences a 1-year exposure to 100 $\mu\text{g Pb/day}$. Default bioavailability assumptions were applied in all three models.

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Table 3-10. Comparison of Slope Factors in Selected Slope Factor Models

Model	Receptor	Slope factor		Absorption fraction
		Intake	Biokinetics	
Bowers et al. 1994	Adult	ND	0.375	0.08
Carisle and Wade 1992	Child	Soil/dust: 0.07 Water: 0.04	ND	ND
Carisle and Wade 1992	Adult	Soil/dust: 0.018 Water: 0.04	ND	ND
EPA 1996	Adult	ND	0.4	0.12
Stern 1994	Child	Residential: T (0.056, 0.16, 0.18)	ND	ND
Stern 1996	Adult	Non-residential: U (0.014, 0.034)	ND	ND

ND = No data; T = triangular probability distribution function (PDF); U = uniform PDF

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the various models presented in Table 3-9, two Bowers et al. (1994) and EPA (2003b) models implement BSFs. The slope factors used in both models (approximately 0.4 $\mu\text{g}/\text{dL}$ per μg Pb/day) are similar to biokinetic slope factors predicted from the O'Flaherty Model (0.65 $\mu\text{g}/\text{dL}$ per μg Pb uptake/day) and Legget Model (0.43 $\mu\text{g}/\text{dL}$ per μg Pb uptake/day) for simulations of adult exposures (Maddaloni et al. 2005). In general, intake slope factors are derived from epidemiologic observations. A review of slope factors relating medium-specific exposures and blood lead concentrations derived from epidemiologic studies is provided in Appendix D (Abadin et al. 1997a).

3.4 MECHANISMS OF ACTION

3.4.1 Pharmacokinetic Mechanisms

Absorption

Gastrointestinal Absorption of Inorganic Lead. Gastrointestinal absorption of inorganic lead occurs primarily in the duodenum (Mushak 1991). The exact mechanisms of absorption are unknown and may involve active transport and/or diffusion through intestinal epithelial cells (transcellular) or between cells (paracellular), and may involve ionized lead (Pb^{+2}) and/or inorganic or organic complexes of lead. *In vitro* studies of lead speciation in simulated human intestinal chyme indicate that the concentration of ionized lead is negligible at lead concentrations below 10^{-3} M (207 mg/L) and that lead phosphate and bile acid complexes are the dominant forms when inorganic lead salts (e.g., lead nitrate) are added to chyme (Oomen et al. 2003a). However, these complexes may be sufficiently labile to provide ionized lead for transport across cell membranes (Oomen et al. 2003b). Saturable mechanisms of absorption have been inferred from measurements of net flux kinetics of lead in the *in situ* perfused mouse intestine, the *in situ* ligated chicken intestine, and in *in vitro* isolated segments of rat intestine (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981). By analogy to other divalent cations, saturable transport mechanisms for Pb^{+2} may exist within the mucosal and serosal membranes and within the intestinal epithelial cell. For calcium and iron, these are thought to represent membrane carriers (e.g., Ca^{2+} - Mg^{2+} -ATPase, $\text{Ca}^{2+}/\text{Na}^{+}$ exchange, DMT1) or facilitated diffusion pathways (e.g., Ca^{2+} channel) and intracellular binding proteins for Ca^{2+} (Bronner et al. 1986; Fleming et al. 1998b; Gross and Kumar 1990; Teichmann and Stremmel 1990). Numerous observations of nonlinear relationships between blood lead concentration and lead intake in humans suggest the existence of a saturable absorption mechanism or some other capacity-limited process in the distribution of lead in humans (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984). In immature swine that received oral doses of lead in soil, lead dose-blood lead relationships were nonlinear; however, dose-tissue lead

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relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for blood lead and linearity for tissues) was observed in swine administered lead acetate intravenously (Casteel et al. 1997). These results raise the question of whether there is an effect of dose on absorption or on some other aspect of the biokinetics of lead.

Gastrointestinal absorption of lead is influenced by dietary and nutritional calcium and iron status. An inverse relationship has been observed between dietary calcium intake and blood lead concentration (Mahaffey et al. 1986; Ziegler et al. 1978). Complexation with calcium (and phosphate) in the gastrointestinal tract and competition for a common transport protein have been proposed as possible mechanisms for this interaction (Barton et al. 1978a; Heard and Chamberlain 1982). Absorption of lead from the gastrointestinal tract is enhanced by dietary calcium depletion or administration of cholecalciferol. This "cholecalciferol-dependent" component of lead absorption appears to involve a stimulation of the serosal transfer of lead from the epithelium, not stimulation of mucosal uptake of lead (Mykkänen and Wasserman 1981, 1982). This is similar to the effects of cholecalciferol on calcium absorption (Bronner et al. 1986; Fullmer and Rosen 1990).

Iron deficiency is also associated with increased blood lead concentration in children (Mahaffey and Annett 1986; Marcus and Schwartz 1987). In rats, iron deficiency increases the gastrointestinal absorption of lead, possibly by enhancing binding of lead to iron binding proteins in the intestine (Morrison and Quateman 1987). Iron (FeCl_2) added to the mucosal fluid of the everted rat duodenal sac decreases serosal transfer, but not mucosal uptake of lead (Barton 1984).

Thus, interactions between iron and lead also appear to involve either intracellular transfer or basolateral transfer mechanisms. When mRNA for DMT1, a mucosal membrane carrier for iron, was suppressed in Caco 2 cells (a human gastrointestinal cell line) the rate of iron and cadmium uptake decreased by 50% compared to cells in which DMT1 mRNA was not suppressed; however, DMT1 mRNA suppression did not alter the rate of lead uptake by Caco 2 cells, indicating that lead may enter Caco 2 cells through a mechanism that is independent of DMT1 (Bannon et al. 2003). The above observations suggest that rate-limiting saturable mechanisms for lead absorption are associated with transfer of lead from cell to blood rather than with mucosal transfer. Similar mechanisms may contribute to lead-iron and lead-calcium absorption interactions in humans, and, possibly interactions between lead and other divalent cations such as cadmium, copper, magnesium and zinc.

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Distribution

Red Blood Cells. Lead in blood is rapidly taken by red blood cells, where it binds to several intracellular proteins. Although the mechanisms by which lead crosses cell membranes have not been fully elucidated, results of studies in intact red blood cells and red blood cell ghosts indicate that there are two, and possibly three, pathways for facilitated transfer of lead across the red cell membrane. The major proposed pathway is an anion exchanger that is dependent upon HCO_3^- and is blocked by anion exchange inhibitors (Bannon et al. 2000, Simons 1985, 1986a, 1986b, 1993). A second minor pathway, which does not exhibit HCO_3^- dependence and is not sensitive to anion exchange inhibitors, may also exist (Simons 1986b). Lead and calcium may also share a permeability pathway, which may be a Ca^{2+} -channel (Calderon-Salinas et al. 1999). Lead is extruded from the erythrocyte by an active transport pathway, most likely a $(\text{Ca}^{2+}, \text{Mg}^{2+})$ -ATPase (Simons 1988).

ALAD is the primary binding ligand for lead in erythrocytes (Bergdahl et al. 1997a, 1998; Sakai et al. 1982; Xie et al. 1998). Lead binding to ALAD is saturable; the binding capacity has been estimated to be approximately 850 $\mu\text{g}/\text{dL}$ red blood cells (or approximately 40 $\mu\text{g}/\text{dL}$ whole blood) and the apparent dissociation constant has been estimated to be approximately 1.5 $\mu\text{g}/\text{L}$ (Bergdahl et al. 1998). Two other lead-binding proteins have been identified in the red cell, a 45 kDa protein (K_d 5.5 $\mu\text{g}/\text{L}$) and a smaller protein(s) having a molecular weight <10 kDa (Bergdahl et al. 1996, 1997a, 1998). Of the three principal lead-binding proteins identified in red blood cells, ALAD has the strongest affinity for lead (Bergdahl et al. 1998) and appears to dominate the ligand distribution of lead (35–84% of total erythrocyte lead) at blood lead levels below 40 $\mu\text{g}/\text{dL}$ (Bergdahl et al. 1996, 1998; Sakai et al. 1982).

Lead binds to and inhibits the activity of ALAD (Gercken and Barnes 1991; Gibbs et al. 1985; Sakai et al. 1982, 1983). Synthesis of ALAD appears to be induced in response to inhibition of ALAD and, therefore, in response to lead exposure and binding of lead to ALAD (Boudene et al. 1984; Fujita et al. 1982). Several mechanisms may participate in the induction of ALAD, including (1) inhibition of ALAD directly by lead; (2) inhibition by protoporphyrin, secondary to accumulation of protoporphyrin as a result of lead inhibition of ferrochelatase; and (3) accumulation of ALA, secondary to inhibition of ALAD, which may stimulate ALAD synthesis in bone marrow cells (Boudene et al. 1984; Fujita et al. 1982).

ALAD is a polymorphic enzyme with two alleles (ALAD 1 and ALAD 2) and three genotypes: ALAD 1,1, ALAD 1,2, and ALAD 2,2 (Battistuzzi et al. 1981). Higher PbBs were observed in individuals with the ALAD 1,2 and ALAD 2,2 genotypes compared to similarly exposed individuals with

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the ALAD 1,1 genotype (Astrin et al. 1987; Hsieh et al. 2000, Schwartz et al. 2000b; Wetmur et al. 1991). This observation has prompted the suggestion that the ALAD-2 allele may have a higher binding affinity for lead than the ALAD 1 allele (Bergdahl et al. 1997b), a difference that could alter lead-mediated outcomes. Several studies have been conducted to specifically evaluate whether ALAD genotypes are associated with differences in partitioning of lead between red blood cells and plasma, differences in distribution of lead to other tissue compartments, and altered susceptibility to lead toxicity. Further details on ALAD and other polymorphisms involved in lead toxicity are presented in Section 3.8, Populations that are Unusually Susceptible.

Lead in Blood Plasma. Lead binds to several constituents in plasma and it has been proposed that lead in plasma exists in four states: loosely bound to serum albumin or other proteins with relatively low affinity for lead, complexed to low molecular weight ligands such as amino acids and carboxylic acids, tightly bound to a circulating metalloprotein, and as free Pb^{2+} (Al-Modhefer et al. 1991). Free ionized lead (i.e., Pb^{2+}) in plasma represents an extremely small percentage of total plasma lead. The concentration of Pb^{2+} in fresh serum, as measured by an ion-selective lead electrode, was reported to be 1/5,000 of the total serum lead (Al-Modhefer et al. 1991). Approximately 40–75% of lead in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980a). Lead may also bind to γ -globulins (Ong and Lee 1980a). Lead in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine). Other potential low molecular weight lead-binding ligands in serum may include citrate, cysteamine, ergothioneine, glutathione, histidine, and oxylate (Al-Modhefer et al. 1991).

Lead in Bone. Approximately 95% of lead in adult tissues, and approximately 70% in children, resides in mineralized tissues such as bone and teeth (Barry 1975, 1981). A portion of lead in bone readily exchanges with the plasma lead pool and, as a result, bone lead is a reservoir for replenishment of lead eliminated from blood by excretion (Alessio 1988; Chettle et al. 1991; Hryhirczuk et al. 1985; Nilsson et al. 1991; Rabinowitz et al. 1976). Lead forms highly stable complexes with phosphate and can replace calcium in the calcium-phosphate salt, hydroxyapatite, which comprises the primary crystalline matrix of bone (Lloyd et al. 1975). As a result, lead deposits in bone during the normal mineralization process that occurs during bone growth and remodeling and is released to the blood during the process of bone resorption (O'Flaherty 1991b, 1993). The distribution of lead in bone reflects these mechanisms; lead tends to be more highly concentrated at bone surfaces where growth and remodeling are most active (Aufderheide and Wittmers 1992). This also gives rise to an age-dependence in bone lead distribution. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood,

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calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Bone lead burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b). The association of lead uptake and release from bone with the normal physiological processes of bone formation and resorption renders lead biokinetics sensitive to these processes. Physiological states (e.g., pregnancy, menopause, advanced age) or disease states (e.g., osteoporosis, prolonged immobilization) that are associated with increased bone resorption will tend to promote the release of lead from bone, which, in turn, may contribute to an increase in the concentration of lead in blood (Berkowitz et al. 2004; Bonithon-Kopp et al. 1986c; Hernandez-Avila et al. 2000; Markowitz and Weinberger 1990; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995; Thompson et al. 1985).

Soft Tissues. Mechanisms by which lead enters soft tissues have not been fully characterized (Bressler et al. 2005). Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of lead transfer and suggest that lead can interact with transport mechanisms for calcium and iron (see Section 3.4.2, Absorption). Lead can enter cells through voltage-gated L-type Ca^{2+} channels in bovine adrenal medullary cells (Legare et al. 1998; Simons and Pocock 1987; Tomsig and Suszkiw 1991) and through store-operated Ca^{2+} channels in pituitary GH3, glial C3, human embryonic kidney, and bovine brain capillary endothelial cells (Kerper and Hinkle 1997a, 1997b). Anion exchangers may also participate in lead transport in astrocytes (Bressler et al. 2005). In addition to the small intestine, DMT1 is expressed in the kidney (Canonne-Hergaux et al. 1999); however, little information is available regarding the transport of lead across the renal tubular epithelium. In Madin-Darby canine kidney cells (MDCK), lead has been shown to undergo transepithelial transport by a mechanism distinct from the anion exchanger that has been identified in red blood cells (Bannon et al. 2000). The uptake of lead into MDCK cells was both time and temperature dependent. Overexpression of DMT1 in the human embryonic kidney fibroblast cells (HEK293) resulted in increased lead uptake compared to HEK293 cells in which DMT1 was not overexpressed (Bannon et al. 2002). Based on this limited information, it appears that DMT1 may play a role in the renal transport of lead.

Lead in other soft tissues such as kidney, liver, and brain exists predominantly bound to protein. High affinity cytosolic lead binding proteins (PbBPs) have been identified in rat kidney and brain (DuVal and Fowler 1989; Fowler 1989). The PbBPs of rat are cleavage products of $\alpha_2\mu$ globulin, a member of the protein superfamily known as retinol-binding proteins (Fowler and DuVal 1991). $\alpha_2\mu$ -Globulin is synthesized in the liver under androgen control and has been implicated in the mechanism of male rat

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hyaline droplet nephropathy produced by certain hydrocarbons (EPA 1991c; Swenberg et al. 1989); however, there is no evidence that lead induces male-specific nephropathy or hyaline droplet nephropathy. The precise role for PbBP in the toxicokinetics and toxicity of lead has not been firmly established; however, it has been proposed that PbBP may serve as a cytosolic lead "receptor" that, when transported into the nucleus, binds to chromatin and modulates gene expression (Fowler and DuVal 1991; Mistry et al. 1985, 1986). Other high-affinity lead binding proteins (K_d approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4 and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Lead also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the lead in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+} , but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, lead will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984).

Metabolism. Metabolism of inorganic lead consists primarily of reversible ligand reactions, including the formation of complexes with amino acids and nonprotein thiols, and binding to various proteins (DeSilva 1981; Everson and Patterson 1980; Goering and Fowler 1987; Goering et al. 1986; Ong and Lee 1980a, 1980b, 1980c; Raghavan and Gonick 1977).

Tetraethyl and tetramethyl lead undergo oxidative dealkylation to the highly neurotoxic metabolites, triethyl and trimethyl lead, respectively (Bolanowska 1968; Kehoe and Thamann 1931). In the liver, the reaction is catalyzed by a cytochrome P-450 dependent monooxygenase system (Kimmel et al. 1977). Complete oxidation of alkyl lead to inorganic lead also occurs (Bolanowska 1968).

Excretion

Urinary Excretion. Mechanisms by which inorganic lead is excreted in urine have not been fully characterized. Such studies have been hampered by the difficulties associated with measuring ultrafilterable lead in plasma and thereby in measuring the rate of glomerular filtration of lead. Renal plasma clearance was approximately 20–30 mL/minute in a subject who received a single intravenous injection of a ^{203}Pb chloride tracer (Chamberlain et al. 1978). Measurement of the renal clearance of ultrafilterable lead in plasma indicates that, in dogs and humans, lead undergoes glomerular filtration and net tubular reabsorption (Araki et al. 1986, 1990; Victory et al. 1979). Net tubular secretion of lead has been demonstrated in dogs made alkalotic by infusions of bicarbonate (Victory et al. 1979). Renal

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clearance of blood lead increases with increasing blood lead concentrations above 25 µg/dL (Chamberlain 1983). The mechanism for this has not been elucidated and could involve a shift in the distribution of lead in blood towards a fraction having a higher glomerular filtration rate (e.g., lower molecular weight complex), a capacity-limited mechanism in the tubular reabsorption of lead, or the effects of lead-induced nephrotoxicity on lead reabsorption.

Mechanisms of secretory and absorptive transfer of lead in the kidney have not been characterized. Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of lead transfer and suggest that lead can interact with transport mechanisms for calcium and iron. Although these observations may be applicable to the kidney, empirical evidence for specific transport mechanisms in the renal tubule are lacking (Diamond 2005).

Fecal Excretion. In humans, absorbed inorganic lead is excreted in feces (Chamberlain et al. 1978; Rabinowitz et al. 1976). The mechanisms for fecal excretion of absorbed lead have not been elucidated; however, pathways of excretion may include secretion into the bile, gastric fluid and saliva (Rabinowitz et al. 1976). Biliary excretion of lead has also been observed in the dog, rat, and rabbit (Klaassen and Shoeman 1974; O'Flaherty 1993).

3.4.2 Mechanisms of Toxicity

Target Organ Toxicity. This section focuses on mechanisms for sensitive health effects of major concern for lead—cardiovascular/renal effects, hematological effects, and neurological effects, particularly in children.

Cardiovascular Effects. A variety of diverse mechanisms may contribute to the increased blood pressure that is observed with chronic exposure to lead. Lead affects important hormonal and neural systems that contribute to the regulation of peripheral vascular resistance, heart rate and cardiac output (Carmignani et al. 2000; Khalil-Manesh et al. 1993; Ni et al. 2004; Vaziri and Sica 2004). Lead-induced hypertension in rats is accompanied by depletion of nitric oxide (NO), which plays an important role in regulating blood pressure, through peripheral (i.e., vasodilation, naturesis) and central (anti-sympathetic) mechanisms (Gonick et al. 1997; Vaziri et al. 1997). NO depletion induced by lead is thought to derive, at least in part, from oxidative stress and associated increased activity of reactive oxygen species (ROS) and reactivity with NO (Ding et al. 2001; Vaziri et al. 1999a, 199b). Lead may also disrupt the vasodilatory actions of NO by altering cell-signaling mechanisms in endothelial cells. Lead exposure in rats is

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associated with a down regulation of the expression of soluble guanylate cyclase, the enzyme that produces cyclic GMP, which mediates NO-induced vasodilation (Marques et al. 2001). Lead-induced hypertension is also associated with abnormalities in the adrenergic system, including increased central sympathetic nervous system activity, elevated plasma norepinephrine, and decreased vascular β -adrenergic receptor density (Carmignani et al. 2000; Chang et al. 1996; Tsao et al. 2000). Chronic lead exposure also activates the renin-angiotensin-aldosterone system, either directly or indirectly, through stimulation of the sympathetic nervous system. Chronic exposure to lead elevates plasma renin activity, plasma angiotensin-converting-enzyme (ACE), and plasma aldosterone concentrations (Boscolo and Carmignani 1988; Carmignani et al. 1988). Lead-induced hypertension is also associated with alterations in the regulation of kallikrein-kinin system and the production of associated vasodilatory hormones (Carmignani et al. 1999) and alterations in production of renal prostaglandins (Gonick et al. 1998; Hotter et al. 1995). Lead exerts direct constrictive effects on vascular smooth muscle, which are thought to be mediated by inhibition of Na-K-ATPase activity and associated elevation of intracellular Ca^{2+} levels, and possibly through activation of protein kinase C (Hwang et al. 2001; Kramer et al. 1986; Piccinini et al. 1977; Watts et al. 1995).

Renal Effects. Lead in cells binds to a variety of proteins, some of which have been implicated in lead toxicity (see Section 3.4.1 for further discussion). A characteristic histologic feature of lead nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b). Inclusion bodies contain lead complexed with protein (Moore et al. 1973). Appearance of nuclear inclusion bodies is associated with a shift in compartmentalization of lead from the cytosol to the nuclear fraction (Oskarsson and Fowler 1985). Sequestration of lead in nuclear inclusion bodies can achieve a lead concentration that is 100 times higher ($\mu\text{g Pb/mg protein}$) than that in kidney cytosol (Goyer et al. 1970a, 1970b; Horn 1970); thus, the bodies can have a profound effect on the intracellular disposition of lead in the kidney.

The sequestration of lead in intranuclear inclusion bodies may limit or prevent toxic interactions with other molecular targets of lead. In rats exposed to nephrotoxic doses of lead acetate, few intranuclear inclusion bodies occurred in the S3 segment of the proximal tubule, where acute injury was most severe, whereas, intranuclear inclusion bodies were more numerous in the S2 segment, where the injury was less severe (Murakami et al. 1983).

The exact identity of the lead-protein complex in inclusion bodies remains unknown, as is the mechanism of formation of the inclusion body itself. Although proteins that appear to be unique to lead-induced

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inclusion bodies have been isolated, their role in the lead sequestration has not been elucidated (Shelton and Egle 1982). Cytosolic proteins may serve as carriers of lead or intermediary ligands for uptake of lead into the nucleus. Two cytosolic proteins, which appear to be cleavage products of 2-microglobulin (Fowler and DuVal 1991), have been isolated from rat kidney cytosol that have high affinity binding sites for lead ($K_d=13$ and 40 nM, respectively) and can mediate uptake of lead into isolated nuclei (Mistry et al. 1985, 1986). These proteins can also participate in ligand exchange reactions with other cytosolic binding sites, including δ -aminolevulinic dehydratase, which binds and is inhibited by lead (Goering and Fowler 1984, 1985). Other high-affinity lead binding proteins (K_d approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4 and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Lead also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the lead in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+} , but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, lead will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984). The precise role of cytosolic lead binding proteins in inclusion body formation has not been determined, although it has been hypothesized that aggregations of 2-microglobulin may contribute to the lead-protein complex observed in nuclear inclusion bodies (Fowler and DuVal 1991).

A consistent feature of lead-induced nephropathy is the finding of structural abnormalities of mitochondria of renal proximal tubule cells (Fowler et al. 1980; Goyer 1968; Goyer and Krall 1969). Mitochondria isolated from intoxicated rats contain lead, principally associated with the intramembrane space or bound to the inner and outer membranes, and show abnormal respiratory function, including decreased respiratory control ratio during pyruvate/malate- or succinate-mediated respiration (Fowler et al. 1980; Oskarsson and Fowler 1985). Lead inhibits uptake of calcium into isolated renal mitochondria and may enter mitochondria as a substrate for a calcium transporter (Kapoor et al. 1985). This would be consistent with evidence that lead can interact with calcium binding proteins and thereby affect calcium-mediated or regulated events in a variety of tissues (Fullmer et al. 1985; Goldstein 1993; Goldstein and Ar 1983; Habermann et al. 1983; Platt and Busselberg 1994; Pounds 1984; Richardt et al. 1986; Rosen and Pounds 1989; Simons and Pocock 1987; Sun and Suszkiw 1995; Tomsig and Suszkiw 1995; Watts et al. 1995). Impairments of oxidative metabolism could conceivably contribute to transport deficits and cellular degeneration; however, the exact role this plays in lead-induced nephrotoxicity has not been elucidated.

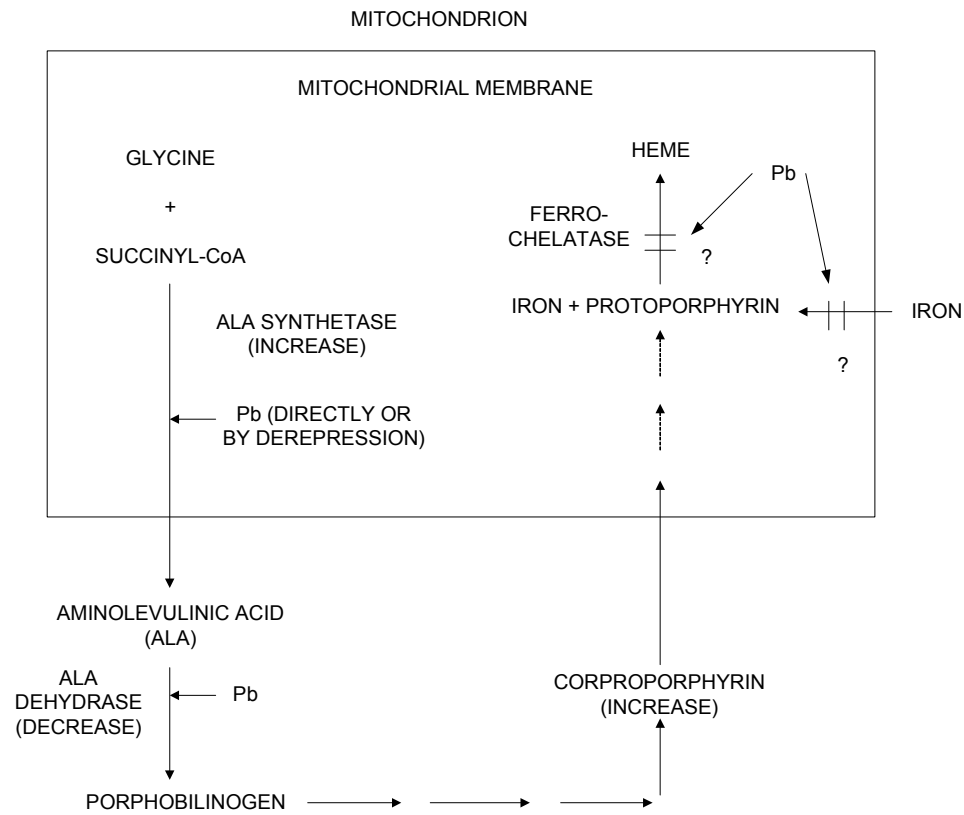
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Lead exposure also appears to produce an oxidative stress of unknown, and possibly multi-pathway, origin (Daggett et al. 1998; Ding et al. 2001; Hermes-Lima et al. 1991; Lawton and Donaldson 1991; Monteiro et al. 1991; Nakagawa 1991; Sandhir et al. 1994; Sugawara et al. 1991). Secondary responses to lead-induced oxidative stress include induction of nitric oxide synthase, glutathione S-transferase and transketolase in the kidney (Daggett et al. 1998; Moser et al. 1995; Vaziri et al. 2001; Witzmann et al. 1999; Wright et al. 1998). Depletion of nitric oxide has been implicated as a contributor to lead-induced hypertension in the rat (Carmignani et al. 2000; Gonick et al. 1997; Vaziri et al. 1997, 1999a, 1999b) and thereby may contribute to impairments in glomerular filtration and possibly in the production of glomerular lesions; however, a direct role of this mechanism in lead-induced proximal tubular injury has not been elucidated. Both lead and L-N-(G)-nitro arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthetase, increased the release of N-acetyl-D-glucosaminidase (NAG) from isolated rat kidneys perfused with an albumin-free perfusate (Dehpour et al. 1999). The addition of L-arginine decreased the effect of lead on NAG release. This observation is consistent with an oxidative stress mechanism possibly contributing to lead-induced enzymuria and increased urinary excretion of NAG (see Section 3.2.2, Renal Effects).

Experimental studies in laboratory animals have shown that lead can depress glomerular filtration rate and renal blood flow (Aviv et al. 1980; Khalil-Manesh et al. 1992a, 1992b). In rats, depressed glomerular filtration rate appears to be preceded with a period of increased filtration (Khalil-Manesh et al. 1992a; O'Flaherty et al. 1986). The mechanism by which lead alters glomerular filtration rate is unknown and, its mechanistic connection to lead-induced hypertension has not been fully elucidated. Glomerular sclerosis or proximal tubule injury and impairment could directly affect renin release (Boscolo and Carmignani 1988) and/or renal insufficiency could secondarily contribute to hypertension.

Hematological Effects. The effects of lead on the hematopoietic system have been well documented. These effects, which are seen in both humans and animals, include increased urinary porphyrins, coproporphyrins, ALA, EP, FEP, ZPP, and anemia. The process of heme biosynthesis is outlined in Figure 3-15. Lead interferes with heme biosynthesis by altering the activity of three enzymes: ALAS, ALAD, and ferrochelatase. Lead indirectly stimulates the mitochondrial enzyme ALAS, which catalyzes the condensation of glycine and succinyl-coenzyme A to form ALA. The activity of ALAS is the rate-limiting step in heme biosynthesis; increase of ALAS activity occurs through feedback derepression. Lead inhibits the zinc-containing cytosolic enzyme ALAD, which catalyzes the condensation of two units of ALA to form protoporphobilinogen. This inhibition is noncompetitive, and occurs through the binding of lead to vicinal sulfhydryls at the active site of ALAD. Lead bridges the vicinal sulfhydryls, whereas Zn,

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Figure 3-15. Effects of Lead on Heme Biosynthesis

Source: EPA 1986a

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which is normally found at the active site, binds to only one of these sulfhydryls. Inhibition of ALAD and feedback derepression of ALAS results in accumulation of ALA. Lead decreases, in a noncompetitive fashion, the activity of the zinc-containing mitochondrial enzyme ferrochelatase, which catalyzes the insertion of iron (II) into the protoporphyrin ring to form heme. Inhibition of ferrochelatase (a mitochondrial enzyme) may occur through binding of lead to the vicinal sulfhydryl groups of the active site. Another possible mechanism is indirect, through impaired transport of iron in the mitochondrion, due to disruption of mitochondrial structure. Some other enzymes of the heme synthesis pathway contain single sulfhydryl groups at their active sites and are not as sensitive to inhibition by lead as are ALAD and ferrochelatase (EPA 1986a; Goering 1993).

Lead inhibition of ferrochelatase results in an accumulation of protoporphyrin IX, which is present in the circulating erythrocytes as ZPP, because of the placement of zinc, rather than iron, in the porphyrin moiety. ZPP is bound in the heme pockets of hemoglobin and remains there throughout the life of the erythrocyte. In the past, assays used in studies of protoporphyrin accumulation measured ZPP or FEP, because ZPP is converted to FEP during extraction and older technology could not differentiate FEP from ZPP. However, contemporary technology permits the direct quantification of ZPP, a far more clinically useful parameter. Because accumulation of ZPP occurs only in erythrocytes formed during the presence of lead in erythropoietic tissue, this effect is detectable in circulating erythrocytes only after a lag time reflecting maturation of erythrocytes and does not reach steady state until the entire population of erythrocytes has turned over, in approximately 120 days (EPA 1986a).

A marked interference with heme synthesis results in a reduction of the hemoglobin concentration in blood. Decreased hemoglobin production, coupled with an increase in erythrocyte destruction, results in a hypochromic, normocytic anemia with associated reticulocytosis. Decreased hemoglobin and anemia have been observed in lead workers and in children with prolonged exposure at higher PbBs than those noted as threshold levels for inhibition or stimulation of enzyme activities involved in heme synthesis (EPA 1986a). Inappropriate renal production of erythropoietin due to renal damage, leading to inadequate maturation of erythroid progenitor cells, also has been suggested as a contributing mechanism for lead-induced anemia (Osterode et al. 1999).

The increase in erythrocyte destruction may be due in part to inhibition by lead of pyrimidine-5'-nucleotidase, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte. This enzyme inhibition and nucleotide accumulation affect erythrocyte membrane stability and survival by alteration of cellular energetics (Angle et al. 1982; EPA

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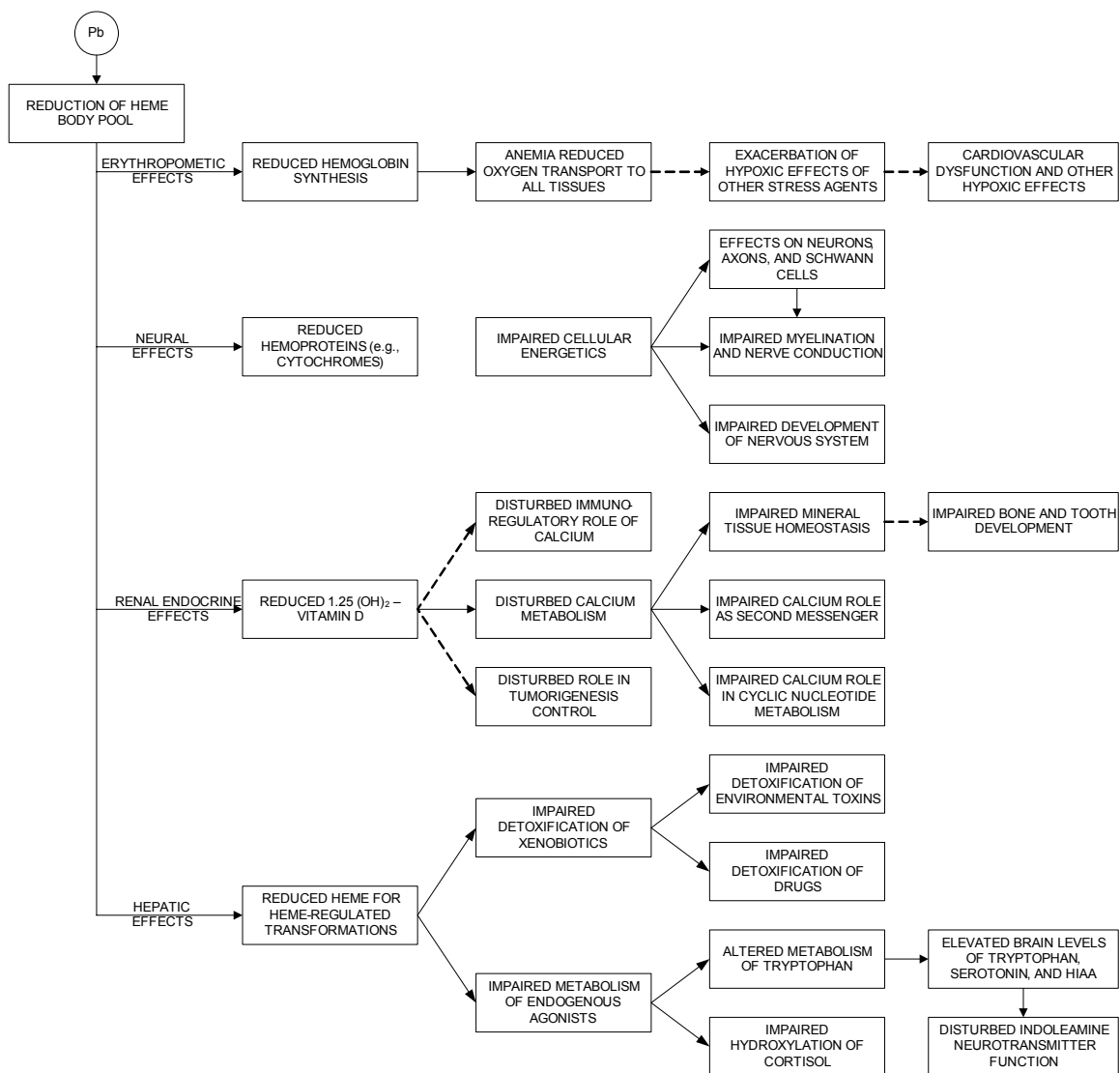
1986a). Formation of the heme-containing cytochromes is inhibited in animals treated intraperitoneally or orally with lead compounds. An inverse dose-effect relationship between lead exposure and P-450 content of hepatic microsomes and also activity of microsomal mixed-function oxygenases has been observed (Goldberg et al. 1978). Increasing duration of exposure to lead was associated with decreasing microsomal P-450 content and decreasing microsomal heme content (Meredith and Moore 1979). In addition, delays in the synthesis of the respiratory chain hemoprotein cytochrome C have been noted during administration of lead to neonatal rats (Bull et al. 1979).

The impairment of heme synthesis by lead may have a far-ranging impact not limited to the hematopoietic system. EPA (1986a) provided an overview of the known and potential consequences of the reduction of heme synthesis as shown in Figure 3-16. Solid arrows indicate well-documented effects, whereas dashed arrows indicate effects considered to be plausible further consequences of the impairment of heme synthesis. More detailed information on the exposure levels or blood lead levels at which these impacts may be experienced was provided in Section 3.2.

Neurotoxicity. The literature on mechanisms of neurotoxicity of lead is enormous. Most studies conducted in recent years have focused on trying to determine the biochemical or molecular basis of the intellectual deficits observed in exposed children using animal models. Trying to cite all of the studies that have contributed to our current knowledge is an almost impossible task. Therefore, the major topics summarized below have been extracted from experts' reviews and the reader is referred to references cited therein for more detailed information (Bouton and Pevsner 2000; Bressler et al. 1999; Cory-Slechta 1995, 2003; Gilbert and Lasley 2002; Lasley and Gilbert 2000; Nihei and Guilarte 2002; Suszkiw 2004; Toscano and Guilarte 2005; Zawia et al. 2000).

Lead can affect the nervous system by multiple mechanisms, one of the most important of which is by mimicking calcium action and/or disruption of calcium homeostasis. Because calcium is involved as a cofactor in many cellular processes, it is not surprising that many cell-signaling pathways are affected by lead. One pathway that has been studied with more detail is the activation of protein kinase C (PKC). PKC is a serine/threonine protein kinase involved in many processes important for synaptic transmission such as the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The γ -isoform is one of several calcium-dependent forms of PKC and is a likely target for lead neurotoxicity; it is neuron-specific and is

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Figure 3-16. Multiorgan Impact of Reduction of Heme Body Pool by Lead

Source: EPA 1986a

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involved in long-term potentiation (see below), spatial learning, and memory processes. PKC has the capacity to both activate and inhibit PKCs. Studies have shown that micromolar concentrations of lead can activate PKC-dependent phosphorylation in cultured brain microvessels, whereas picomolar concentrations of lead activate preparations of PKC *in vitro*. Interestingly, studies in rats exposed to low lead levels have shown few significant changes in PKC activity or expression, suggesting that the whole animal may be able to compensate for lead PKC-mediated effects compared to a system *in vitro*. PKC induces the formation of the AP-1 transcriptional regulatory complex, which regulates the expression of a large number of target genes via AP-1 promoter elements. A gene regulated by lead via AP-1 promoters is the glial fibrillary acidic protein (GFAP), an astrocytic intermediate filament protein that is induced during periods of reactive astrocytic gliosis. Astrocytes along with endothelial cells make up the blood brain barrier (BBB). Studies in rats exposed chronically to low lead levels have reported alterations in the normal pattern of GFAP gene expression in the brain, and the most marked long-lasting effects occurred when the rats were exposed during the developmental period. In immature brain microvessels, most of the protein kinase C is in the cytosol, whereas in mature brain microvessels, this enzyme is membrane-bound. Activation of protein kinase C in other systems is known to result in a change in distribution from cytosol to membrane, and has been observed with exposure of immature brain microvessels to lead. An inhibition of microvascular formation has been observed with lead concentrations that are effective in activating PKC. Thus, it appears that premature activation of PKC by lead may impair brain microvascular formation and function, and at high levels of lead exposure, may account for gross defects in the blood-brain barrier that contribute to acute lead encephalopathy. The blood-brain barrier normally excludes plasma proteins and many organic molecules, and limits the passage of ions. With disruption of this barrier, molecules such as albumin freely enter the brain and ions and water follow. Because the brain lacks a well-developed lymphatic system, clearance of plasma constituents is slow, edema occurs, and intracranial pressure rises. The particular vulnerability of the fetus and infant to the neurotoxicity of lead may be due in part to immaturity of the blood-brain barrier and to the lack of the high-affinity lead-binding protein in astroglia, which sequester lead.

Another enzyme altered by lead is calmodulin, a major intracellular receptor for calcium in eukaryotes. Normally, calcium induces a conformational change in calmodulin that converts the protein to an active form; lead improperly activates the enzyme. Some studies suggest that activation of calmodulin by lead results in protein phosphorylation in the rat brain and brain membrane preparations and can alter proper functioning of cAMP messenger pathways. It has been shown that calmodulin can mediate gene expression via calmodulin-dependent kinases. The effects of lead on gene expression via activation of

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calmodulin are not as marked as those via PKC because activation of calmodulin requires 100-fold more lead than activation of PKC.

Lead also can substitute for zinc in some enzymes and in zinc-finger proteins, which coordinate one or more zinc cations as cofactors. The substitution of lead for zinc in zinc-finger proteins can have significant effects on *de novo* expression of the bound proteins and in any genes transcriptionally-regulated by a particular protein. Lead has been found to alter the binding of zinc-finger transcriptional regulator Sp1 to its specific DNA sequences. This is accompanied by aberrant expression of Sp1 target genes such as myelin basic protein and proteolipid protein. Another gene regulated by Sp1 is the β -amyloid precursor protein (APP) gene. Recently, it was shown that lead exposure in neonatal rats transiently induces APP mRNA, which is overexpressed with a delay of 20 months after exposure to lead ceased. In contrast, APP expression, Sp1 activity, as well as APP and β -amyloid protein levels, were unresponsive to lead during old age, suggesting that exposures occurring during brain development may predetermine the expression and regulation of APP later in life. It has been suggested that the multiple responses to lead exposure are due to lead specifically targeting zinc-finger proteins found in enzymes, channels, and receptors.

Lead affects virtually every neurotransmitter system in the brain, but most information on changes is available on the glutamatergic, dopaminergic, and cholinergic systems. Of these, special attention has been paid to the glutamatergic system and its role in hippocampal long-term potentiation (LTP). Hippocampal LTP is a cellular model of learning and memory characterized by a persistent increase in synaptic efficacy following delivery of brief tetanic stimulation (high-frequency stimulation). LTP provides a neurophysiological substrate for learning and storing information and is thought to utilize the same synaptic mechanisms as the learning process. LTP is established only with complex patterns of stimulation but not with single pulse stimulation. While it has been studied primarily in the hippocampal subregions CA1 and dentate gyrus, it can also be evoked in cortical areas. Exposure of intact animals or tissue slices to lead diminishes LTP by a combination of three actions: increasing the threshold for induction, reducing the magnitude of potentiation, and shortening its duration by accelerating its rate of decay. This effect on LTP involves actions of lead on glutamate release (presynaptic effects) and on the N-methyl-D-aspartate (NMDA) receptor function. Studies have shown that the effects of lead vary as a function of the developmental exposure period and that lead exposure early in life is critical for production of impaired LTP in adult animals. LTP is more readily affected by lead during early development, but exposure initiated after weaning also affects synaptic plasticity. Studies also have shown that both LTP magnitude and threshold exhibit a U-shape type response with increasing lead

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doses. While LTP is primarily a glutamatergic phenomenon, it can be modulated through input from extrahippocampal sources including noradrenergic, dopaminergic, and cholinergic sources.

Studies in animals treated with lead (PbB 30–40 µg/dL) have shown that induction of pair-pulse facilitation in dentate gyrus is impaired. Since the phenomenon is mediated primarily by increased glutamate release, the reasonable assumption is that lead reduces glutamate release. Support for this assumption is also derived from studies in which depolarization-induced hippocampal glutamate release was reduced in awake animals with similar PbBs. This inhibition of glutamate release was shown to be due to lead-related decrements in a calcium-dependent component. The exact mechanism for the inhibition of glutamate release by lead is not known, but is consistent with lead at nanomolar concentrations preventing maximal activation of PKC, rather than lead blocking calcium influx into the presynaptic terminal through voltage-gated calcium channels. Reduced glutamate release can be observed in rats exposed from conception through weaning and tested as adults, when lead was no longer present, suggesting that a direct action of lead is not necessary and that other mechanisms, such as reductions in synaptogenesis, also may be involved. As with LTP, depolarization-evoked hippocampal glutamate release in rats treated chronically with several dose levels of lead exhibited a U-shaped response. That is, glutamate release was inhibited in rats treated with the lower lead doses, but not in those exposed to the higher concentrations of lead. Although speculative, this was interpreted as lead at the higher doses mimicking calcium in promoting transmitter release and overriding the inhibitory effects of lead that occur at lower lead levels.

The findings regarding the effects of lead on postsynaptic glutamatergic function have been inconsistent across laboratories, but a direct inhibitory action of lead on the NMDA receptor is unlikely at environmentally relevant exposure levels. Some studies have shown that continuous exposure of rats from gestation to adulthood results in a significant increase in NMDA receptor numbers in cortical areas, hippocampus, and forebrain. This was observed in the forebrain at PbB of 14 µg/dL. Other studies, however, have reported changes in the opposite direction and the reason for the discrepancy in results may be due to the different exposure protocols used. From a functional point of view, it seems plausible that a lead-induced reduction in presynaptic transmitter release be compensated by a postsynaptic increase in number or density of receptors in order to maintain a viable function.

The dopaminergic system also has a role in aspects of cognitive function since lesions of dopaminergic neurons impair behavior in various types of learning and cognitive tasks. Also, individuals who suffer from Parkinson's disease, a disease associated with dopamine depletion in the striatum, sometimes show

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difficulties in cognitive functions. Most of the evidence available suggests that lead may impair regulation of dopamine synthesis and release, indicating a presynaptic site of action. Studies in animals often report opposing effects of lead on nigrostriatal and mesolimbic dopamine systems regarding receptor binding, dopamine synthesis, turnover, and uptake. Postweaning exposure of rats to lead resulted in supersensitivity of D1 and D2 dopamine receptors, which can be interpreted as a compensatory response to decreased synthesis and/or release of dopamine. Lesions to the nucleus accumbens (a terminal dopamine projection area) and the frontal cortex result in perseverative deficits, suggesting that the mesolimbic system is preferentially involved in the effects of lead. Results of studies using dopaminergic compounds seem to indicate that changes in dopamine systems do not play a role in the effects of lead on learning. Instead, it has been suggested that changes in dopaminergic systems may play a role in the altered response rates on Fixed-Interval (FI) schedules of reinforcement that have been observed in animals exposed to lead. This type of changes has been thought to represent a failure to inhibit inappropriate responding.

It is widely accepted that the cholinergic system plays a role in learning and memory processes. Some cognitive deficits observed in patients with Alzheimer's disease have been attributed to impaired cholinergic function in the cortex and hippocampus. Exposure to lead induces numerous changes in cholinergic system function, but the results, in general, have been inconsistently detected, or are of opposite direction in different studies, which may be attributed to the different exposure protocols used in the different studies. However, it is clear that lead blocks evoked release of acetylcholine and diminishes cholinergic function. This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction showed that lead reduces acetylcholine release by blocking calcium entry into the terminal. At the same time, lead prevents sequestration of intracellular calcium by organelles, which results in increased spontaneous release of the neurotransmitter. Studies *in vitro* show that lead can block nicotinic cholinergic receptors, but it is unclear whether such effects occur *in vivo* or whether lead alters the expression of nicotinic cholinergic receptors in developing brain. Evidence for an involvement in lead-induced behavioral deficits has been presented based on the observation that intrahippocampal transplants of cholinergic-rich septal and nucleus basalis tissue improve the deficits and that treatment with nicotinic agonists can improve learning and memory impairments following perinatal lead treatment of rats. Chronic exposure of rats to lead has resulted in decreased muscarinic-receptor expression in the hippocampus. Whether or not lead exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with opposite results. The preponderance of the binding data suggests that lead does not directly affect muscarinic receptors with the exception of visual cortex, where lead may have a direct inhibitory effect on muscarinic receptors from rods and bipolar of the retina.

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3.4.3 Animal-to-Human Extrapolations

Studies in rodents, dogs, and nonhuman primates have demonstrated all of the major types of health effects of lead that have been observed in humans, including cardiovascular, hematological, neurodevelopmental, and renal effects (EPA 1986a). These studies also provide support for the concept of blood lead concentration as a metric of internal dose for use in dose-response assessments in humans.

The effects of low-level lead exposure on cognitive development and function in humans are difficult to discern against the background of genetic, environmental, and socioeconomic factors that would be expected to affect these end points in children. Experimental studies in animals have been helpful for establishing the plausibility of the hypothesis that low-level exposures to lead can affect cognitive function in mammals and for providing insights into possible mechanisms for these effects. Studies in rats and nonhuman primates have demonstrated deficits in learning associated with blood lead concentrations between 10 and 15 $\mu\text{g}/\text{dL}$, a range that is comparable to those reported in epidemiological studies, which found learning deficits in children (Cory-Slechta 2003; Rice 1996b).

The lead-induced nephropathy observed in humans and rodents shows a comparable early pathology (Goyer 1993). However, in rodents, proximal tubular cell injury induced by lead can progress to adenocarcinomas of the kidney (see Section 3.2.2). The observation of lead-induced kidney tumors in rats may not be relevant to humans. Conclusive evidence for lead-induced renal cancers (or any other type of cancer) in humans is lacking, even in populations in which chronic lead nephropathy is evident.

3.5 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

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Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

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Health effects that have been associated with lead exposures during infancy or childhood include anemia (Schwartz et al. 1990) (and related disorders of heme synthesis), neurological impairment (e.g., encephalopathy), renal alterations, colic (Chisolm 1962, 1965; Chisolm and Harrison 1956), and impaired metabolism of vitamin D (Mahaffey et al. 1982; Rosen and Chesney 1983). Death from encephalopathy may occur with PbBs ≥ 125 $\mu\text{g/dL}$. In addition to the above effects, the following health effects have been associated with lead exposures either *in utero*, during infancy, or during childhood: delays or impairment of neurological development, neurobehavioral deficits including IQ deficits, low birth weight, and low gestational age, growth retardation, and delayed sexual maturation in girls (Bellinger et al. 1992; Canfield et al. 2004; Coscia et al. 2003; Lanphear et al. 2000a; Ris et al. 2004; Schnaas et al. 2000; Selevan et al. 2003; Tong et al. 1998; Wu et al. 2003a). These effects, which are discussed in Section 3.2, are consistent with findings in animals exposed to lead. Effects of lead observed at relatively high exposures such as anemia, colic, and encephalopathy, also occur in adults. There is no evidence that exposure to lead causes structural birth defects in humans or in animals, although Needleman et al. (1984) reported an association between cord blood lead and the incidence of minor anomalies (hemangiomas and lymphangiomas, hydrocele, skin anomalies, undescended testicles) in a study of 5,183 women who delivered neonates of at least 20 weeks of gestational age. Exposure to lead during childhood may result in neurobehavioral effects that persist into adulthood (e.g., Byers and Lord 1943; Stokes et al. 1998; White et al. 1993).

Children and developing organisms in general, are more susceptible to lead toxicity than adults. This higher susceptibility derives from numerous factors. Children exhibit more severe toxicity at lower exposures than adults, as indicated by lower PbB concentrations and time-integrated PbB concentrations that are associated with toxicity in children (see Section 3.2 for more detailed discussion). This suggests that children are more vulnerable to absorbed lead than adults. The mechanism for this increased vulnerability is not completely understood. Lead affects processes such as cell migration and synaptogenesis, as well as pruning of unnecessary connections between neurons, all key processes during brain development. Lead also affects glial cells and the blood brain barrier. Alterations in any of these parameters can produce permanent improper connections that will lead to altered specific brain functions. Children also absorb a larger fraction of ingested lead than do adults; thus, children will experience a higher internal lead dose per unit of body mass than adults at similar exposure concentrations (Alexander et al. 1974; Blake et al. 1983; James et al. 1985; Rabinowitz et al. 1980; Ziegler et al. 1978). Absorption of lead appears to be higher in children who have low dietary iron or calcium intakes; thus, dietary insufficiencies, which are not uncommon in lower socioeconomic children, may contribute to their lead absorption (Mahaffey and Annest 1986; Mahaffey et al. 1986; Marcus and Schwartz 1987; Ziegler et al.

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1978) (see Section 3.3.1.2 for more detailed discussion of lead absorption in children). Insufficient dietary zinc, also not uncommon in children, may contribute to their increased susceptibility to lead, since lead impairs the activity of zinc-requiring enzymes in the heme biosynthesis pathway (see Section 3.4.2). Infants are born with a lead body burden that reflects the burden of the mother (Goyer 1990; Graziano et al. 1990; Schuhmacher et al. 1996). During gestation, lead from the maternal skeleton is transferred across the placenta to the fetus (Gulson 2000; Gulson et al. 1997b, 1999b, 2003). Additional lead exposure may occur during breast feeding (Gulson et al. 1998b) (see Section 3.3.2 for more detailed discussion). This means that lead stored in the mother's body from exposure prior to conception can result in exposure to the fetus or nursing neonate. Behavioral patterns of children can result in higher rates of ingestion of soil and dust, both of which are often important environmental depots for lead (Barnes 1990; Binder et al. 1986; Calabrese et al. 1989, 1997a; Clausen et al. 1987). Examples of activities that tend to promote soil and dust ingestion preferentially in children include playing and crawling on the ground and floor, hand-to-mouth activity, mouthing of objects, and indiscriminate eating of food items dropped or found on the ground or floor (see Section 6.6 for more detailed discussion). Some children engage in pica, or the ingestion of nonfood items (e.g., soil). This behavior can lead to excess exposure if a child consumes soil contaminated with lead.

The toxicokinetics of lead in children appears to be similar to that in adults, with the exception of the higher absorption of ingested lead in children. Most of the lead body burden in both children and adults is in bone; a slightly large fraction of the body burden in adults resides in bone (Barry 1975). The difference may reflect the larger amount of trabecular bone and bone turnover during growth; trabecular bone has a shorter retention half-time for lead than does cortical bone (see Section 3.3.2 for details). Limited information suggests that organic lead compounds undergo enzymatic (cytochrome P-450) biotransformation and that inorganic lead is complexed (nonenzymatically) with proteins and nonprotein ligands. However, the information available is insufficient to determine whether the metabolism of lead in children is similar to adults. Several models of lead pharmacokinetics in children have been developed (EPA 1994a, 1994b; Leggett 1993; O'Flaherty 1993, 1995a); these are described in Section 3.3.5.

The important biomarkers of exposure that have been explored in children include PbB concentration (CDC 1991), bone lead levels (as measured from noninvasive XRF measurements of phalanx, patella, tibia, or ulna), and lead levels in deciduous teeth (Hu et al. 1998). Lead in blood has a much shorter retention half-time than lead in bone (days compared to years); therefore, PbB concentration provides a marker for more recent exposure, while lead in bone appears to reflect longer-term cumulative exposures (Borjesson et al. 1997; Nilsson et al. 1991; Schutz et al. 1987). Lead in tooth enamel is thought to reflect

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exposures *in utero* and during early infancy, during which development of tooth enamel and coronal dentine is completed. Lead appears to accumulate in dentin after formation of the dentin is complete; therefore, lead in dentin is thought to reflect exposures that occur up to the time the tooth is shed (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). A more detailed discussion of the above biomarkers of exposure, as well as other less important biomarkers, is presented in Section 3.6.1. The most sensitive biomarkers of effects of lead in children relate to the effects of lead on heme metabolism, they include ALAD activity, EP, FEP, and ZPP; however, these are not specific for lead (Bernard and Becker 1988; CDC 1991; Hernberg et al. 1970). EP has been used as a screening test. However, it is not sensitive below a PbB of about 25 µg/dL. These and other biomarkers of effects of lead are discussed in Section 3.6.2.

Methods for preventing or decreasing the absorption of lead following acute exposures to potentially toxic levels of lead include removal of the child from the exposure source, removal of lead-containing dirt and dust from the skin, and, if the lead has been ingested, standard treatments to induce vomiting. Ensuring a diet that is nutritionally adequate in calcium and iron may decrease the absorbed dose of lead associated with a given exposure level, because lead absorption appears to be higher in children who have low levels of iron or calcium in their diets (Mahaffey and Annest 1986; Mahaffey et al. 1986; Marcus and Schwartz 1987; Ziegler et al. 1978). Diets that are nutritionally adequate in zinc also may be helpful for reducing the risks of lead toxicity because zinc may protect against lead-induced inhibition of zinc-dependent enzymes, such as ALAD (Chisolm 1981; Johnson and Tenuta 1979; Markowitz and Rosen 1981). Methods for reducing the toxicity of absorbed lead include the injection or oral administration of chelating or complexing agents (e.g., EDTA, penicillamine, dimercaptosuccinic acid [DMSA]) (CDC 1991). These agents form complexes with lead that are more rapidly excreted and thereby decrease the body burden of lead. These methods for reducing the toxic effects of lead are described in greater detail in Section 3.9. Several studies (described in Section 3.9) have examined whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes reportedly altered by lead (Dietrich et al. 2004; Liu et al. 2002; Rogan et al. 2001; Ruff et al. 1993). The conclusion of these studies was that chelation therapy is not indicated in children with moderate PbB (≤ 40 µg/dL).

3.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

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Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to lead are discussed in Section 3.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by lead are discussed in Section 3.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.8, Populations That Are Unusually Susceptible.

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3.6.1 Biomarkers Used to Identify or Quantify Exposure to Lead

The ideal biomarker of lead exposure would be a measurement of total lead body burden. Biomarkers of exposure in practical use today are measurements of total lead levels in tissues or body fluids, such as blood, bone, urine, or hair; or measurement of certain biological responses to lead (e.g., zinc protoporphyrin). Tetraalkyl lead compounds may also be measured in the breath. Of these, blood lead concentration (PbB) is the most widely used and considered to be the most reliable biomarker for general clinical use and public health surveillance. Currently, blood lead measurement is the screening test of choice to identify children with elevated PbBs (CDC 1991). Venous sampling of blood is preferable to finger prick sampling, which has a considerable risk of surface lead contamination from the finger if proper finger cleaning is not carried out. In children, PbBs between 10 and 14 µg/dL should trigger community-wide childhood lead poisoning prevention activities (CDC 1991). Since the elimination half-time of lead in blood is approximately 30 days, PbBs generally reflect relatively recent exposure and cannot be used to distinguish between low-level intermediate or chronic exposure and high-level acute exposure. In 1997, the CDC issued new guidance on screening children for lead poisoning that recommends a systematic approach to the development of appropriate lead screening in states and communities (CDC 1997c). The objective of the new guidelines is maximum screening of high-risk children and reduced screening of low-risk children, as contrasted with previous guidelines (CDC 1991), which recommended universal screening.

Blood Lead Concentration. Measurement of PbB is the most widely used biomarker of lead exposure. Elevated blood lead concentration (e.g., >10 µg/dL) is an indication of excessive exposure in infants and children (CDC 1991) and is considered to be excessive for women of child-bearing age (ACGIH 1998). The biological exposure index (BEI) for lead in blood of exposed workers is 30 µg/dL (ACGIH 2004). The NIOSH recommended exposure limit (REL) for workers (50 µg/m³ air, 8-hour TWA) is established to ensure that the blood lead concentration does not exceed 60 µg/dL (NIOSH 2005).

The extensive use of blood lead as a dose metric reflects mainly the greater feasibility of incorporating blood lead measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as lead in kidney, plasma, urine, or bone (Skerfving 1988). PbB measurements have several limitations as measures of lead body burden. Blood comprises <2% of the total lead burden; most of the lead burden resides in bone (Barry 1975). The elimination half-time of lead in blood is approximately 30 days (Chamberlain et al. 1978; Griffin et al. 1975; Rabinowitz et al. 1976); therefore, the lead concentration in blood relatively reflects, mainly, the exposure history of the previous few

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months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone (Graziano 1994; Lyngbye et al. 1990b). The relationship between lead intake and PbB is curvilinear; the increment in PbB per unit of intake decreases with increasing PbB (Ryu et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1982, 1984). Lead intake-blood lead relationships also vary with age as a result of age-dependency of gastrointestinal absorption of lead, and vary with diet and nutritional status (Mushak 1991). A practical outcome of the above characteristics of PbB is that PbB can change relatively rapidly (e.g., weeks) in response to changes in exposure; thus, PbB can be influenced by short-term variability in exposure that may have only minor effects on lead body burden. A single blood lead determination cannot distinguish between lower-level intermediate or chronic exposure and higher-level acute exposure. Similarly, a single measurement may fail to detect a higher exposure that occurred (or ended) several months earlier. Time-integrated measurements of PbB may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Roels et al. 1995).

Bone and Tooth Lead Measurements. The development of noninvasive XRF techniques for measuring lead concentrations in bone has enabled the exploration of bone lead as a biomarker of lead exposure in children and in adults (Batuman et al. 1989; Hu 1991b; Hu et al. 1989, 1990, 1995; Rosen et al. 1993; Wedeen 1988, 1990, 1992). Lead in bone is considered a biomarker of cumulative exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect lead in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna reflect primarily lead in cortical bone. Lead levels in cortical bone may be a better indicator of long-term cumulative exposure than lead in trabecular bone, possibly because lead in trabecular bone may exchange more actively with lead in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of lead in cortical bone, compared to trabecular bone (Borjesson et al. 1997; Brito et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal measures of bone lead over a 3-year period showed no significant decline in cortical bone lead, whereas trabecular bone lead declined by approximately 15% (Kim et al. 1997). Estimates of cortical bone lead elimination half-times (5–50 years) show a dependence on lead burden, with longer half-times in people who have higher bone lead burdens (Bruto et al. 2005). Further evidence that cortical

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bone lead measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone lead measurements have been compared to PbB. Lead levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of lead in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone lead measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary blood lead measurements (Borjesson et al. 1997; Roels et al. 1994). Bone lead levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone lead may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Relationships between bone lead levels and health outcomes have been studied in several epidemiology studies, but not as extensively as have other biomarkers of exposure such as PbB. These studies suggest that bone lead levels may be predictors of certain health outcomes, including neurodevelopmental and behavioral outcomes in children and adolescents (Campbell et al. 2000a; Needleman et al. 1996, 2002; Payton et al. 1998); and hypertension and declines in renal function in adults (Cheng et al. 2001; Gerr et al. 2002; Hu et al. 1996a, 1998; Korrick et al. 1999; Rothenberg et al. 2002a; Tsaih et al. 2004).

Tooth lead has been considered a potential biomarker for measuring long-term exposure to lead (e.g., years) because lead that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Ericson 2001; Gomes et al. 2004; Omar et al. 2001; Rabinowitz et al. 1989; Steenhout and Pourtois 1987). Formation of enamel and coronal dentin of deciduous teeth is complete prior to the time children begin to crawl; however, lead in shed deciduous teeth is not uniformly distributed. Differences in lead levels and stable isotope signatures of the enamel and dentin suggest that lead uptake occurs differentially in enamel and dentin after eruption of the tooth (Gulson 1996; Gulson and Wilson 1994). Lead in enamel is thought to reflect primarily lead exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate lead after eruption of the tooth, therefore, dentin lead is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). Accumulation of lead in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because it is in direct contact with the external environment, enamel lead levels may be more influenced than dentin lead by external lead levels and tooth wear (Purchase and Fergusson 1986).

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An analysis of eight cross-sectional and/or prospective studies that reported tooth lead and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth lead levels ranged from <3 to >12 $\mu\text{g/g}$. In a study of 63 subjects, dentin lead was found to be predictive of concentrations of lead in the tibia, patella, and mean bone lead 13 years after tooth lead assessment in half of them (Kim et al. 1996b). The authors estimated that a 10 $\mu\text{g/g}$ increase in dentin lead levels in childhood was predictive of a 1 $\mu\text{g/g}$ increase in tibia lead levels, a 5 $\mu\text{g/g}$ in patella lead levels, and a 3 $\mu\text{g/g}$ increase in mean bone lead among the young adults.

Plasma Lead Concentration. The concentration of lead in plasma is extremely difficult to measure accurately because levels in plasma are near the quantitation limits of most analytical techniques (e.g., approximately 0.4 $\mu\text{g/L}$ at blood lead concentration of 100 $\mu\text{g/L}$ (Bergdahl and Skerfving 1997; Bergdahl et al. 1997a) and because hemolysis that occurs with typical analytical practices can contribute substantial measurement error (Bergdahl et al. 1998, 2006; Cavalleri et al. 1978; Smith et al. 1998a). Recent advances in inductively-coupled plasma mass spectrometry (ICP-MS) offer sensitivity sufficient for measurements of lead in plasma (Schütz et al. 1996). The technique has been applied to assessing lead exposures in adults (Cake et al. 1996; Hernandez-Avila et al. 1998; Manton et al. 2001; Smith et al. 2002; Tellez-Royo et al. 2004). A direct comparison of lead concentrations in plasma and serum yielded similar results (Bergdahl et al. 2006); however, the interchangeability of plasma and serum lead measurements for biomonitoring of lead exposure or body burden had not been thoroughly evaluated in large numbers of subjects (Bergdahl et al. 2006; Manton et al. 2001; Smith et al. 2002).

Urinary Lead. Measurements of urinary lead levels have been used to assess lead exposure (e.g., Fels et al. 1998; Gerhardsson et al. 1992; Lilis et al. 1968; Lin et al. 2001; Mortada et al. 2001; Roels et al. 1994). However, like PbB, urinary lead excretion reflects, mainly, recent exposure and, thus, shares many of the same limitations for assessing lead body burden or long-term exposure (Sakai 2000; Skerfving 1988). The measurement is further complicated by variability in urine volume, which can affect concentrations independent of excretion rate (Diamond 1988) and the potential effects of decrements in kidney function on excretion, in association with high, nephrotoxic lead exposures or kidney disease (Lilis et al. 1968; Wedeen et al. 1975). Urinary lead concentration increases exponentially with PbB and can exhibit relatively high intra-individual variability, even at similar PbBs (Gulson et al. 1998a; Skerfving et al. 1985). Urinary diethyl lead has been proposed as a qualitative marker of exposure to tetraethyl lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

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The measurement of lead excreted in urine following an injection (intravenous or intramuscular) of the chelating agent, calcium disodium EDTA (*EDTA provocation*) has been used to detect elevated body burden of lead in adults (Biagini et al. 1977; Lilis et al. 1968; Wedeen 1992; Wedeen et al. 1975) and children (Chisolm et al. 1976; Markowitz and Rosen 1981), and is considered to be a reliable measure of the potentially toxic fraction of the lead body burden (WHO 1995). The assay is not a substitute for blood lead measurements in the clinical setting. Children whose PbBs are ≥ 45 $\mu\text{g/dL}$ should not receive a provocative chelation test; they should be immediately referred for appropriate chelation therapy (CDC 1991). Further limitations for routine use of the test are that EDTA must be given parenterally and requires timed urine collections. A study conducted in rats found that intraperitoneal administration of a single dose of EDTA following 3–4-month exposures to lead in drinking water increased levels of lead in the liver and brain (Cory-Slechta et al. 1987) raising concern for similar effects in humans who undergo the EDTA provocation test. The use of EDTA to assess bone stores of lead (Wedeen 1992) are largely being supplanted by more direct, noninvasive procedures for measuring lead in bone.

Lead in Saliva and Sweat. Lead is excreted in human saliva and sweat (Lilley et al. 1988; Rabinowitz et al. 1976; Stauber and Florence 1988; Stauber et al. 1994). However, sweat has not been widely adopted for monitoring lead exposures. Lilley et al. (1988) found that lead concentrations in sweat were elevated in lead workers; however, sweat and blood lead concentrations were poorly correlated. This may reflect excretion of lead in or on the skin that had not been absorbed into blood. Studies conducted in rats have found relatively strong correlations between lead concentrations in plasma and saliva (e.g., $r^2 > 0.9$), compared to blood lead and saliva; therefore, saliva may serve as a better predictor of plasma lead than blood lead concentration (Timchalk et al. 2006).

Hair and Nail Lead. Lead is incorporated into human hair and hair roots (Bos et al. 1985; Rabinowitz et al. 1976) and has been explored as a possibly noninvasive approach for estimating lead body burden (Gerhardsson et al. 1995b; Wilhelm et al. 1989). The method is subject to error from contamination of the surface with environmental lead and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and is a relatively poor predictor of PbB, particularly at low concentrations (< 12 $\mu\text{g/dL}$) (Campbell and Toribara 2001; Drasch et al. 1997; Esteban et al. 1999). Nevertheless, levels of lead in hair were positively correlated with children's classroom attention deficit behavior in a study (Tuthill 1996). Lead in hair was correlated with liver and kidney lead in a study of deceased smelter workers (Gerhardsson et al. 1995b). Nail lead has also been utilized as a marker (Gerhardsson et al. 1995b).

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Semen Lead. Correlations between concentrations of lead in semen and blood have been reported and vary in strength across studies (Alexander et al. 1998a, 1998b; Farias et al. 2005; Telisman et al. 2000). This variation may relate, in part, to analytical challenges in the measurement of the relatively low concentrations of lead in semen. Using ICP-MS and rigorous collection methods to avoid contamination, Farias et al. (2005) reported a detection limit of 0.2 µg/L semen. Mean semen lead concentration in a group of 160 adults (age range: 19–48 years) who were not exposed to lead occupationally was 2.66 µg/L (range: 0.08–19.42) and significantly correlated with blood lead concentration (mean: 10.8 µg/dL, range: 4.5–40.2) and tibia bone lead (mean: 14.51 µg/g, range: non-detect–44.71 µg/g).

Stable Lead Isotopes. Analysis of the relative abundance of stable isotopes of lead in blood and other accessible body fluids (e.g., breast milk, urine) has been used to differentiate exposures from multiple sources (Flegal and Smith 1995). Relative abundances of stable isotopes of lead (^{204}Pb , ^{206}Pb , ^{207}Pb , and ^{208}Pb) in lead ores vary with the age of the ore (which determines the extent to which the parent isotopes have undergone radioactive decay to stable lead). Humans have lead isotope abundance profiles that reflect the profiles of lead deposits to which they have been exposed. Conversely, if exposure is to lead from a predominant deposit, that source can be identified by the relative abundance profile in blood (or other biological sample). Similarly, if exposure abruptly changes to a lead source having a different isotope abundance profile, the kinetics of the change in profile in the person can be measured, reflecting the kinetics of uptake and distribution of lead from the new source (Gulson et al. 2003; Maddaloni et al. 1998; Manton et al. 2003). Numerous examples of the application of stable isotope abundance measurements for studying sources of lead exposures have been reported (Angle et al. 1995; Graziano et al. 1996; Gulson and Wilson 1994; Gulson et al. 1996; Manton 1977, 1998).

Effect Biomarkers Used to Assess Exposure to Lead. Certain physiological changes that are associated with lead exposure have been used as biomarkers of exposure (see Section 3.6.2). These include measurement of biomarkers of impaired heme biosynthesis (blood zinc protoporphyrin, urinary coproporphyrin, erythrocyte ALAD activity). These types of measurements have largely been supplanted with measurement of blood lead concentration for the purpose of assessing lead exposure.

3.6.2 Biomarkers Used to Characterize Effects Caused by Lead

One of the most sensitive effects of lead exposure is the inhibition of the heme biosynthesis pathway, which is necessary for the production of red blood cells. Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is not specific for lead (Bernard and Becker 1988). However,

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inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). Most protoporphyrin in erythrocytes (about 90%) exists as ZPP. This fraction is preferentially measured by hematofluorometers. Extraction methods measure all of the protoporphyrin present, but strip the zinc from the ZPP during the extraction process. For this reason, extraction results are sometimes referred to as (zinc) FEP. Although the chemical forms measured by the two methods differ slightly, on a weight basis they are roughly equivalent; thus, results reported as EP, ZPP, or FEP all reflect essentially the same analyte. An elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis and reflects average lead levels at the site of erythropoiesis over the previous 4 months (Janin et al. 1985). The concentration of EP rises above background at PbBs of 25–30 µg/dL, above which, there is a positive correlation between PbB and EP (CDC 1985; Gennart et al. 1992a; Roels and Lauwerys 1987; Soldin et al. 2003; Wildt et al. 1987). Lead toxicity is generally considered to be present when a PbB ≥ 10 µg/dL is associated with an EP level of ≥ 35 µg/dL (CDC 1991; Somashekaraiah et al. 1990). This effect is detectable in circulating erythrocytes only after a lag time reflecting maturation in which the entire population of red blood cells has turned over (i.e., 120 days) (EPA 1986a; Moore and Goldberg 1985). Similarly, elevated erythrocyte protoporphyrin can reflect iron deficiency, sickle cell anemia, and hyperbilirubinemia (jaundice). Therefore, reliance on EP levels alone for initial screening could result in an appreciable number of false positive cases (CDC 1985; Mahaffey and Annest 1986; Marcus and Schwartz 1987). Conversely, since EP does not go up until the PbB exceeds 25 µg/dL, and the level of concern is 10 µg/dL, relying on EP measures would result in many false negative cases. Some have estimated that relying only on ZPP screening to predict future lead toxicity would miss approximately 3 cases with toxic blood lead concentrations in every 200 workers at risk (Froom et al. 1998). A limitation of measuring porphyrin accumulation is that porphyrin is labile because of photochemical decomposition; thus, assay samples must be protected from light. However, other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis (Somashekaraiah et al. 1990).

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of lead effect (Graziano 1994; Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). ALAD activity is negatively correlated with PbBs of 5–95 µg/dL, with >50% inhibition occurring at PbBs >20 µg/dL (Hernberg et al. 1970; Morita et al. 1997; Roels and Lauwerys 1987). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990). ALAD was found to be a more sensitive biomarker than urinary ALA and ZPP at PbBs between 21 and 30 µg/dL (Schuhmacher et al. 1997). A marked increase in urinary excretion of ALA, the intermediate that accumulates from decreased ALAD, can be detected

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when PbB exceeds 35 µg/dL in adults and 25–75 µg/dL in children (NAS 1972; Roels and Lauwerys 1987; Sakai and Morita 1996; Schuhmacher et al. 1997).

Another potential biomarker for hematologic effects of lead is the observation of basophilic stippling and premature erythrocyte hemolysis (Paglia et al. 1975, 1977). Lead can impair the activity of pyrimidine 5'-nucleotidase, resulting in a corresponding increase in pyrimidine nucleotides in red blood cells, which leads to a deficiency in maturing erythroid elements and thus, decreased red blood cells. However, this effect is nonspecific; it is encountered with benzene and arsenic poisoning (Smith et al. 1938) and in a genetically-induced enzyme-deficiency syndrome (Paglia et al. 1975, 1977). Furthermore, since basophilic stippling is not universally found in chronic lead poisoning, it is relatively insensitive to lesser degrees of lead toxicity (CDC 1985). The activity of adenine dinucleotide synthetase (NADS) in erythrocytes has also been explored as a biomarker for predicting PbBs >40 µg/dL; NADS activity is negatively correlated with PbB over the range 5–80 µg/dL (Morita et al. 1997).

A multisite study of populations living near four NPL sites was conducted to assess the relationship between exposure (PbB and area of residence) and biomarkers of four organ systems: immune function disorders, kidney dysfunction, liver dysfunction, and hematopoietic dysfunction (Agency for Toxic Substances and Disease Registry 1995). The geometric mean PbB in those living in the target areas was 4.26 µg/dL (n=1,645) compared with 3.45 µg/dL for a group living in comparison areas (n=493). In children <6 years old, the corresponding means were 5.37 versus 3.96 µg/dL. In subjects ≥15 years old, the target and comparison values were 3.06 and 3.63 µg/dL, respectively. Ninety percent of target and 93% of comparison area participants had PbBs <10 µg/dL. Lead in soil and in water was found to be higher in comparison areas than in the target areas, but lead in house dust and in interior paint was higher in the target areas. PbB correlated with lead in soil and dust, but not with lead in paint and water. Multivariate regression analyses showed that of all the biomarkers analyzed, PbB was significantly associated with and predictive of hematocrit in adults 15 years of age or older and with increased mean serum IgA in children 6–71 months of age. The biological significance of these associations is unclear since both hematocrit and IgA levels were well within normal ranges and were hardly different than levels in subjects from the comparison areas.

Reduction in the serum 1,25-dihydroxyvitamin D concentration has been reported as an indicator of increased lead absorption or lead concentrations in the blood (Rosen et al. 1980). Lead inhibits the formation of this active metabolite of vitamin D, which occurs in bone mineral metabolism (EPA 1986a; Landrigan 1989). Children with PbBs of 12–120 µg/dL showed decreased serum 1,25-dihydroxyvita-

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min D concentrations comparable to those found in patients with hypoparathyroidism, uremia, and metabolic bone disease (Mahaffey et al. 1982; Rosen et al. 1980). This biomarker is clearly not specific for lead exposure and several diseases can influence this measurement.

One of the most sensitive systems affected by lead exposure is the nervous system. Encephalopathy is characterized by symptoms such as coma, seizures, ataxia, apathy, bizarre behavior, and incoordination (CDC 1985). Children are more sensitive to neurological changes. In children, encephalopathy has been associated with PbBs as low as 70 µg/dL (CDC 1985). An early sign of peripheral manifestations of neurotoxicity is gastrointestinal colic, which can occur with PbBs above 50 µg/dL. The most sensitive peripheral index of neurotoxicity of lead is reported to be slowed conduction velocity in small motor fibers of the ulnar nerve in workers with PbBs of 30–40 µg/dL (Landrigan 1989). Other potential biomarkers of lead suggested for neurotoxicity in workers are neurological and behavioral tests, as well as cognitive and visual sensory function tests (Williamson and Teo 1986). However, these tests are not specific to elevated lead exposure.

Functional deficits associated with lead-induced nephrotoxicity increase in severity with increasing PbB. Effects on glomerular filtration evident at PbBs below 20 µg/dL, enzymuria and proteinuria occurs above 30 µg/dL, and severe deficits in function and pathological changes occur in association with PbBs exceeding 50 µg/dL (see Table 3-3 and Figure 3-3). Biomarkers for these changes include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β₂µ-globulin, α₁µ-globulin, retinol binding protein). However, none of these markers are specific for lead-induced nephrotoxicity. A characteristic histologic feature of lead nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b).

3.7 INTERACTIONS WITH OTHER CHEMICALS

The toxicokinetics and toxicological behavior of lead can be affected by interactions with essential elements and nutrients (for a review, see Mushak and Crocetti 1996). In humans, the interactive behavior of lead and various nutritional factors is particularly significant for children, since this age group is not only sensitive to the effects of lead, but also experiences the greatest changes in relative nutrient status. Nutritional deficiencies are especially pronounced in children of lower socioeconomic status; however, children of all socioeconomic strata can be affected.

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Available data from a number of reports document the association of lead absorption with suboptimal nutritional status. In infants and children 1–6 years of age, lead retention (as measured by PbB content) was inversely correlated with calcium intake, expressed either as a percentage of total or on a weight basis (Johnson and Tenuta 1979; Mahaffey et al. 1986; Sorrell et al. 1977; Ziegler et al. 1978). Dietary intakes of calcium and vitamin D were significantly ($p < 0.001$) lower in children with PbBs $> 60 \mu\text{g/dL}$ (Johnson and Tenuta 1979). The gastrointestinal uptake of ^{203}Pb was monitored in eight adult subjects as a function of dietary calcium and phosphorus intakes (Heard and Chamberlain 1982). The label absorption rate was 63% without supplementation of these minerals in fasting subjects, compared with 10% in subjects supplemented with 200 mg calcium plus 140 mg phosphorus, the amounts present in an average meal. Calcium and phosphorus alone reduced lead uptake by a factor of 1.3 and 1.2, respectively; both together yielded a reduction factor of 6. Copper, iron, and zinc have also been postulated to affect lead absorption (Klauder and Petering 1975).

Children with elevated PbB (12–120 $\mu\text{g/dL}$) were found to have significantly lower serum concentrations of the vitamin D metabolite 1,25-dihydroxyvitamin D compared with age-matched controls ($p < 0.001$), and showed a negative correlation of serum 1,25-dihydroxyvitamin D with lead over the range of blood lead levels measured (Mahaffey et al. 1982; Rosen et al. 1980).

Zinc is in the active site of ALAD and can play a protective role in lead intoxication by reversing the enzyme-inhibiting effects of lead. Children with high PbBs (50–67 $\mu\text{g/dL}$) were reported to consume less zinc than children with lower PbB (12–29 $\mu\text{g/dL}$) (Johnson and Tenuta 1979). In a group of 13 children, Markowitz and Rosen (1981) reported that the mean serum zinc levels in children with plumbism were significantly below the values seen in normal children; chelation therapy reduced the mean level even further. An inverse relationship between ALA in urine and the amount of chelatable or systemically active zinc was reported in 66 children challenged with EDTA and having PbBs ranging from 45 to 60 $\mu\text{g/dL}$ (Chisolm 1981). Zinc sulfate administration to a lead-intoxicated man following calcium disodium EDTA therapy restored the erythrocyte ALAD activity that was inhibited by lead (Thomasino et al. 1977).

Forty-three children with elevated PbB ($> 30 \mu\text{g/dL}$) and EP ($> 35 \mu\text{g/dL}$) had an increased prevalence of iron deficiency (Yip et al. 1981). An inverse relationship between chelatable iron and chelatable body lead levels as indexed by urinary ALA levels was observed in 66 children with elevated PbB (Chisolm 1981). Another study reported that the lead absorption rate was 2–3 times greater in iron-deficient adults compared to subjects who were iron-replete (Watson et al. 1980). Daily nutritional intake of dietary fiber,

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iron, and thiamine were negatively correlated with PbB in male workers occupationally exposed to lead in a steel factory (Ito et al. 1987). Results from the NHANES II national survey showed that in children low iron status increases the lead hematotoxic dose response curves (Marcus and Schwartz 1987) and that iron deficiency plus elevated PbB produce a greater degree of hematotoxicity compared with either factor alone (Mahaffey and Annett 1986). A study of 299 children from 9 months to 5 years old from an urban area found a significant negative association between PbB and dietary iron intake (Hammad et al. 1996). Graziano et al. (1990) studied a population of pregnant women in Kosovo, Yugoslavia. They found that serum ferritin concentrations were associated with lower PbBs, suggesting that dietary iron may inhibit lead absorption. A study of 319 children ages 1–5 from Sacramento, California found that iron-deficient children had an unadjusted geometric mean PbB 1 µg/dL higher than iron-replete children (Bradman et al. 2001). The difference persisted after adjusting for potential confounders by multivariate regression; the largest difference in PbB was approximately 3µg/dL and was present among those living in the most contaminated areas. While the studies mentioned above point to a link between iron deficiency and lead poisoning, it is unclear whether there is a causal link or whether iron deficiency is just a marker of high environmental lead. Also considered should be the possibility that children who do not get adequate nutrition (including iron) may be more prone to ingestion of paint chips and this may confound the type of study that attempts to associate iron deficiency with lead poisoning. A longitudinal analysis of 1,275 children whose blood was screened for lead and complete blood count on two consecutive visits to a clinic suggested that the risk of subsequent lead poisoning associated with iron deficiency is 4–5 times greater than the baseline risk of lead poisoning (Wright et al. 2003c). The subject of lead/iron interactions was recently reviewed by Kwong et al. (2004).

The relationship between nutritional factors, other than those mentioned above, and PbB of preschool children was examined by Lucas et al. (1996). The objective of the study was to determine whether total caloric intake, dietary fat, dietary protein, and carbohydrates are associated with PbB while simultaneously controlling for other nutrient and environmental exposures. The cohort comprised 296 children aged 9–72 months, predominantly black (82%), from an urban area. The mean PbB was 11.4 µg/dL (range, 1–55 µg/dL). After adjusting for confounders, the study found significant positive associations for total caloric intake and dietary fat with PbB. Lucas et al. (1996) speculated that bile secreted into the gastrointestinal tract to aid in the digestion and absorption of fat may increase lead absorption, as shown in rats (Cikrt and Tichy 1975). The influence of total caloric intake may just reflect increased intake of lead through contaminated food.

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Reports of lead-nutrient interactions in experimental animals have generally described such relationships in terms of a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the data are concerned with the impact of dietary levels of calcium, iron, phosphorus, and vitamin D. These interaction studies are summarized in Table 3-11.

People who live near waste sites may be simultaneously exposed to more than one chemical, and there is concern that chemicals in a mixture may interact with each other in such a manner that the toxicity of chemical A may be increased in the presence of chemical B. Studies have shown that both the toxicity and toxicokinetics of lead can be influenced by the presence of other chemicals that are commonly found together with lead at hazardous waste sites, particularly other metals. The studies available indicate that the outcome of the interaction of lead with other metals depends on many factors such as exposure levels, timing of exposure, and end point examined, to name a few. As a result, global statements cannot be made. However, it appears that, in general, zinc and copper are protective of the effects of lead. For details on the interactive effects of lead with other metals, the reader is referred to the *Interaction Profile for Arsenic, Cadmium, Chromium, and Lead* (Agency for Toxic Substances and Disease Registry 2004a), *Interaction Profile for Lead, Manganese, Zinc, and Copper* (Agency for Toxic Substances and Disease Registry 2004b), and *Interaction Profile for Chlorpyrifos, Lead, Mercury, and Methylmercury* (Agency for Toxic Substances and Disease Registry 2006).

3.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to lead than will most persons exposed to the same level of lead in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of lead, or compromised function of organs affected by lead. Populations who are at greater risk due to their unusually high exposure to lead are discussed in Section 6.7, Populations with Potentially High Exposures.

Certain subgroups of the population may be more susceptible to the toxic effects of lead exposure. These include crawling and house-bound children (<6 years old), pregnant women (and the fetus), the elderly, smokers, alcoholics, and people with genetic diseases affecting heme synthesis, nutritional deficiencies, and neurological or kidney dysfunction. This is not an exhaustive list and reflects only current data available; further research may identify additional susceptible subgroups.

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Table 3-11. Effects of Nutritional Factors on Lead Uptake in Animals

Factor	Species	Index of effect	Interactive effect	References
Calcium	Rat	Lead in tissues and severity of effect at low levels of dietary calcium	Low dietary calcium (0.1%) increase lead absorption and severity of effects	Mahaffey et al. 1973; Six and Goyer 1970
Calcium	Rat	Lead retention	Retention increased in calcium deficiency	Barton et al. 1978a
Calcium	Rat	Lead in tissues at high levels of dietary calcium during pregnancy	Reduced release of lead from bone	Bogden et al. 1995
Calcium	Pig	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Hsu et al. 1975
Calcium	Horse	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Willoughby et al. 1972
Calcium	Lamb	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Morrison et al. 1977
Iron	Rat	Tissue levels and relative toxicity of lead	Iron deficiency increases lead absorption and toxicity	Six and Goyer 1972
Iron	Rat	Lead absorption in everted duodenal sac preparation	Reduction in intubated iron increases lead absorption; increased levels decrease lead uptake	Barton et al. 1978b
Iron	Rat	<i>In utero</i> or milk transfer of lead in pregnant or lactating rats	Iron deficiency increases both <i>in utero</i> and milk transfer of lead to sucklings	Cerklewski 1980
Iron	Mouse	Lead retention	Iron deficiency has no effect on lead retention	Hamilton 1978
Protein	Rat	Body lead retention	Low dietary protein either reduces or does not affect retention in various tissues	Quarterman et al. 1978
Protein	Rat	Tissue levels of lead	Casein diet increases lead uptake compared to soybean meal	Anders et al. 1982
Protein	Rat	Lead uptake by tissues	Both low and high protein in diet increases lead absorption	Barltrop and Khoo 1975
Milk components	Rat	Lead absorption	Lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does	Bell and Spickett 1981
Milk components	Rat	Lead absorption	Lactose in diet enhances lead absorption compared to glucose	Bushnell and DeLuca 1981
Zinc	Rat	Lead absorption	Low zinc in diets increases lead absorption	Cerklewski and Forbes 1976

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Table 3-11. Effects of Nutritional Factors on Lead Uptake in Animals

Factor	Species	Index of effect	Interactive effect	References
Zinc	Rat	Lead transfer <i>in utero</i> and in milk during lactation	Low-zinc diet of mother increases lead transfer <i>in utero</i> and in maternal milk	Cerklewski 1979
Zinc	Rat	Tissue retention	Low zinc diet enhances brain lead levels	Bushnell and Levin 1983
Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder and Petering 1975
Phosphorus	Rat	Lead uptake in tissues	Reduced phosphorus increases ²⁰³ Pb uptake 2.7-fold	Barltrop and Khoo 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances lead retention; no effect on lead resorption in bone	Quarterman and Morrison 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances both lead retention and lead deposition in bone	Barton and Conrad 1981
Vitamin D	Rat	Lead absorption using everted sac techniques	Increasing vitamin D increases intubated lead absorption	Smith et al. 1978
Vitamin D	Rat	Lead absorption using everted sac techniques	Both low and excess levels of vitamin D increase lead uptake by affecting motility	Barton et al. 1980
Thiamin	Mouse	Whole-body lead retention	Increased retention with increased thiamin concentration	Kim et al. 1992
Lipid	Rat	Lead absorption	Increases in lipid (corn oil) content up to 40% enhance lead absorption	Barltrop and Khoo 1975

²⁰³Pb = Lead 203

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Children. Children are at the greatest risk for experiencing lead-induced health effects, particularly in the urbanized, low-income segments of this pediatric population. Young children (<5 years old) have been documented to absorb lead via the gastrointestinal tract more efficiently (50% relative absorption) than adults (15% relative absorption) (Chamberlain et al. 1978). The use of leaded seams in cans used for canned food is not nearly as prevalent as it once was, so this is no longer as important a source of dietary exposure to lead. Behavior such as thumb sucking and pica result in an elevated transfer of lead-contaminated dust and dirt to the gastrointestinal tract (Schroeder and Hawk 1987). Also, children frequently have a greater prevalence of nutrient deficiency (Yip et al. 1981; Ziegler et al. 1978). For example, the diets of young children are commonly deficient in zinc, a condition that exacerbates some of the toxic effects of lead. Children have also been documented to have lower blood thresholds for the hematological and neurological effects induced by lead exposure. In addition, the resultant encephalopathy, central nervous system deficits, and neurologic sequelae tend to be much more severe in children than adults (Bellinger et al. 1989a; Bradley et al. 1956; Wang et al. 1989). Breast-fed infants of lead-exposed mothers are also a susceptible group since lead is also secreted in the breast milk (Dabeka et al. 1988; Ettinger et al. 2006; Gulson et al. 1998a). Calcium supplementation during lactation has been shown to decrease both maternal PbB and lead concentration in breast milk (Ettinger et al. 2006; Hernandez-Avila et al. 2003).

Susceptibility to lead toxicity is influenced by dietary levels of calcium, iron, phosphorus, vitamins A and D, dietary protein, and alcohol (Calabrese 1978). Low dietary ingestion of calcium or iron increased the predisposition to lead toxicity in animals (Barton et al. 1978a; Carpenter 1982; Hashmi et al. 1989; Six and Goyer 1972; Waxman and Rabinowitz 1966). Iron deficiency combined with lead exposure acts synergistically to impair heme synthesis and cell metabolism (Waxman and Rabinowitz 1966).

Nutritional surveys indicate that children of low-income groups consume less than recommended dietary allowances of calcium and iron. Dietary deficiencies of these two minerals have been shown to increase the risk of lead poisoning (Bradman et al. 2001; Johnson and Tenuta 1979; Wright et al. 2003c; Yip et al. 1981; Ziegler et al. 1978). Thus, nutrient deficiencies in conjunction with a developmental predisposition to absorb lead makes this subset of children at a substantially elevated risk. More information on children's susceptibility to lead is presented in Section 3.5.

Embryo/Fetus. The embryo/fetus are at increased risk because of transplacental transfer of maternal lead (Bellinger et al. 1987a; Moore et al. 1982). Thompson et al. (1985) reported the case of a woman whose PbB increased to 74 µg/dL over the course of pregnancy resulting in the baby's PbB level of 55 µg/dL and showing clinical signs of intoxication. No evidence of increased exposure to external lead source

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during this period was apparent, but it was found that the mother had excessive exposure to lead 30 years prior to the pregnancy. Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). Lead has been demonstrated in animal studies to increase the incidence of fetal resorptions (McClain and Becker 1972) and to induce adverse neurobehavioral effects in offspring exposed *in utero* (Section 3.2.4).

Women. Studies of women suggest that conditions of pregnancy, lactation, and osteoporosis may intensify bone demineralization, thus mobilizing bone lead into the blood resulting in increased body burdens of lead (Silbergeld et al. 1988). For example, women show an increased rate of bone lead loss with age relative to men (Drasch et al. 1987). Women with postmenopausal osteoporosis may be at an increased risk since lead inhibits activation of vitamin D, uptake of calcium, and several aspects of bone cell function to aggravate the course of osteoporosis. An increased release of bone lead to blood occurs in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowitz et al. 2004; Bonithon-Kopp et al. 1986c; Ewers et al. 1990; Hernandez-Avila et al. 2000; Korrick et al. 2002; Markowitz and Weinberger 1990; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995). Long-term effects of lead exposure were also reported by Hu (1991b) who found that pregnant women who had experienced childhood plumbism had a higher rate of spontaneous abortion or stillbirth than matched controls, and their offspring were more likely to experience learning disabilities.

Elders. The aged population may be at an increased risk for toxic effects of lead as suggested by two studies that found an association between decreased neurobehavioral performance and PbB in aging subjects with PbB around 5 µg/dL (Muldoon et al. 1996; Payton et al. 1998). A more recent study of 526 participants of the Normative Aging Study with a mean age of 67.1 years and mean PbB of 6.3 µg/dL reported that patellar lead was significantly associated with psychiatric symptoms such as anxiety, depression, and phobic anxiety (Rhodes et al. 2003). In yet an additional study of Normative Aging Study participants (mean PbB, 4.5 µg/dL), it was found that both bone and blood lead were associated with poor test performance (Wright et al. 2003c). According to the investigators, these findings are consistent with the theory that bone lead chronically remobilizes into blood, thus accelerating cognitive decline.

People with Genetic Diseases and Gene Polymorphisms. The toxic effects of lead exposure become exacerbated in individuals with inherited genetic diseases, such as thalassemia, which is characterized by

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an abnormality in the rate of hemoglobin synthesis (Calabrese 1978). Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are also unusually susceptible and may exhibit hemolytic anemia following lead exposure (Calabrese 1978). In a study of 148 subjects, Cocco et al. (1991) found that chronic lead poisoning tended to decrease total cholesterol and LDL in both G6PD-deficient and G6PD-nondeficient populations, but positive slopes were seen for cholesterol esters in G6PD deficient subjects and for HDL in G6PD normal subjects. Another study from the same group found that mortality from all causes and cancer mortality were lower among lead smelter workers with the G6PD-deficient phenotype compared to coworkers with the wild phenotype; the study comprised 867 workers with the wild phenotype and 213 with the deficient phenotype (Cocco et al. 1996). Because of the relatively small number of subjects with the deficient phenotype, the study may have lacked statistical power to examine deaths among this group. It has also been postulated that children with sickle cell disease have an increased risk of developing neuropathy with exposure to lead (Erenberg et al. 1974). People with metabolic disorders associated with the synthesis of porphyrins (important intermediates in the synthesis of hemoglobin, cytochromes, and vitamin B12), collectively known as porphyrias, are especially susceptible to lead exposure since lead inhibits two critical enzymes, ALAD and ferrochelatase, concerned with heme synthesis in erythrocytes (Hubermont et al. 1976; Silbergeld et al. 1982). The presence of genetic disorders that induce excessive ALA synthetase activity in addition to lead exposure produce higher than normal levels of ALA, resulting in excessive ALA excretion, accumulation, and lack of negative feedback on the ALA synthetase activity from heme (Calabrese 1978).

ALAD is a polymorphic enzyme with two alleles (ALAD-1 and ALAD-2) and three genotypes: ALAD 1,1; ALAD 1,2; and ALAD 2,2 (Battistuzzi et al. 1981). Various single nucleotide polymorphisms of the ALAD gene have been reported (Chia et al. 2005). Approximately 80% of Caucasians have the ALAD 1,1 genotype, 19% have the ALAD 1,2 genotype, and only 1% have the ALAD 2,2 genotype (Astrin et al. 1987; Battistuzzi et al. 1981). Studies of the relationship between ALAD genotype and blood lead levels have yielded conflicting results. Higher blood lead levels were observed in individuals with the ALAD 1,2 and ALAD 2,2 genotypes compared to similarly exposed individuals with the ALAD 1,1 genotype (Astrin et al. 1987; Hsieh et al. 2000; Schwartz et al. 2000b; Wetmur et al. 1991). There are also reports of children with the ALAD 2,2 having higher PbB than noncarriers (Pérez-Bravo et al. 2004; Shen et al. 2001). However, results of several other studies have found no association between blood lead levels and ALAD genotype in lead-exposed workers (Alexander et al. 1998b; Bergdahl et al. 1997b; Schwartz 1995; Schwartz et al. 1997a, 1997b; Smith et al. 1995; Süzen et al. 2003), although ALAD-2 carriers were 2.3 times more likely to have blood levels ≥ 40 $\mu\text{g/dL}$ (Schwartz et al. 1997a). The observations of higher blood level levels in ALAD 2 carriers has prompted

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the suggestion that the ALAD-2 allele may have a higher binding affinity for lead than the ALAD-1 allele (Bergdahl et al. 1997b), a difference that could alter lead-mediated outcomes. Several studies have been conducted to specifically evaluate whether ALAD genotypes are associated with differences in partitioning of lead between red blood cells and plasma, differences in distribution of lead to other tissue compartments, and altered susceptibility to lead toxicity.

Studies investigating the effects of ALAD polymorphism on the distribution of lead in the blood have also yielded conflicting results. In lead-exposed workers, a higher percentage of erythrocyte lead was bound to ALAD in carriers of the ALAD-2 allele (84%) compared to carriers of the ALAD-1 allele (81%) (Bergdahl et al. 1997b). Although this difference is small, it did reach statistical significance ($p < 0.03$), supporting the hypothesis that the ALAD-2 allele has a higher binding affinity for lead than the ALAD-1 allele. However, higher whole blood levels were not observed for ALAD-2 carriers compared to ALAD-1 homozygotes. Furthermore, no ALAD allele-specific differences were detected for the ratio of blood lead to plasma lead. Results of studies by Fleming et al. (1998a) substantiate earlier reports of higher blood lead levels for carriers of the ALAD-2 allele and indicate that ALAD polymorphism has an effect on the distribution of lead in the blood and, ultimately, to other tissue compartments. Serum lead levels for carriers of the ALAD-2 allele were higher than for ALAD-1 homozygotes (ALAD-2 carriers = 0.335 ± 0.025 $\mu\text{g/dL}$; ALAD-1 homozygotes = 0.285 ± 0.009 $\mu\text{g/dL}$), an 18% difference that approached statistical significance ($p < 0.06$) (Fleming et al. 1998a).

Based on the higher plasma lead levels observed for ALAD-2 carriers, it is reasonable to project that distribution of lead to other tissue compartments could be higher for ALAD-2 carriers, in which case, the ALAD genotype could exert effects on the dose-response relationship for lead. In lead-exposed workers, urinary excretion of lead following oral administration of DMSA was less in ALAD-2 carriers than in ALAD-1 homozygotes ($p = 0.07$), suggesting that carriers of the ALAD-2 allele may have lower levels of lead, or, at least, lower amounts of lead accessible to complexation with DMSA (Schwartz et al. 1997b). Studies investigating the effects of ALAD polymorphism on the distribution of lead to bone have also yielded conflicting results. No ALAD allele-specific differences were observed for the net accumulation of lead in bone (Bergdahl et al. 1997b, Fleming et al. 1998a; Lee et al. 2001) or for patellar bone (Lee et al. 2001; Theppeang et al. 2004). However, ALAD-2 carriers accumulated slightly more lead in bone than ALAD-1 homozygotes ($p = 0.06$) (Fleming et al. 1998a). Higher bone lead levels were reported in lead-exposed workers carrying the ALAD-2 gene compared to ALAD-1 homozygotes (Smith et al. 1995). The cortical-trabecular bone lead differential (patellar minus tibial lead concentration) in ALAD-1 homozygotes was lower than in ALAD-2 carriers ($p = 0.06$). In these same workers, blood urea

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nitrogen (BUN) and uric acid (UA) were elevated in ALAD-2 carriers (BUN, $p=0.03$; UA, $p=0.07$), indicating that ALAD-2 carriers could be more susceptible to the renal toxicity of lead. However, in a multivariate logistic regression model that included PbB and ALAD genotype (along with age and alcohol consumption), increases in BUN and serum uric acid concentration were significantly associated with increases in PbB (regression coefficient, 0.13 mg/dL per $\mu\text{g Pb/dL}$; $p=0.005$), but not ALAD genotype ($p=0.06$). Wu et al. (2003a) also found apparent effects of ALAD genotype on the relationship between bone lead levels and serum uric acid levels in a study conducted as part of the Normative Aging Study. Increasing patella bone lead levels above a threshold of 15 $\mu\text{g/g}$ was positively associated with serum uric acid levels among ALAD 1-1/2-2 heterozygotes; however, among ALAD 1-1 homozygotes, the threshold for the association was 101 $\mu\text{g/g}$. In contrast, young adults with ALAD 1-2 genotype did better on cognitive tests given the same amount of lead exposure (Bellinger et al. 1994), suggesting possible age-specific interactions. Chia et al. (2005) examined interactions between PbB and the presence of various single nucleotide polymorphisms (SNP) in the ALAD gene on various kidney outcomes among a group of lead workers in Vietnam ($n=323$). This study found significant interactions between increasing PbB and the HpyCH4 SNP on increasing urinary retinal binding protein, $\alpha 1\mu$ -globulin, $\beta 2\mu$ -globulin, and albumin. Lee et al. (2001) examined the possible influence of ALAD genotype on systolic and diastolic blood pressure in a cohort of Korean lead workers (789 workers, 135 controls). Lead body burden measures (i.e., PbB, tibia blood lead, DMSA-chelatable lead) and blood pressures were not significantly different between ALAD 1-1 and ALAD 1-2 genotypes.

The finding of associations between ALAD-2 and bone lead concentrations and ALAD-2 and markers of renal toxicity suggest that differential binding of lead to ALAD-2 may influence both the toxicokinetics and certain aspects of the toxicodynamics of lead. No information is available on the distribution of lead to other tissue compartments relative to ALAD genotype. Thus, based on the limited data available, it appears that ALAD polymorphism may be a genetic factor in the kinetic behavior of lead in the body. However, the exact nature and significance of ALAD polymorphism remains to be elucidated. A recent meta-analysis of 24 studies that included lead workers, the general population, and children found a statistically significant association between ALAD-2 carriers and higher PbB in lead-exposed workers (Scinicariello et al. 2007). However, the ALAD-2 genotype did not appear to be a significant determinant of PbB among adults with PbBs $<10 \mu\text{g/dL}$. The study also found that ALAD-2 carriers appeared to be protected against adverse hematopoietic effects of lead as measured by hemoglobin levels, possibly because of decreased lead bioavailability to enzymes of the heme pathway.

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The role of the vitamin D receptor (VDR) polymorphism in lead intoxication also has been studied. The VDR gene regulates the production of calcium-binding proteins and is reported to account for up to 75% of the total genetic effect on bone density (Onalaja and Claudio 2000). The VDR exists in several polymorphic forms in humans (Morrison et al. 1992). Restriction enzyme digestion of the VDR results in three genotypes commonly termed bb, when the restriction site is present, BB when the site is absent, and Bb when the two alleles are present. Schwartz et al. (2000a) studied the association of tibial lead and VDR genotype in 504 former organolead manufacturing workers in the United States. Tibial and blood lead concentrations were relatively low, with means of 14.4 ppm, and 4.6 µg/dL, respectively. Analyses of unadjusted data showed that there were only small differences in tibial lead concentrations by VDR genotype. However, in a multiple linear regression model of tibial lead concentrations, subjects with the B allele had larger increases in tibial lead concentrations with increasing age. In addition, whereas in subjects with the bb genotype, tibial lead declined since their last exposure to lead, subjects with Bb and BB showed increases in tibial lead. A study of 798 Korean lead workers whose mean tibial lead concentration and mean PbB were 37.2 ppm and 32 µg/dL, respectively, reported that lead workers with the VDR B allele had significantly higher PbB, chelatable lead level, and tibial lead than did workers with the VDR bb genotype (Schwartz et al. 2000b). A more recent study of this cohort reported that workers with the VDR B allele had significantly higher patellar lead than lead workers with the VDR bb genotype (Theppeang et al. 2004).

Two other genetic polymorphisms have been studied in the context of potential influence on lead associations with blood pressure. The endothelial nitric oxide synthase (eNOS) converts L-arginine into nitric oxide in the endothelium, resulting in the relaxation of vascular smooth muscle and contributes to the regulation of peripheral vascular resistance and blood pressure. Theppeang et al. (2004) reported that, in a cohort of Korean lead workers, there was no association of the endothelial nitric oxide synthase (eNOS) gene with patella lead. Polymorphisms in the $\alpha 2$ subunit of Na⁺-K⁺ ATPase (ATP1A2) have also been shown to influence associations between lead exposure and blood pressure (Glenn et al. 2001).

Another genetic susceptibility that has been studied in relation to lead toxicity is that of the hemochromatosis gene. Results published so far provided seemingly conflicting results. Hemochromatosis is a disease in which the absorption of iron is increased, resulting in excess iron depositing in many internal organs, particularly the liver, and leading to progressive damage (Onalaja and Claudio 2000). The gene codes for a protein designated HFE and has two variants: C282Y and H63D. Wright et al. (2004) studied 730 men from the Normative Aging Study and found that the presence of a hemochromatosis variant, either C282Y or H63D, predicted lower bone and blood lead concentration. Based on the fact that iron

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status is inversely related to lead absorption, Wright et al. (2004) hypothesized that the results may be secondary to increased iron stores among HFE variant carriers leading to decreased lead absorption in the gastrointestinal tract. Previously, Barton et al. (1994) found that homozygous individuals who suffered from hemochromatosis had higher PbB than individuals who did not have the gene. An additional study found no difference in PbB between subjects with hemochromatosis and controls (Åkesson et al. 2000). Wright et al. (2004) speculated that the different results could be due to the different characteristics of the participants studied in terms of age, health status, and sex.

Finally, the possible association between Apolipoprotein E (APOE) genotype and susceptibility to lead toxicity also has been studied. APOE is an intracellular transporter of cholesterol and fatty acids that is synthesized by astrocytes in the brain and that plays a key role in the structure of cell membranes and myelin. There are three alleles of the APOE gene: E2, E3, and E4. Wright et al. (2003b) evaluated the relationship between the APOE gene and infant neurodevelopment in a sample of 311 mother-infant pairs living in and around Mexico City. The primary outcome assessed in the study was the 24-month MDI of the Bayley Scale. The authors also evaluated the modifying effect of APOE genotype on the association between PbB in umbilical cord and MDI score. After adjustment for potential confounders, infants carrying at least one copy of the APOE4 allele scored 4.4 points higher in the MDI than E3/E2 carriers. Furthermore, APOE genotype modified the dose-response relationship between umbilical PbB and MDI score in a manner that suggested that those with APOE4 were more protected against lead exposure than E3/E2 carriers. The APOE genotype also was reported to influence the relation between tibia lead and neurobehavioral test scores in a group of 529 former organolead workers (Stewart et al. 2002). The authors used linear regression to model the relations between each of 20 neurobehavioral test scores and tibia lead, a binary variable for APOE genotype. In 19 of the 20 regression models, the coefficients for the APOE and tibia lead interaction were negative. This meant that the slope for the relation between tibia lead and each neurobehavioral test was more negative for individuals with at least one APOE4 allele than for those who did not have an APOE4 allele. Stewart et al. (2002) concluded that some persistent effects of lead may be more toxic in individuals who have at least one APOE4 allele. The apparent contrast between the results of Stewart et al. (2002) and Wright et al. (2003b) may reflect age-specific gene-lead interactions.

Alcoholics and Smokers. Alcoholics, and people who consume excess amounts of alcohol, may be at increased risk of hematological, neurological, and hepatotoxic effects. In animal studies, lead and alcohol synergistically inhibited blood ALAD activity and hepatic glutamic oxaloacetic transaminase (GOT, AST) and glutamic pyruvic transaminase (GPT, ALT) activity, depressed dopamine and 5-hydroxy-

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tryptamine levels in rat brain, increased lead burdens in tissue organs, and elevated blood ZPP (Dhawan et al. 1989; Flora and Tandon 1987). Smokers are also at elevated risks of lead intoxication since cigarette smoke contains lead and other heavy metals such as cadmium and mercury (Calabrese 1978), which have been shown to be synergistic in experimental animals (Congiu et al. 1979; Exon et al. 1979; Fahim and Khare 1980).

People with Neurologic Dysfunction or Kidney Disease. This population is unusually susceptible to lead exposure. The neurologic and renal systems are the primary target organs of lead intoxication, which may become overburdened at much lower threshold concentrations to elicit manifestations of lead intoxication (Benetou-Marantidou et al. 1988; Chisolm 1962, 1968; Lilis et al. 1968; Pollock and Ibels 1986).

3.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to lead:

Ellenhorn MJ. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. Metals and related compounds. 2nd ed. Baltimore, MD: Williams and Wilkins, 1563-1579.

Homan CS, Brogan GX, Orava RS. 1998. Emergency toxicology: Lead toxicity. Philadelphia, PA: Lippincott-Raven, 363-378.

Leikin JB, Paloucek FP. 2002. Poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 725-731.

3.9.1 Reducing Peak Absorption Following Exposure

Individuals potentially exposed to lead can prevent inhalation exposure to particles by wearing the appropriate respirator. The mechanism and rate of lead absorption from the gastrointestinal tract is not completely understood, but it is believed that absorption occurs in the small intestine by both active and passive transport following solubilization of lead salts by gastric acid (see Section 3.3, Toxicokinetics). Lead is poorly absorbed from the gastrointestinal tract; however, toxic effects can result from the relatively small amount of lead that is absorbed. It has been estimated that adults absorb approximately

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10% of an administered dose, whereas children absorb 4–50% of ingested lead (see Section 3.3, Toxicokinetics). Lead absorption from the gut appears to be blocked by calcium, iron, and zinc. Although no treatment modalities to reduce lead absorption have yet been developed that make use of these observations, it is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead and that children eat regular meals since more lead is absorbed on an empty stomach (CDC 1991). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of lead following acute exposure include removing the individual from the source of exposure and decontaminating exposed areas of the body. Contaminated skin is washed with soap and water, and eyes exposed to lead are thoroughly flushed with water or saline (Stutz and Janusz 1988). Once lead is ingested, it is suggested that syrup of ipecac be administered to induce emesis. Administration of activated charcoal following emesis has not been proven to reduce absorption of any lead remaining in the gastrointestinal system, but is frequently recommended (Kosnett 2004; Stutz and Janusz 1988). Gastric lavage has been used to remove ingested lead compounds. Whole gut lavage with an osmotically neutral polyethylene glycol electrolyte solution (GO-Lytely®, Co-lyte®) has successfully removed ingested lead-containing pottery glazes according to anecdotal case reports. However, this procedure is not universally accepted. Patients who ingest lead foreign objects should be observed for the possible, although rare, development of signs or symptoms of lead poisoning until the ingested object has been proven to have passed through the gut. Surgical excision has been recommended when lead bullets or shrapnel are lodged near joint capsules (reaction with synovial fluid leads to systemic uptake of lead in some cases) (Kosnett 2004). The blood lead level can be monitored and used as an indication for surgical removal of the projectile.

3.9.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94 and 73% of the total body burden of lead is found in bones, respectively. Lead may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 3.3.2).

All of the currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its

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excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL), $\text{CaNa}_2\text{-EDTA}$ (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; Succimer[®]). Most of the information below regarding chelators has been extracted from Homan et al. (1998).

Dimercaprol (BAL) is the chelator of choice in the presence of renal compromise. Sulfhydryl ligands in BAL form stable chelate-metal compounds intra- and extracellularly. The onset of action for BAL is 30 minutes. BAL increases fecal excretion of lead as chelated lead is excreted predominantly in bile within 4–6 hours; BAL also increases urinary excretion of chelated lead. The use of BAL is indicated in cases of high lead levels without symptoms, in acute encephalopathy, and in symptomatic plumbism characterized by abdominal pain, anemia, headache, peripheral neuropathy, ataxia, memory loss, lethargy, anorexia, dysarthria, and encephalopathy. BAL is administered intramuscularly as a 10% solution in oil and the recommended dosage is 50–75 mg/m² every 4 hours. The full course is 3–5 days. Contraindications for the use of BAL include liver failure, since BAL chelates are excreted primarily in bile. Also, patients with glucose-6-phosphate dehydrogenase deficiency develop hemolysis if BAL is administered. Concurrent administration of iron is contraindicated due to the high toxicity of the BAL-iron chelate. BAL also is contraindicated in subjects with a history of peanut oil allergy and in pregnancy. A number of adverse reactions have been described in BAL user including nausea, vomiting, hypertension, tachycardia, headache, increased secretions, anxiety, abdominal pain, and fever. Premedication with diphenylhydramine may mitigate these effects. Elevated liver function tests and sterile abscesses may also occur.

$\text{CaNa}_2\text{-EDTA}$ (or EDTA) works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of lead 20–50 times. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. EDTA should be used together with BAL (4 hours after the first dose of BAL) because acute lead encephalopathy may progress if EDTA given alone secondary to lead from soft tissue lead mobilization resulting in increased PbB. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage. The dosage recommended for children is 1,000–1,500 mg/m²/24 hours in 0.5% procaine i.m. to avoid fluid overload, although the preferred route of administration of EDTA is intravenously. This dose

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may be given in up to six divided daily doses. For adults, the recommended dose is 1.5 g/24 hours in two divided doses. The full course for EDTA therapy is 5 days, but the course may be repeated if the patient is still symptomatic or when PbB is $>50\mu\text{g/dL}$.

D-Penicillamine is an orally-administered lead chelator whose mechanism of action is unknown, and that increased urinary excretion of lead. The FDA has not approved the use of d-penicillamine during pregnancy. Administration of d-penicillamine is contraindicated in subjects allergic to penicillin because of cross-reactivity with the latter. Among the adverse effects are rash, fever, anorexia, nausea, vomiting, leucopenia, thrombocytopenis, eosinophilia, hemolytic anemia, Stevens-Johnson syndrome (severe erythema multiforme), nephrotoxicity, and proteinuria. Furthermore, continued exposure to lead will result in continued absorption of lead at a higher rate. The recommended dose is 10 mg/kg/24 hours for 7 days, but may be increased to 10–15 mg/kg every 12 hours over 2–4 weeks. One way to minimize toxicity is to start medication at $\frac{1}{4}$ the dosage and gradually increase it to full dosage over 3–4 weeks. The CDC recommends giving children an entire dose on an empty stomach 2 hours before breakfast and to give adults an entire dose in two or three divided doses on an empty stomach 2 hours before meals.

2,3-Dimercaptosuccinic acid (DMSA; Succimer[®]) has a mechanism of action similar to BAL, but is far less toxic than BAL. DMSA is currently approved for asymptomatic children with PbB $<45\mu\text{g/dL}$ and an experimental protocol is available for mild encephalopathy and use in the adult. DMSA can be used with concurrent administration of iron. DMSA has been shown to be as effective as EDTA in increasing the urinary excretion of lead. Minimal adverse effects that have been reported include anorexia, nausea, vomiting, and rashes. DMSA increases the excretion of zinc, but to a much lesser extent than other chelators, and has minimal effects on Ca, Fe, Mg, and Cu. The recommended dosage is 10 mg/kg 3 times/day for 5 days, then 10 mg/kg 3 times/day for 14 days.

The following are treatment guidelines for lead exposure in children developed by the American Academy of Pediatrics (Berlin et al. 1995).

1. *Chelation treatment is not indicated in patients with blood lead levels of less than $25\mu\text{g/dL}$, although environmental intervention should occur.*
2. *Patients with blood levels of 25 to $45\mu\text{g/dL}$ need aggressive environmental intervention but should not routinely receive chelation therapy, because no evidence exists that chelation avoids or reverses neurotoxicity. If blood lead levels persist in this range despite repeated environmental study and abatement, some patients may benefit from (oral) chelation therapy by enhanced lead excretion.*

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3. *Chelation therapy is indicated in patients with blood lead levels between 45 and 70 µg/dL. In the absence of clinical symptoms suggesting encephalopathy (e.g., obtundation, headache, and persisting vomiting), patients may be treated with succimer at 30 mg/kg per day for 5 days, followed by 20 mg/day for 14 days. Children may need to be hospitalized for the initiation of therapy to monitor for adverse effects and institute environmental abatement. Discharge should be considered only if the safety of the environment after hospitalization can be guaranteed. An alternate regimen would be to use CaNa₂EDTA as inpatient therapy at 25 mg/kg for 5 days. Before chelation with either agent is begun, if an abdominal radiograph shows that enteral lead is present, bowel decontamination may be considered as an adjunct to treatment.*
4. *Patients with blood lead levels of greater than 70 µg/dL or with clinical symptoms suggesting encephalopathy require inpatient chelation therapy using the most efficacious parenteral agents available. Lead encephalopathy is a life-threatening emergency that should be treated using contemporary standards or intensive care treatment of increased intracranial pressure, including appropriate pressure monitoring, osmotic therapy, and drug therapy in addition to chelation therapy. Therapy is initiated with intramuscular dimercaprol (BAL) at 25 mg/kg per day divided into six doses. The second dose of BAL is given 4 hours later, followed immediately by intravenous CaNa₂EDTA at 50 mg/day as a single dose infused during several hours or as a continuous infusion. Current labeling of CaNa₂EDTA does not support the intravenous route of administration, but clinical experience suggests that it is safe and more appropriate in the pediatric population. The hemodynamic stability of these patients, as well as changes in neurologic status that may herald encephalopathy, needs to be closely monitored.*
5. *Therapy needs to be continued for a minimum of 72 hours. After this initial treatment, two alternatives are possible: (1) the parenteral therapy with two drugs (CaNa₂EDTA and BAL) may be continued for a total of 5 days; or (2) therapy with CaNa₂EDTA alone may be continued for a total of 5 days. If BAL and CaNa₂EDTA are used for the full 5 days, a minimum of 2 days with no treatment should elapse before considering another 5-day course of treatment. In patients with lead encephalopathy, parenteral chelation should be continued with both drugs until they are clinically stable before therapy is changed.*
6. *After chelation therapy, a period of reequilibration of 10 to 14 days should be allowed, and another blood lead concentration should be obtained. Subsequent treatment should be based on this determination, following the categories presented above.*

3.9.3 Interfering with the Mechanism of Action for Toxic Effects

Lead has multiple mechanisms of action at many different levels that affect many enzyme systems and cellular processes throughout the body. Thus, while it seems plausible that specific effects could be prevented or at least minimized, it is unlikely that one could prevent all of the physiological alterations that have been attributed to exposure to lead. However, several studies have examined whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes

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reportedly altered by lead. For example, Ruff et al. (1993) studied a group of 154 children with PbB between 25 and 55 µg/dL who were treated with CaNa₂EDTA if eligible and/or with orally administered iron supplement if iron deficient. The outcome measured was a global index of cognitive functioning. It was found that within a period of 6 months, improvement in performance was significantly related to decreases in PbB, but there was no effect of chelation treatment. Ruff et al. (1993) speculated that a reduction or elimination of exposure may have led to decreases in PbB, and this may have occurred for chelated and nonchelated children.

Rogan et al. (2001) studied a group of 780 children enrolled in a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer. The PbB for the group ranged from 20 to 44 µg/dL. Although treatment with succimer lowered PbB by a mean of 4.5 µg/dL during the 6 months after initiation of treatment, it did not improve scores on tests of cognition, behavior, or neuropsychological function in children with PbB below 45 µg/dL. Rogan et al. (2001) noted that the failure to demonstrate a significant difference in test scores could have been due to the small difference in PbB between the two groups. Re-analysis of these data using change in PbB as the independent variable showed that improvement in test scores was associated with greater falls in PbB only in the placebo group and suggested that factors other than declining PbB were responsible for cognitive improvement (Liu et al. 2002). A further evaluation of this cohort at the age of 7 years showed that chelation therapy with succimer, although lowering mean PbB for approximately 6 months, produced no benefit in cognitive, behavioral, and neuromotor end points (Dietrich et al. 2004). Also in this cohort, treatment with succimer did not have a beneficial effect on blood pressure (Chen et al. 2006) or growth during or after treatment (Peterson et al. 2004). In fact, from baseline to 9 months, children receiving succimer were on the average 0.27 cm shorter than children receiving placebo, and 0.43 cm shorter during 34 months of follow-up. The conclusion of this series of studies reached by the investigators was that chelation therapy is not indicated in children with moderate PbB (≤ 40 µg/dL). Additional information regarding the safety and efficacy of succimer in children can be found in O'Connor and Rich (1999) and Chisolm (2000).

In a study similar to those described above, Kordas et al. (2005) tested the hypothesis that iron and zinc supplementation could improve behavior ratings in a population of first-grade children who attended a school near a metal foundry in Torreón, Mexico. The mean PbB for the whole sample was 11.5 µg/dL (SD, ± 6.1 µg/dL). The overall prevalency of iron and zinc deficiency was 21.7 and 28.9%, respectively. During the trial, which lasted 6 months, parents and teachers provided ratings of child behavior using the Conners Rating Scales. Neither iron nor zinc (combined or separately) induced a marked reduction in PbB. Although all parent ratings and some teacher ratings improved with time, the change was unrelated

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to treatment and the clinical significance was unclear. The only beneficial change was that children receiving any zinc had a higher likelihood of no longer receiving clinically-significant teacher ratings of oppositional behaviors.

A series of studies in monkeys provide relevant information regarding lead exposure and succimer. In adult Rhesus monkeys treated chronically with lead to maintain a target PbB of 35–40 µg/dL, treatment with succimer was ineffective in reducing brain lead levels (Cremin et al. 1999). However, cessation of exposure reduced brain lead levels by 34% both in succimer- and placebo-treated monkeys. In addition, the concentration of lead in the prefrontal cortex prior to treatment with succimer was significantly correlated with the integrated PbB (AUC) over the period of exposure to lead, but not with the single pretreatment PbB sample collected concurrently with the brain biopsy. These results indicated that succimer treatment did not reduce brain lead levels beyond the cessation of lead exposure alone. A subsequent study in this series showed that treatment with succimer did not reduce skeletal levels of lead and that the efficacy of succimer in reducing PbB did not persist beyond the completion of treatment due to posttreatment rebounds in PbB from endogenous sources (Smith et al. 2000).

3.10 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of lead.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.10.1 Existing Information on Health Effects of Lead

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to lead are summarized in Figure 3-17. The purpose of this figure is to illustrate the existing information

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Figure 3-17. Existing Information on Health Effects of Lead

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●	●	●	●	●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal										

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation			●		●	●		●		
Oral	●	●	●	●	●	●	●	●	●	●
Dermal										

Animal

● Existing Studies

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concerning the health effects of lead. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

There is a wealth of information regarding the health effects of lead in humans and in animals. In fact, lead may be a chemical for which there is as much information in humans as there is in animals. Human data consist of studies of children and adults, occupational exposures, and exposures of the general population. A number of studies of children are studies of cohorts that have been followed for years, and these have provided the most valuable information. Children and developing organisms, in general, are more vulnerable to the toxic effects of lead than adults, and therefore, much of the lead research in the past decades has focused on these populations. The most sensitive end points for lead toxicity are the developing nervous system, and the cardiovascular, renal, and hematological systems, but lead can affect any system or organ in the body. The most significant routes of exposure to lead for humans are the inhalation and oral routes; the latter is the main route of exposure for young children mainly due to their hand-to-mouth activities. The toxicity of lead is not route-specific. Studies in animals support the findings in humans and have been of great utility in elucidating the underlying mechanisms of lead toxicity.

3.10.2 Identification of Data Needs

Acute-Duration Exposure. There are relatively few data available for acute exposures in humans and most are derived from cases of accidental or intentional ingestion of lead-containing dirt or lead-based paint in adults and children. Exposure to high amounts of lead can induce encephalopathy, a general term that describes various diseases that affect brain function. Symptoms develop following prolonged exposure and include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death (Chisolm 1962, 1965; Chisolm and Harrison 1956; Kehoe 1961; Kumar et al. 1987). The utility of further acute-duration exposure studies in animals for the sole purpose of obtaining dose-response relationships is questionable. However, further short-term studies or studies

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in vitro designed to elucidate mechanisms of action for the various toxicities discussed below might be useful.

Intermediate-Duration Exposure. Intermediate and chronic exposures in humans should be considered together because the duration of exposure is not usually known. Specific studies that have evaluated a variety of end points are presented below under *Chronic-Duration Exposure and Cancer*. As with acute-duration exposure, additional standard 90-day toxicity studies in animals are unlikely to produce new key information about the toxicity of lead, but studies could be designed to elucidate mechanisms of action involved in the specific toxicities described below. For example, exposures during different developmental periods can help identify critical periods of vulnerability for immunocompetence, development of sex organs, or neurobehavioral parameters.

Chronic-Duration Exposure and Cancer. The effects of chronic-duration exposure to lead in humans and in animals have been relatively well-studied. In humans, exposure to lead has been associated with (only representative citations are included) cardiovascular effects (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994), hematological effects (Chisolm et al. 1985; Hernberg and Nikkanen 1970; Roels and Lauwerys 1987; Roels et al. 1976), musculoskeletal effects (Holness and Nethercott 1988; Marino et al. 1989; Pagliuca et al. 1990), effects on teeth in children (Gemmell et al. 2002; Moss et al. 1999), renal effects (Kim et al. 1996a; Muntner et al. 2003), alterations in serum hormone levels (Gustafson et al. 1989; López et al. 2000; Singh et al. 2000a), cataracts (Schaumberg et al. 2004), alterations in electroretinograms (Cavalleri et al. 1982; Otto and Fox 1993; Rothenberg et al. 2002a), altered vitamin D metabolism (Rosen et al. 1980), alterations in immunological parameters (Fischbein et al. 1993; Karmaus et al. 2005; Lutz et al. 1999; Pinkerton et al. 1998; Sata et al. 1998; Sun et al. 2003; Ünder et al. 1996), neurobehavioral effects in adults (Awad El Karim et al. 1986; Baker et al. 1979, 1983; Haenninen et al. 1979; Holness and Nethercott 1988; Lucchini et al. 2000; Matte et al. 1989; Pagliuca et al. 1990; Pollock and Ibels 1986; Schwartz et al. 2005; Stollery 1996; Stollery et al. 1991) and children (Bellinger et al. 1992; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a; Ris et al. 2004; Schnaas et al. 2000; Téllez-Rojo et al. 2006; Tong et al. 1998; Wasserman et al. 2003), reproductive effects in females (Borja-Aburto et al. 1999; Nordstrom et al. 1979; Torres-Sánchez et al. 1999) and males (Gennart et al. 1992b; Hernández-Ochoa et al. 2005; Lancranjan et al. 1975; Sällmen et al. 2000a), altered children's growth (Dietrich et al. 1987a; Hernández-Avila et al. 2002; Schwartz et al. 1986), delayed sexual maturation in girls (Selevan et al. 2003; Wu et al. 2003a), decreased erythropoietin in children (Graziano et al. 2004), genotoxic effects in workers (Forni et al. 1976; Fracasso et al. 2002; Nordenson et al. 1978; Vaglenov et al. 2001; Wu et al. 2002), and possibly increased risk of

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lung cancer and stomach cancer in lead workers (Steenland and Boffetta 2000). It is unlikely that additional standard chronic-duration exposure studies in animals would provide new key information on the toxicity of lead, but special studies that examine biochemical and morphological effects of lead may provide new information on mechanisms of action of lead, particularly for the effects of greatest concern such as neurobehavioral alterations in children. However, as indicated below under *Epidemiological Studies*, the children and adolescents from the prospective studies should continue to undergo periodic comprehensive evaluations.

There are several studies of cancer on lead-exposed workers (Anttila et al. 1995; Cocco et al. 1997, 1998a, 1998b; Cooper et al. 1985; Fanning 1988; Gerhardsson et al. 1986b; Lundstrom et al. 1997; Malcolm and Barnett 1982; Wong and Harris 2000), which provided inconclusive evidence of carcinogenicity. A meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure concluded that there is some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer (Steenland and Boffetta 2000). The results also showed weak evidence for an association with kidney cancer and gliomas. Follow-up of the cohorts from the prospective lead studies may provide information on possible shifts in age-related cancer incidence and on associations between perinatal exposure to lead and increased cancer risk.

Exposure of rodents to lead has produced mainly renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). In a study in mice exposed to lead during pregnancy, the offspring developed renal proliferative lesions and renal tumors; no renal tumors occurred in controls (Waalkes et al. 1995). Replication of these findings would be useful. In addition, studies could be conducted in which animals are exposed at different times during pregnancy to determine the existence of potential windows of vulnerability. Silbergeld et al. (2000) suggest that the hypothesis that lead-induced cancer is secondary to cytotoxicity and target organ damage needs further testing. Silbergeld et al. (2000) also identified the need for studies examining the potential role of lead-zinc interactions in transcription regulation and DNA protection using reporter gene systems and combined exposures to lead and other mutagens. Other types of studies suggested include evaluation of the effects of lead on the expression of specific genes, such as oncogenes and suppressor genes, and evaluation of the potential role of lead-induced inhibition of DNA repair on systems where the fidelity of DNA replication can be directly studied.

Genotoxicity. Lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei, and sister chromatid exchanges in peripheral blood cells from lead workers (i.e., Duydu et al.

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2001; Forni et al. 1976; Nordenson et al. 1978; Vaglenov et al. 1998, 2001). *In vitro* mutagenicity studies in microorganisms have yielded mostly negative results for lead, and additional studies of this type are unlikely to provide new key information. The lines of research suggested previously with regard to cancer also apply for genotoxicity. In addition, studies of chromosomal changes in germ cells involved in gametogenesis would provide valuable information on potential transgenerational effects of lead.

Reproductive Toxicity. Some studies of humans occupationally or environmentally exposed to lead have reported associations between PbB and abortion and pre-term delivery in women (Borja-Aburto et al. 1999; Nordstrom et al. 1979) and alterations in sperm and decreased fertility in men (Gennart et al. 1992b; Sällmen et al. 2000a; Shiao et al. 2004). For the effects in males, the threshold PbB appears to be in the range of 30–40 µg/dL. Additional research might be warranted to study the effects of lead on the gonado-hypothalamic-pituitary axis. An earlier study by Cullen et al. (1984) found increased serum FSH and LH and borderline low serum testosterone levels in one of seven men with symptomatic occupational lead poisoning and a mean PbB of 87.4 µg/dL. Although serum testosterone concentration was normal in most of these patients, five had defects in spermatogenesis. Studies in monkeys using protocols designed to evaluate age of exposure on lead-induced effects have reported structural alterations in the testis at PbBs relevant to the human population (Foster et al. 1996, 1998). Studies in rats exposed to lead concentrations that produced relatively high PbB have suggested that continuous lead exposure delays sexual maturation by suppressing normal sex steroid surges at birth and during puberty (Ronis et al. 1998b, 1998c). Replication of these studies in primates would be useful. Also, further research on the interaction of lead and protamines could provide valuable information on lead-induced effects in sperm. Protamines specifically are bound to sperm DNA and their interaction with lead has been suggested to possibly decrease the protection of DNA to mutagens (Quintanilla-Vega et al. 2000).

Developmental Toxicity. In addition to inducing neurobehavioral alterations in developing organisms (see below under Neurotoxicity), exposure to lead has been associated in some studies with reduced birth weight and gestational age (Dietrich et al. 1987a; Jelliffe-Pawlowski et al. 2006), reduced stature in children (Hernández-Avila et al. 2002; Sanín et al. 2001; Schwartz et al. 1986), and delayed sexual maturation in girls (Selevan et al. 2003; Wu et al. 2003a). These findings are supported by results from studies in animals (Dearth et al. 2002; Grant et al. 1980; Ronis et al. 1996, 1998a, 1998b, 1998c, 2001). It would be useful to collect data on growth of children from the ongoing lead prospective studies, although some information is available from the Cincinnati Prospective Study (Shukla et al. 1989, 1991), the Cleveland Prospective Study (Greene and Ernhart 1991), and a study of children from Boston (Kim et al. 1995). Because of the enormous influence of nutrition on growth and on lead toxicity, it would be

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advantageous to conduct studies of populations of children as homogeneous as possible with respect to nutrition, even if the cohort size is less than optimal. A study in rats reported that lead reduced somatic longitudinal bone growth and bone strength during the pubertal period by a mechanism that appeared not to involve disruption of the growth hormone axis (Ronis et al. 2001). Further studies in animals as well as in bone cells *in vitro* should help elucidate the mechanism(s) of lead on growth.

Studies have shown that exposure of rats and mice to lead during various developmental periods alters sexual maturation of both male and female animals (Dearth et al. 2002; Iavicoli et al. 2004; Ronis et al. 1996, 1998a, 1998b, 1998c). Therefore, it would be desirable to evaluate adolescents of both sexes who are participating in the ongoing prospective lead studies to determine possible delays in sexual maturation, and if found, determine which lead biomarker best predicts the outcome. Follow-up of the children studied by Selevan et al. (2003) and Wu et al. (2003a) or the cohorts studied longitudinally could provide information on whether lead exposure during infancy has long-term effects on parameters such as fertility in males and females or on female's ability to maintain pregnancy. Dearth et al. (2004) recently reported that Fisher 344 rats are more sensitive than Sprague-Dawley rats regarding puberty-related effects. Researchers should be aware of this strain difference when comparing results between these two strains of rats. As with other lead-induced toxicities, the role of some polymorphisms (i.e., ALAD genotype) on growth and sexual maturation could be evaluated.

Immunotoxicity. Altered immune parameters have been described in lead workers. Reported effects have included changes in some T-cell subpopulations (Fischbein et al. 1993; Pinkerton et al. 1998; Sata et al. 1998; Ündeger et al. 1996), altered response to T-cell mitogens (Mishra et al. 2003), and reduced chemotaxis of polymorphonuclear leukocytes (Valentino et al. 1991). Three studies of children reported significant associations between PbB and increases in serum IgE levels (Karmaus et al. 2005; Lutz et al. 1999; Sun et al. 2003). IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma; therefore, the suggestion has been raised that *in utero* exposure to lead may be a risk factor for childhood asthma (Dietert et al. 2002). Perinatal exposure of rodents to lead also has induced increased IgE levels in the offspring (Miller et al. 1998; Snyder et al. 2000). Additional studies in which animals are exposed at different developmental periods are necessary to identify vulnerable periods during development and to determine potential long-term consequences of exposures during discrete periods of development (Dietert et al. 2002, 2004). Also, studies that compare the effects of lead on immunological end points in different species, different strains, and animals of both sexes would provide valuable information, as there is some evidence that the immune response may depend on the species, strain, and/or gender (Bunn et al. 2001a, 2001b, 2001c). In addition, further information on

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how lead-induced changes in immune balance (Heo et al. 1998; McCabe et al. 1999) affect the immune response profile and the host's defense capabilities would be valuable. This is important because there is evidence that suggests that lead or other chemicals during development may cause inappropriate Th1 development and a potentially serious imbalance toward Th2-associated capacity resulting in elevated IgE production and increased risk for atopy and asthma (Peden 2000).

Neurotoxicity. The nervous system is a sensitive target for lead toxicity in humans (for representative references, see Chronic-Duration Exposure and Cancer, above) and in animals. Of special concern are the results of recent studies that have reported neurobehavioral deficits in children associated with PbBs <10 µg/dL and an apparent lack of threshold down to even the lowest PbBs recorded in these studies (Bellinger and Needleman 2003; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a, 2005; Téllez-Rojo et al. 2006). Some of these studies found that the slope of the dose-response is steeper at lower PbBs than at higher PbBs; that is, the effects of lead on cognitive function is greater in children with lower PbB than in children with higher PbB. However, a mechanism that could produce this result has not yet been identified, and this represents a data need. The neurotoxicity of lead is the result of multiple modes of action and research needs can be identified at almost any level of action, from studies of basic biochemical and physiological mechanisms (i.e., transport of lead across biological barriers in general and nerve membranes in particular) to studies of populations. There are several ongoing prospective studies of lead in children (i.e., Bellinger et al. 1992; Ris et al. 2004; Schnaas et al. 2000; Tong et al. 1998; Wasserman et al. 2003) and it is assumed that follow-up of some of these cohorts will continue. With regard to these and other studies in humans, researchers have identified some specific needs. For example, there is a need to develop new and more sensitive tests of specific neuropsychological functions (Bellinger 1995). Also, not enough research has been conducted in adults using measures of cumulative exposure to lead. Another area where additional research would be valuable is to determine the extent to which lead contributes as a risk factor to disease and dysfunction. There is a limited number of studies that have linked lead to amyotrophic lateral sclerosis (Kamel et al. 2002), essential tremor (Louis et al. 2003), schizophrenia (Opler et al. 2004), and Parkinson's disease (Gorell et al. 1997, 1999). Also, the possibility that lead contributes to attention deficit disorder has never been adequately addressed, despite the increased levels of diagnosis of this disorder in children over the past 20 years. Studies in animal models of these diseases can provide valuable information to answer such questions. With regard to the interpretation of studies with seemingly differing results, it would be important to identify the basis of individual differences in sensitivity to neurotoxicants (Bellinger 2000). In addition, epidemiological studies should be designed in a manner that permits more rigorous assessments of effect modification. In order to minimize confounding and effect modification,

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researchers should make greater use of more focused sampling frames that ensure adequate representation of specific subgroups of interest (Bellinger 2000). Additional information is needed to characterize the nature of the relationships between lead and nutritional factors, as well as determining what dietary modifications might be particularly beneficial in alleviating lead uptake and or effects. Banks et al. (1997) suggest that further studies using electrophysiological methods in infancy and early childhood can add to knowledge about the effects of lead on specific sensory systems such as vision and audition, as well as on higher, more cortically-controlled cognitive processes.

With regard to studies in animals, further studies of the specific behavioral nature of lead-induced learning impairments and of the behavioral mechanisms contributing to such effects would be valuable (Cory-Slechta 1995). Such studies in conjunction with microdialysis and microinjection techniques could provide critical information related to the roles of various neurotransmitter systems and different brain regions in behavioral manifestations (Cory-Slechta 1995). Such research may also shed light on possible interactions between neurotransmitter systems that might contribute to lead effects and allow researchers to examine the efficacy of potential behavioral or chemical therapeutic approaches for reversing behavioral impairments (Cory-Slechta 2003). Additional studies of the roles of developmental periods of lead exposure and the levels of lead exposure should be conducted to resolve the possibility of differential mechanisms at different stages of the life cycle (Cory-Slechta 1997). Further development of molecular techniques to study the action of lead on the function of specific components of proteins associated with synaptic transmission also would be helpful (Atchison 2004; Suszkiw 2004). Additional research on lead-gene interactions is critical to further the understanding of these issues.

Epidemiological and Human Dosimetry Studies. There are dozens of epidemiological studies that investigated the health effects of lead in both adults and children. The studies listed above under *Chronic-Duration Exposure and Cancer* and others cited throughout Section 3.2, *Discussion of Health Effects*, provide information on lead-induced effects on multiple systems and organs, but the most sensitive targets for lead toxicity are the nervous system, heme synthesis, and kidney function. Children are more sensitive than adults to lead toxicity and a great number of studies conducted in the last decades have focused on the evaluation of neurobehavioral effects of lead in children that have been associated with relative low blood lead levels (i.e., <10 µg/dL) (Bellinger and Needleman 2003; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a, 2005; Téllez-Rojo et al. 2006). Although the preponderance of the evidence suggests that lead exposure in children is associated with small decrements in intelligence, there are studies that have not found such an association. In this regard, a major information need regarding epidemiological studies of lead is identifying the basis of individual

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differences in sensitivity to lead toxicity. Another important issue that future studies need to consider is the presence of modifying factors. Bellinger (2000) states that effect modification is a property of a true association and should be distinguished from confounding. Effect modification can explain inconsistencies in findings, and if it exists, failure to address it will lead to an error in inference. Maternal stress and environmental enrichment have recently been identified as modifying factors of lead-induced behavioral effects in studies in animals (Cory-Slechta 2006; Cory-Slechta et al. 2004; Guilarte et al. 2003; Schneider et al. 2001) and continued research in these areas may provide valuable information for understanding effects in humans. Effects of lead through alterations in corticoids may have enormous implications since changes in the hypothalamic-pituitary-adrenal axis could be a mechanism for multiple effects of lead, including those on the immune system as well as on the brain.

Most of the research gaps identified in the preceding sections could also be listed in this section. For example, it is expected that children from some of the prospective studies of lead will continue to be evaluated periodically with appropriate neurobehavioral tests. As children in these cohorts (or in newly identified cohorts) go through adolescence and eventually into adulthood, it would be desirable also to evaluate other end points for potential late-appearing effects. Such evaluations may include, but not be limited to, immunocompetence, sexual development, fertility, kidney and cardiovascular functions, or cancer incidence. The usefulness of studies involving adult populations exposed to lead as adults (i.e., lead workers) in understanding neurotoxicity of lead in children is questionable. This is because the impact of a brain lesion experienced as an adult can be dramatically different than that of a lesion incurred during periods in which the brain is still undergoing substantial changes (Bellinger 2004). However, studies regarding other end points of interest would be useful. For example, associations between lead exposure and decreases in glomerular filtration rate have been observed, but not fully characterized (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992; Weaver et al. 2003a). Major uncertainties in the dose-response relationship include: (1) the appropriate exposure biomarker (i.e., PbB or bone lead concentration); and (2) the strength of the interactions between glomerular filtration rate, blood pressure, and certain diseases such as diabetes. Regarding cardiovascular effects, meta-analyses of the association between blood pressure and PbB have found an average effect size of approximately 1 mmHg increase in blood pressure per doubling of PbB (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994); however, more recent studies have observed a larger effect in older populations and associations between blood pressure and bone lead concentrations that is stronger than the association with PbB (Cheng et al. 2001; Korrick et al. 1999; Nash et al. 2003). Major uncertainties in the dose-response relationship for blood pressure effects include: (1) the appropriate exposure

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biomarker (i.e., PbB or bone lead concentration); and (2) the strength of the association in older males and post-menopausal women.

Biomarkers of Exposure and Effect.

Exposure. Inorganic lead can be measured in blood, serum, urine, sweat, cerebrospinal fluid, tissues, bone, teeth, and hair and nails (see Section 3.6.1). While measurements of lead in any of the above tissues can be useful as an indicator of excessive exposure to lead, quantitative associations with exposure levels and health effects have been most rigorously explored for blood lead concentration (PbB). Currently, PbB is the most widely used biomarker of lead exposure in humans. However, because of the relatively rapid elimination of lead from blood (elimination half-time <30 days), PbB reflects exposures that occurred within a few months previous to the measurement. The need exists for the development of a biomarker that would accurately reflect the total body burden from both acute and chronic durations at both low- and high-level exposures. Bone lead concentration may serve as a more reliable biomarker of long-term exposure because lead is eliminated slowly from bone (elimination half-time of decades). It may also provide a better reflection of long-term time-integrated plasma lead concentration (Coke et al. 1996; Chuang et al. 2001; Tellez-Rojo et al. 2004). This may explain why bone lead concentration has been observed to be a better predictor of cardiovascular/renal effects in older populations than is PbB (Cheng et al. 1998, 2001; Korrick et al. 1999; Tsaih et al. 2004). Further characterization of bone lead concentration as a biomarker of exposure for various effect end points in adults may improve lead dose-response assessment and characterization of health risks from exposure to lead in humans.

The development of inductively-coupled plasma mass spectrometry (ICP-MS) (see Chapter 7) has provided adequate analytical sensitivity to measure plasma lead concentrations with greater confidence than in the past (Schutz et al. 1996). Recent studies using this technique have shown that plasma lead concentrations in adults correlate more strongly with bone lead levels than do PbB (Coke et al. 1996; Chuang et al. 2001; Hernandez-Avila et al. 1998; Tellez-Rojo et al. 2004). Since most of the body lead burden resides in bone, measurements of plasma lead concentration may turn out to be a better predictor of lead body burden than measurements of PbB. This observation has not been explored in children, and few studies have attempted to explore relationships between plasma lead concentration and health outcomes in children.

Effect. No clinical disease state is pathognomonic for lead exposure. The neurotoxic and hematopoietic effects of lead are well recognized. The primary biomarkers of effect for lead are EP, ALAD, basophilic

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stippling and premature erythrocyte hemolysis, and presence of intranuclear lead inclusion bodies in the kidneys. Of these, activity of ALAD is a sensitive indicator of lead exposure (see Section 3.6.1). Biomarkers for the nephrotoxic effects of lead in humans include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, $\beta_2\mu$ -globulin, $\alpha_1\mu$ -globulin, retinol binding protein; see Table 3-3 and Figure 3-3). However, none of these markers are specific for lead-induced nephrotoxicity. More specific biomarkers of effects for lead may improve the assessment of health risks derived from exposure to lead.

Absorption, Distribution, Metabolism, and Excretion. Inhalation of airborne lead-bearing surface dusts can be an important exposure pathway for human. However, available studies of the deposition and absorption of inhaled lead in humans are of exposures of adults to submicron lead-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). No studies are available on deposition and absorption of larger particles that might be encountered from inhalation of airborne surface dusts. No data are available on the deposition and absorption of inhaled lead in children. However, models of age-related changes in airway geometry and physiology predict that particle deposition in the various regions of the respiratory tract in children may be higher or lower than in adults depending on particle size; for submicron particles, fractional deposition in 2-year-old children has been estimated to be 1.5 times greater than in adults (Xu and Yu 1986).

Ingestion of lead can occur as a result of consuming lead-containing food, drinking water, and beverages, from ingesting lead-containing dusts, and from swallowing lead deposited in the upper respiratory tract after inhalation exposure. Children can ingest lead-containing dusts, lead-based paint, and other nonfood materials through their normal mouthing activity and pica (abnormal ingestion of nonfood items). Fractional absorption of ingested lead appears to vary in magnitude with age, being as much as 5–10 times greater in infants and young children than in adults (Alexander et al. 1974; Chamberlain et al. 1978; James et al. 1985; Ziegler et al. 1978). However, there are no data on the absorption of lead in older children and adolescents; thus, it is uncertain whether lead absorption in this population is more similar to that of adults or to that of infants and young children. While no absorption studies have been conducted on subjects in this age group, the kinetics of the change in stable isotope signatures of blood lead in mothers and their children, as both come into equilibrium with a novel environmental lead isotope profile, suggest that children ages 6–11 years and their mothers may absorb a similar percentage of ingested lead (Gulson et al. 1997b).

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Ingested soil lead is less readily absorbed than ingested water-soluble lead acetate (Casteel et al. 1997; EPA 2004b; Freeman et al. 1996). This difference may reflect a lower solubility of soil lead because of its chemical or physical form; for example, there is an inverse relationship between lead particle size and gastrointestinal absorption (Barltrop and Meek 1979). There is one published study that assessed the bioavailability of lead in adults who ingested hazardous waste site soil (Maddaloni et al. 1998).

Additional studies of this type would provide an improved basis for estimating lead uptake in people who are exposed to lead in soil and soil-derived dusts. A variety of other factors are known to influence the absorption of ingested lead, including the chemical form of the ingested lead, the presence of food in the gastrointestinal tract, diet, and nutritional status with respect to calcium, vitamin D, and iron (Mushak 1991); however, for the most part, the mechanisms by which these interactions occur are not fully understood. This reflects, in part, a lack of understanding of the mechanisms by which lead is absorbed in the gastrointestinal tract and studies aimed at elucidating such mechanisms are needed. A better understanding of absorption mechanisms is critical to developing physiologically based models that accurately simulate relationships between lead exposure and lead in blood and other target and biomarker tissues.

Few studies are available on the absorption after dermal exposure of inorganic lead compounds in humans. In contrast, alkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). Recent studies provide evidence for rapid dermal absorption of inorganic lead in adults; however, these studies have not quantified the fraction of applied dose that was absorbed (Stauber et al. 1994; Sun et al. 2002). The quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty. In children who may experience extensive dermal contact with lead in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic lead compounds from both aqueous media and from soil, in particular, studies that enable measurements to be extrapolated to children, are important for estimating internal doses that children might receive in relatively common exposure scenarios.

Several models of the toxicokinetics of lead in humans have been developed (Bert et al. 1989; EPA 1994a, 1994c; Leggett 1993; Marcus 1986a, 1986b, 1986c; O'Flaherty 1993; Rabinowitz et al. 1976). Major uncertainties in these models include: (1) absence of calibration data for the kinetics of lead in blood and bone in children in association with exposures that have been quantified with high certainty; (2) absence of calibration data on bone lead concentrations in adolescents and adults in association with

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exposures that have been quantified with high certainty; (3) absence of data on the absolute bioavailability of ingested lead in older children and adolescents; (4) incomplete understanding of lead kinetics during periods of changing bone metabolism, including adolescence, pregnancy, and menopause; and (5) incomplete understanding of inter- and intra-individual variability in model parameters values in humans. In addition, there is a need for models that predict concentrations of lead in tissues other than blood.

Comparative Toxicokinetics. The immature swine has been used extensively as a model for assessing relative bioavailability of lead in ingested soil in humans (Casteel et al. 1997; EPA 2004c) and for evaluating *in vitro* approaches to assessing bioaccessibility of lead (EPA 2004c; Ruby et al. 1999). However, no studies are available in which the absolute or relative bioavailability of ingested lead has been quantitatively compared in swine and humans. Such studies would be useful for validating both the *in vivo* swine model and the *in vitro* bioaccessibility model.

Methods for Reducing Toxic Effects. The extent of lead absorption in the gastrointestinal tract depends on numerous factors including nutritional factors and the presence or absence of other metals that interact with lead (Kwong et al. 2004; Mahaffey and Annest 1986; Mahaffey et al. 1986; Ziegler et al. 1978). Thus, further studies that could identify additional factors that affect lead absorption would be valuable. These factors may be nutritional factors or specific pathologic conditions. Chelators have been used in the management of lead poisoning, particularly in children (Berlin et al. 1995; Homan et al. 1998). However, further research should address questions such as what blood lead levels warrant chelation therapy and whether chelation therapy may redistribute lead from bone to other tissues. Moreover, the effectiveness of chelation therapy in reducing neuropsychologic impairment in children with clinically inapparent lead poisoning is questionable, as shown in a series of recent studies (Dietrich et al. 2004; Liu et al. 2002; Rogan et al. 2001). Clinical studies of oral chelation should monitor not only PbB, but also the possibility of ongoing lead exposure, the child's age, sources of lead exposure, length of exposure, and general health status. Also, the potential benefits of chelation in reducing chronic impairments in adults are completely unknown. Lead inhibits heme synthesis by inhibiting the enzyme ALAD, and this results in a diffuse effect that involves many systems and organs. Even if ALAD inhibition could be prevented, because of the ability of lead to inhibit and/or substitute for calcium in many cellular processes (such as neurotransmitter exocytosis), it is unlikely that one could prevent all of the physiological alterations that have been attributed to exposure to lead.

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Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Many of the known health effects that have been associated with low-level lead exposure have been detected in children who experienced lead exposures both *in utero* and postnatally. Considerable uncertainty remains about the relative contribution of *in utero* and postnatal exposures to the development of health outcomes that are expressed later in childhood. This information is important for distinguishing those health outcomes that might be mitigated during the postnatal period from those that must be mitigated by limiting *in utero* exposure. Considerable uncertainty also remains about the long-term consequences of the lead-related neurobehavioral deficits detected in infants and children with respect to manifestation of chronic neurobehavioral problems in adolescence and adulthood. An additional important issue that needs to be studied is the potential prevalence of elevated bone lead stores in women of reproductive age and the associated risk that this poses to fetal development by mobilization of maternal bone stores during pregnancy.

The interaction between exposure intensity and duration of exposure in the development of neurobehavioral deficits is not understood, in part because of a lack of biomarkers of long-term lead exposure. The strongest evidence for health effects of low-level lead exposures on neurodevelopmental deficits is based on relationships between measured health outcomes and PbB. Although these studies suggest that a significant amount of the variability in the health outcomes (e.g., neurobehavioral deficits) can be attributed to variability in PbB, a substantial amount of variability in the outcomes usually cannot be assigned to PbB, even after many known potential confounders have been considered (i.e., Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994; Winneke et al. 1996).

Efforts to explore alternative biomarkers of exposure that provide a better reflection of long-term cumulative exposure may be of value for exploring the above issues. Two potential biomarkers of long-term exposure are bone lead measurements and plasma lead measurements (Cake et al. 1996; Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Recent advances in XRF techniques have made it possible to estimate lead levels in bone. Such measurements hold promise as biomarkers of long-term cumulative exposure during childhood. However, standard techniques for measuring bone lead have not yet been developed. Moreover, there continues to be uncertainty about how to interpret bone lead measurements in terms of lead exposure, their relationship to PbB concentrations, and their relationships to the various health effects that have been associated with lead

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exposure in children. Thus, while dose-response relationships based on PbB are becoming understood, much less is known about bone lead-response relationships. This information is important for gaining a better understanding of the relationship between cumulative exposures and toxicity. The development of ICP-MS (see Chapter 7) has provided adequate analytical sensitivity to measure plasma lead concentrations with greater confidence than in the past. Studies using this technique have shown that plasma lead concentrations in adults correlate more strongly with bone lead levels than does PbB (Cake et al. 1996; Hernandez-Avila et al. 1998). Since most of the body lead burden resides in bone, measurements of plasma lead concentration may turn out to be a better predictor of lead body burden than are measurements of PbB. This observation has not been explored in children, and few studies have attempted to explore relationships between plasma lead concentration and health outcomes in children.

Studies in animals have provided abundant support for the plausibility of the neurodevelopmental effects of lead that have been associated with lead exposure in children, and researchers have begun to identify potential mechanisms (i.e., Cory-Slechta 1995, 2003; Rice 1993, 1996a). However, mechanistic connections between behavioral deficits, or changes observed in animals, and those that have been associated with lead exposure in children have not been completely elucidated. Understanding of such connections would be valuable for developing better and more relevant animal models of lead toxicity.

Studies of the effects of lead on bone metabolism indicate that, in addition to being a reservoir for the lead body burden, bone may also be a toxicological target (Hamilton and O'Flaherty 1994, 1995). Studies in rats have shown effects of lead on bone mineralization and bone growth. The effects observed in rats may be relevant to our understanding of the mechanisms for the growth deficits that have been associated with low-level *in utero* and childhood lead exposures (Ballew et al. 1999; Frisanchio and Ryan 1991; Shukla et al. 1989, 1991). Additional studies of the effects of lead on bone metabolism in humans and in animal models would improve our understanding of the toxicological significance of lead in bone.

Further research on the relationship between paternal lead exposure and fetal/infant development should be conducted. Additional information on relationships between nutritional deficits and vulnerability of the fetus and child to lead would be valuable.

Absorption of ingested lead is higher in infants and young children than in adults; however, available data on lead absorption during the ages between childhood and adulthood are very limited (Alexander et al. 1974; Ziegler et al. 1978). The higher absorption of lead in childhood contributes to the greater susceptibility of children to lead; therefore, it is important to know at what age the higher absorption

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status of the child changes to the lower absorption status observed in adults. Limited data suggest that this conversion may occur early in adolescence. This information is particularly important for accurately simulating biokinetics of lead in older children and adolescents. Additional information on interactions between nutritional deficiencies and lead absorption and other aspects of lead biokinetics would be valuable.

Dermal absorption of inorganic lead compounds occurs, but the quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty, although it is generally considered to be much lower than absorption by the inhalation or oral routes of exposure. In children who experience extensive dermal contact with lead in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic lead compounds from both aqueous media and soil, in particular, studies that enable measurements to be extrapolated to children, are important for estimating internal doses that children might receive in relatively common exposure scenarios.

The kinetics of bone formation and remodeling are important factors in the overall biokinetics of lead. Most of the body burden of lead resides in bone; a portion of the maternal bone lead stores is transferred to the fetus during gestation and incorporated into fetal bone during the development of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003). Thus, changes in maternal bone metabolism (e.g., formation and remodeling) are likely to have a significant impact on *in utero* exposure of the fetus. Approximately 80% of lead in cord blood appears to derive from maternal bone stores (Gulson et al. 2003). Further information about the kinetics of the mobilization of maternal bone lead, or its incorporation into the fetal skeleton is critical for developing models that accurately simulate *in utero* exposures and maternal lead biokinetics during pregnancy and for understanding how changes in maternal bone metabolism might affect the susceptibility of the fetus to lead toxicity. Bone formation undergoes rapid changes during infancy, childhood, and adolescence. These changes may give rise to periods of greater or lower susceptibility to environmental lead; however, little is known about the potential consequences of these changes on the biokinetics of lead in children.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

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3.10.3 Ongoing Studies

Ongoing studies pertaining to lead have been identified and are shown in Table 3-12.

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Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Audesirk GJ	University of Colorado at Denver/Health Science Center, Denver, Colorado	Differential lead toxicity in neurons and astrocytes	National Institute of Environmental Health Sciences
Benoff SH	Jewish Research Institute, Manhasset, New York	Developing an understanding of toxic metal action in the human testis	National Institute of Environmental Health Sciences
Berkowitz GS	Mount Sinai School of Medicine, New York, New York	Lead mobilization during pregnancy and lactation in urban women	National Center for Research Resources
Blum CB	Columbia University Health Sciences, New York, New York	Bioavailability of soil lead and arsenic in humans	National Institute of Environmental Health Sciences
Bornschein RL	University of Cincinnati, Cincinnati, Ohio	Treatment of lead exposed children follow up	National Institutes of Health
Brain JD	Harvard School of Public Health, Boston, Massachusetts	Transport of lead, manganese, iron, and cadmium from the environment to critical organs	National Institutes of Health
Burchiel SW	University of New Mexico School of Medicine, Albuquerque, New Mexico	Effects of immunotoxic xenobiotics on human peripheral blood	National Center for Research Resources
Burt BA	University of Michigan Dental School, Ann Arbor, Michigan	Lead exposure/dietary factors in children's oral health	National Institute of Dental and Craniofacial Research
Cecil KM	Children's Hospital Medical Center, Cincinnati, Ohio	MR assessment of brain function altered by lead exposure	National Institute of Environmental Health Sciences
Cohen MD	New York University School of Medicine, Tuxedo, New York	Investigation of how properties of metals may govern toxicities in the lungs	National Institute of General Medical Sciences
Cory-Slechta DA	University of Rochester, Rochester, New York	Behavioral toxicity of lead-- a pharmacological analysis	National Institute of Environmental Health Sciences
Ehrich M, Meldrum JB, Parran D, Magnin-Bissel G, and Inzana KD	Virginia Polytechnic Institute, College of Veterinary Medicine, Blacksburg, Virginia	Insecticide exposure and the permeability of the blood-brain barrier to lead	Department of Agriculture
Ercal N	University of Missouri, Rolla, Missouri	Role of selenocystine in lead toxicity	National Institute of Environmental Health Sciences

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Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Evanylo GK, Daniels WL, and Zelazny LW	Virginia Polytechnic Institute, Crop and Soil Environmental Sciences, Blacksburg, Virginia	Chemistry and bioavailability of waste constituents in soils	Department of Agriculture
Fox DA	University of Houston, Houston, Texas	Low-level prenatal lead exposure and retinal toxicity	National Institute of Environmental Health Sciences
Gao F-B	J David Gladstone Institutes, San Francisco, California	Genetic analysis of heavy metals neurotoxicity	National Institute of Neurological Disorders and Stroke
Garshick E	Department of Veterans Affairs, Medical Center, Brockton, Massachusetts	Lead intoxication-prevalence and its relation to anemia in India	Department of Veterans Affairs
Gonick H	Department of Veterans Affairs, Medical Center, West Los Angeles, California	Influence of lead on blood vessel contraction	Department of Veterans Affairs
Godwin HA	Northwestern University, Evanston, Illinois	Mechanisms of lead toxicity	National Institute of General Medical Sciences
Gray LC	University of Texas, Health Science Center, Houston, Texas	Effects of lead on deficits in hearing rapid changes in sound	National Institute on Deafness and Other Communication Disorders
Graziano JH	Columbia University Health Sciences, New York, New York	Health effects and geochemistry of arsenic and lead	National Institute of Environmental Health Sciences
Guilarte TR	Johns Hopkins University, Baltimore, Maryland	NMDA receptor function in lead neurotoxicity	National Institute of Environmental Health Sciences
Harry GJ	Not specified	Environmental effects and development of neuron and glia	National Institute of Environmental Health Sciences
Hassett JJ	University of Illinois, Natural Resources and Environmental Sciences, Urbana, Illinois	Continued studies on bioavailability of lead in soil	Department of Agriculture
Henkens RW	Alderon Biosciences, Inc., Durham, North Carolina	One-step rapid screening for childhood lead poisoning	National Institute of Environmental Health Sciences
Hu H	Harvard University School of Public Health, Boston, Massachusetts	Dietary supplements and suppression of bone resorption and lead mobilization	National Institute of Environmental Health Sciences

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Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Lead, blood pressure, neurologic and renal function in two study populations	National Center for Research Resources
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Lead-gene interactions and cognition	National Institute of Environmental Health Sciences
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Development of Parkinson's disease and the exposure to lead	National Institute of Environmental Health Sciences
Ike JO	Fisk University, Nashville, Tennessee	Lead toxicity and serotonergic system in developing rat brain	National Institute of General Medical Sciences
Kamel F	Not specified	Lead and other neurotoxins as risk factors for amyotrophic lateral sclerosis	National Institute of Environmental Health Sciences
Knight JQ	Safer Pest Control Project, Chicago, Illinois	Asthma and lead prevention in Chicago public housing	National Institute of Environmental Health Sciences
Korrick SA	Harvard University School of Public Health, Boston, Massachusetts	<i>In utero</i> PCB, pesticide and metal exposure and childhood cognition	National Institute of Environmental Health Sciences
Korrick SA	Brigham and Women's Hospital, Boston, Massachusetts	Lead exposure, genetics and osteoporosis epidemiology	National Center for Research Resources
Lanphear BP	Children's Hospital Medical Center, Cincinnati, Ohio	Neurobehavioral effects of prevalent toxicants in children	National Institute of Environmental Health Sciences
Lawrence DA	Wadsworth Center, Rensselaer, New York	Immunotoxic effects of lead on cytokine expression	National Institute of Environmental Health Sciences
Lubin BH	University of California San Francisco, California	Erythrocyte isozyme biomarkers of low lead overburden	National Center for Research Resources
Lurie D	University of Montana, Center of Environmental Health Sciences, Missoula, Montana	Lead on development of auditory temporal process	National Center for Research Resources
Lutz PM	University of Missouri Rolla, Rolla, Michigan	Immunity in children with exposure to environmental lead	National Institute of Environmental Health Sciences
Mori S	Johns Hopkins University, Baltimore, Maryland	MR-based study of hypomyelination by lead poisoning	National Institute of Environmental Health Sciences

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Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Neary JT	Department of Veterans Affairs, Medical Center, Miami, Florida	Molecular mechanisms of lead neurotoxicity	Department of Veterans Affairs
Oteiza P	University of California, Davis, California	Exposure during gestation and infancy and its impact on neurobehavioral and learning capacities	Not specified
Pettit DL	Albert Einstein College of Medicine, Yeshiva University, New York, New York	Micromapping of lead induced changes to NMDA receptors	National Institute of Environmental Health Sciences
Pevsner JA	Kennedy Krieger Research Institute, Inc., Baltimore, Maryland	Effects of lead on calcium-binding proteins in rats	National Institute of Environmental Health Sciences
Pitts DK	Wayne State University, College of Pharmacy and AHP, Wayne State University, Detroit, Michigan	Lead toxicity—midbrain dopaminergic system	National Institute of Environmental Health Sciences
Pollitt E	University of California, Independent, Davis, California	The relationship between lead and iron and behavioral development in infants and young children	Department of Agriculture
Poretz RD	Rutgers University, Biochemistry and Microbiology, New Brunswick, New Jersey	A mechanism for lead-induced neurotoxicity	Department of Agriculture
Puzas JE	University of Rochester, Rochester, New York	Lead toxicity in the skeleton and its role in osteoporosis	National Institute of Environmental Health Sciences
Rajanna B	Alcorn State University, Lorman, Mississippi	Mechanism of lead neurotoxicity	National Institute of General Medical Sciences
Ris MD	Children's Hospital Medical Center, Cincinnati, Ohio	Early exposure to lead and adult antisocial outcome	National Institute of Environmental Health Sciences
Rogan W	Not specified	Toxicity of lead in children—clinical trial	National Institute of Environmental Health Sciences
Rosen HN	Beth Israel Deaconess Medical Center, Boston, Massachusetts	Lead and skeletal health in Boston area women	National Center for Research Resources
Ruden DM	University of Alabama at Birmingham, Birmingham, Alabama	QTL and microarray mapping lead sensitivity genes	National Institute of Environmental Health Sciences

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Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Schwab AP and Joern BC	Purdue University, Agronomy, West Lafayette, Indiana	Bioavailability and chemical lability of lead in agricultural soils amended with metal-containing biosolids	Department of Agriculture
Schwartz BS	Johns Hopkins University, Baltimore, Maryland	Role of lead in the decline in cognitive function in older adults	National Institute of Aging
Schwarz D	Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	Treatment of lead in children	National Center for Research Resources
Shine JP	Harvard University, School of public Health, Boston, Massachusetts	Transport and fate of metals from mine wastes	National Institute of Environmental Health Sciences
Soliman KFA	Florida Agricultural and Mechanical University, Tallahassee, Florida	Neonatal lead exposure effects on the adrenal cortex function	National Institute of General Medical Sciences
Sparrow D	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Neurochemical and genetic markers of lead toxicity	Department of Veterans Affairs
Sparrow D	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Lead biomarkers, aging, and chronic disease	Department of Veterans Affairs
Timchalk C	Battelle Memorial Institute, Pacific Northwest Laboratories, Richland, Washington	Innovative biomonitoring for lead in saliva	National Institute of Environmental Health Sciences
Todd AC	Mount Sinai, School of Medicine, New York, New York	African-Americans, hypertension and lead exposure	National Institute of Diabetes and Digestive and Kidney Diseases
Watson GE, II	Department of Dentistry, University of Rochester, Rochester, New York	A longitudinal study of lead exposure and dental caries	National Institute of Dental and Craniofacial Research
Weisskopf MG	Harvard University, School of Public Health, Boston, Massachusetts	New biomarkers of neurotoxicity	National Institute of Environmental Health Sciences
White RF	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Functional neuroimaging in lead exposed adults	Department of Veterans Affairs, Research And Development

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Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Worobey J	Rutgers University, Nutritional Sciences, New Brunswick, New Jersey	Behavioral outcomes in children screened for lead burden and nutritional risk	Department of Agriculture
Wright RO	Harvard School of Public Health, Boston, Massachusetts	Metals, nutrition, and stress in child development	National Institute of Environmental Health Sciences
Wright RO	Brigham And Women's Hospital, Boston, Massachusetts	Neurochemical and genetic markers of lead toxicity	National Institute of Environmental Health Sciences

MR = magnetic resonance; NMDA = N-methyl-D-aspartate; PCBs = polychlorinated biphenyls; QTL = quantitative trait loci

Source: FEDRIP 2005