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Health Effects Associated with Coal Combustion Residues

Compiled by

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Based on my review of the literature (summarized below), it is my expert opinion that the Coal Combustion Residue (CCR) landfill proposed for Labadie, Missouri poses a potential health risk to the residents of the area surrounding the landfill particularly if a flood would result in release of these CCRs into the groundwater and/or into the adjoining river and tributaries.

Individuals can be exposed to the constituents of concern found in Coal Combustion Residues (CCRs) through a number of exposure routes. Potential contaminant releases from landfills include: leaching to ground water; overland transport from erosion and runoff; and air emissions. If the landfill is located in an area subject to flooding, then there is potential runoff to surface water. In this report, I focus on the oral exposure route because of the possibility of release of CCRs from the landfill into drinking water and recreational waterways through contamination of ground water and rivers and streams. I reference only epidemiological studies of the potential health effects of coal combustion waste constituents.

I do not reference animal studies in this report, I only reported human health effects. This research was conducted by reviewing the Toxicological Profiles developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and reporting the results below.

This report will present evidence of human health effects for the primary CCRs reported in the Enviornmental Protection Agency proposed rule: **HAZARDOUS AND SOLID WASTE MANAGEMENT SYSTEM; IDENTIFICATION AND LISTING OF SPECIAL WASTES; DISPOSAL OF COAL COMBUSTION RESIDUALS FROM ELECTRIC UTILITIES 40 CFR Parts 257, 261, 264, 265, 268, 271 and 302, [EPA-HQ-RCRA-2009-0640; FRL-9149-4] RIN-2050-AE81**

The constituents of concern associated with CCRs addressed in the EPA report include antimony, arsenic, barium, beryllium, cadmium, hexavalent chromium, lead, mercury, nickel, selenium, silver, and thallium. Based on the information in ASTDR's Tox FAQs, EPA's IRIS system and TOXNET, the EPA believes that the metals identified are sufficiently toxic that they are capable of posing a substantial present or potential hazard to human health when improperly treated, stored, transported disposed of, or otherwise managed. I will present an overview of the health consequences of the four hazardous constituents that were estimated in the EPA groundwater risk assessment to pose high-end (90th percentile) risks at or above the risk criteria in one or more situations, and that were also found to present risk to human health in one or more damage cases (arsenic, cadmium, lead, and selenium). I will not address in detail the other constituents; however a brief description of the health consequences of each is presented below:

Arsenic. Ingestion of arsenic has been shown to cause skin cancer and cancer in the liver, bladder and lungs.
Antimony. Antimony is associated with altered glucose and cholesterol levels, myocardial effects, and spontaneous abortions. EPA has set a limit of 145 ppb in lakes and streams to protect human health from the harmful effects of antimony taken in through water and contaminated fish and shellfish.
Barium. Barium has been found to potentially cause gastrointestinal disturbances and muscular weaknesses when people are exposed to it at levels above the EPA drinking water standards for relatively short periods of time.
Beryllium. Beryllium can be harmful if you breathe it. If beryllium air levels are high enough (greater than 1,000 ug/m3), an acute condition can result. This condition resembles pneumonia and is called acute beryllium disease.
Cadmium and Lead. Cadmium and lead have the following effects: kidney disease, lung disease, fragile bone, decreased nervous system function, high blood pressure, and anemia.

Hexavalent Chromium. Hexavalent chromium has been shown to cause lung cancer when inhaled.
Mercury. Exposure to high levels of metallic, inorganic, or organic mercury can permanently damage the brain, kidneys, and developing fetus.
Nickel. The most common harmful health effect of nickel in humans is an allergic reaction. Approximately 10-20% of the population is sensitive to nickel. The most common reaction is a skin rash at the site of contact. Less frequently, some people who are sensitive to nickel have asthma attacks following exposure to nickel. Some sensitized people react when they consume food or water containing nickel or breathe dust containing it.
Selenium. Selenium is associated with selenosis.
Silver. Exposure to high levels of silver for a long period of time may result in a condition called arygria, a blue-gray discoloration of the skin and other body tissues.
Thallium. Thallium exposure is associated with hair loss, as well as nervous and reproductive system damage.

Toxicological Profile for Arsenic.

Cardiovascular Effects. ***Inorganic Arsenicals.*** A number of studies in humans indicate that arsenic ingestion may lead to serious effects on the cardiovascular system. Characteristic effects on the heart from both acute and long-term exposure include altered myocardial depolarization (prolonged QT interval, nonspecific ST segment changes) and cardiac arrhythmias (Cullen et al. 1995; Glazener et al. 1968; Goldsmith and From 1986; Heyman et al. 1956; Little et al. 1990; Mizuta et al. 1956; Moore et al. 1994b; Mumford et al. 2007). A significant dose-related increase in the prevalence of cardiac electrophysiologic abnormalites was observed in residents of Inner Mongolia, China; the incidences of QT prolongation were observed in 3.9, 11.1, and 20.6% of the residents with drinking water levels of <21, 110–300, and 430–690 μg/L, respectively (Mumford et al. 2007). Hypertrophy of the ventricular wall was observed at autopsy after acute exposure to 93 mg of arsenic (Quatrehomme et al. 1992). Long-term, low-level exposures may also lead to damage to the vascular system. The most dramatic example of this is "Blackfoot Disease," a condition that is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm (Tseng 1977), corresponding to doses of about 0.014–0.065 mg As/kg/day (IRIS 2007). The disease is characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene (Chen et al. 1988b; Ch'i and Blackwell 1968; Tseng 1977, 1989; Tseng et al. 1968, 1995, 1996).

Arsenic exposure in Taiwan has been associated with an increased incidence of cerebrovascular and microvascular diseases (Chiou et al. 1997; Wang et al. 2002, 2003) and ischemic heart disease (Chang et al. 2004; Chen et al. 1996; Hsueh et al. 1998b; Tsai et al. 1999; Tseng et al. 2003). Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, hypertension, defined as a systolic blood pressure of ≥140 mm Hg in combination with a diastolic blood pressure of ≥90 mm Hg, was associated with estimated lifetime doses of approximately 0.055 mg As/kg/day (0.25 mg/L in water) in a study of people in Bangladesh (Rahman et al. 1999); no significant association was found with estimated doses of 0.018 mg As/kg/day (0.75 mg/L in water). Wang et al. (2003) found an increased incidence of microvascular and macrovascular disease among subjects in Taiwan living in an

arseniasis-endemic area in which the water of artesian wells had arsenic concentrations >0.35 mg/L (estimated doses of >0.03 mg As/kg/day). An additional study of Taiwanese subjects reported a significant increase in incidence of hypertension associated with concentrations of arsenic in the water >0.7 mg/L (estimated doses of >0.06 mg As/kg/day) (Chen et al. 1995). Studies in Chile indicate that ingestion of 0.6–0.8 ppm arsenic in drinking water (corresponding to doses of 0.02– 0.06 mg As/kg/day, depending on age) increases the incidence of Raynaud's disease and of cyanosis of fingers and toes (Borgoño and Greiber 1972; Zaldívar 1974, 1977; Zaldívar and Guillier 1977). Autopsy of five children from this region who died of apparent arsenic toxicity showed a marked thickening of small and medium sized arteries in tissues throughout the body, especially the heart (Rosenberg 1974). In addition, cardiac failure, arterial hypotension, myocardial necrosis, and thrombosis have been observed in children who died from chronic arsenic ingestion (Zaldívar 1974), as well as adults chronically exposed to arsenic (Dueñas et al. 1998). Likewise, thickening and vascular occlusion of blood vessels were noted in German vintners exposed to arsenical pesticides in wine and in adults who drank arsenic-contaminated drinking water (Roth 1957; Zaldívar and Guillier 1977). A survey of Wisconsin residents using private wells for their drinking water found that residents exposed for at least 20 years to water concentrations of >10 µg As/L had increased incidences of cardiac bypass surgery, high blood pressure, and circulatory problems as compared with residents exposed to lower arsenic concentrations (Zierold et al. 2004). Similarly, Lewis et al. (1999) reported increased mortality from hypertensive heart disease in both men and women among a cohort exposed to arsenic in their drinking water in Utah, as compared with the general population of Utah. Limitations in the study included lack of evaluation of smoking as a confounder and of other dietary sources of arsenic, and the lack of a dose-response for hypertensive heart disease. Another ecological study (Engel and Smith 1994) found significant increases in deaths from arteriosclerosis, aortic aneurysm, and all other diseases of the arteries, arterioles, and capillaries among U.S. residents with arsenic drinking waters of >20 µg/L; the increase in deaths from congenital anomalies of the heart and other anomalies of the circulatory system also observed in this subpopulation limits the interpretation of the findings.

Gastrointestinal Effects.

Inorganic Arsenicals. Clinical signs of gastrointestinal irritation, including nausea, vomiting, diarrhea, and abdominal pain, are observed in essentially all cases of short-term high-dose exposures to inorganic arsenic (e.g., Armstrong et al. 1984; Bartolome et al. 1999; Campbell and Alvarez 1989; Chakraborti et al. 2003a; Cullen et al. 1995; Fincher and Koerker 1987; Goebel et al. 1990; Kingston et al. 1993; Levin- Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994b; Muzi et al. 2001; Uede and Furukawa 2003; Vantroyen et al. 2004). Similar signs are also frequently observed in groups or individuals with longerterm, lower-dose exposures (e.g., Borgoño and Greiber 1972; Cebrián et al. 1983; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a; Haupert et al. 1996; Holland 1904; Huang et al. 1985; Mizuta et al. 1956; Nagai et al. 1956; Silver and Wainman 1952; Wagner et al. 1979; Zaldívar 1974), but effects are usually not detectable at exposure levels below about 0.01 mg As/kg/day (Harrington et al. 1978; Valentine et al. 1985). These symptoms generally decline within a short time after exposure ceases. Gastrointestinal irritation symptoms form the basis (in part) for the acute oral MRL of 0.005 mg/kg/day for inorganic arsenic. More severe symptoms (hematemesis, hemoperitoneum, gastrointestinal hemorrhage, and necrosis) have been reported in some cases with acute exposure

to 8 mg As/kg or more (Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), and also in some people with long-term ingestion of 0.03–0.05 mg As/kg/day as a medicinal preparation (Lander et al. 1975; Morris et al. 1974).

Hematological Effects. ***Inorganic Arsenicals.*** Anemia and leukopenia are common effects of arsenic poisoning in humans, and have been reported following acute (Armstrong et al. 1984; Goldsmith and From 1986; Mizuta et al. 1956; Muzi et al. 2001; Westhoff et al. 1975), intermediate (Franzblau and Lilis 1989; Heyman et al. 1956; Nagai et al. 1956; Wagner et al. 1979), and chronic oral exposures (Chakraborti et al. 2003a; Glazener et al. 1968; Guha Mazumder et al. 1988; Hopenhayn et al. 2006; Kyle and Pease 1965; Tay and Seah 1975) at doses of 0.002 mg As/kg/day or more. These effects may be due to both a direct cytotoxic or hemolytic effect on the blood cells (Armstrong et al. 1984; Fincher and Koerker 1987; Goldsmith and From 1986; Kyle and Pease 1965; Lerman et al. 1980) and a suppression of erythropoiesis (Kyle and Pease 1965; Lerman et al. 1980). However, hematological effects are not observed in all cases of arsenic exposure (EPA 1981b; Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952) or even all acute poisoning cases (Cullen et al. 1995; Moore et al. 1994b). In an acute animal study, Tice et al. (1997) found that there was a decrease in polychromatic erythrocytes in the bone marrow of mice treated with 6 mg As/kg/day for 1 or 4 days. There was no effect at 3 mg As/kg/day.

Hepatic Effects. ***Inorganic Arsenicals.*** A number of studies in humans exposed to inorganic arsenic by the oral route have noted signs or symptoms of hepatic injury. Clinical examination often reveals that the liver is swollen and tender (Chakraborty and Saha 1987; Franklin et al. 1950; Guha Mazumder et al. 1988, 1998a; Liu et al. 2002; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953; Zaldívar 1974), and analysis of blood sometimes shows elevated levels of hepatic enzymes (Armstrong et al. 1984; Franzblau and Lilis 1989; Guha Mazumder 2005; Hernández-Zavala et al. 1998). These effects are most often observed after repeated exposure to doses of 0.01–0.1 mg As/kg/day (Chakraborty and Saha 1987; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953), although doses as low as 0.006 mg As/kg/day have been reported to have an effect following chronic exposure (Hernández-Zavala et al. 1998). Hepatic effects have also been reported in acute bolus poisoning cases at doses of 2 mg As/kg/day or more (Hantson et al. 1996; Kamijo et al. 1998; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Vantroyen et al. 2004), although acute exposure to 19 mg As/kg did not cause hepatic effects in an infant (Cullen et al. 1995). Histological examination of the livers of persons chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis (Guha Mazumder 2005; Guha Mazumder et al. 1988; Morris et al. 1974; Piontek et al. 1989; Szuler et al. 1979), leading in some cases to portal hypertension and bleeding from esophageal varices (Szuler et al. 1979); cirrhosis has also been reported at an increased frequency in arsenic-exposed individuals (Tsai et al. 1999). Several researchers consider that these hepatic effects are secondary to damage to the hepatic blood vessels (Morris et al. 1974; Rosenberg 1974), but this is not directly established.

Neurological Effects ***Inorganic Arsenicals.*** A large number of epidemiological studies and case reports indicate that ingestion of inorganic arsenic can cause injury to the nervous system. Acute, high-dose exposures (2 mg As/kg/day or above) often lead to encephalopathy, with signs and

symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (Armstrong et al. 1984; Bartolome et al. 1999; Civantos et al. 1995; Cullen et al. 1995; Danan et al. 1984; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Uede and Furukawa 2003; Vantroyen et al. 2004). Repeated exposures to lower levels (0.03–0.1 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Chakraborti et al. 2003a, 2003b; Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Lewis et al. 1999; Mizuta et al. 1956; Muzi et al. 2001; Silver and Wainman 1952; Szuler et al. 1979; Wagner et al. 1979). This neuropathy usually begins as numbness in the hands and feet, but later may develop into a painful "pins and needles" sensation. Both sensory and motor nerves are affected, and muscle weakness often develops, sometimes leading to wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). Diminished sensitivity to stimulation and abnormal patellar reflexes have also been reported (Mizuta et al. 1956). Histological examination of nerves from affected individuals reveals a dying-back axonopathy with demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). Some recovery may occur following cessation of exposure, but this is a slow process and recovery is usually incomplete (Fincher and Koerker 1987; Le Quesne and McLeod 1977; Murphy et al. 1981). Peripheral neuropathy is also sometimes seen following acute highdose exposures, with or without the previously described encephalopathy (Armstrong et al. 1984; Baker et al. 2005; Fincher and Koerker 1987; Goebel et al. 1990; Hantson et al. 1996; Kamijo et al. 1998). Neurological effects were not generally found in populations chronically exposed to doses of 0.006 mg As/kg/day or less (EPA 1981b; Harrington et al. 1978; Hindmarsh et al. 1977), although fatigue, headache, dizziness, insomnia, nightmare, and numbness of the extremities were among the symptoms reported at 0.005, but not 0.004 mg As/kg/day in a study of 31,141 inhabitants of 77 villages in Xinjiang, China (Lianfang and Jianzhong 1994), and depression was reported in some Wisconsin residents exposed to 2–10 μg As/L in the drinking water for 20 years or longer (Zierold et al. 2004). There is emerging evidence suggesting that exposure to arsenic may be associated with intellectual deficits in children. For example, Wasserman et al. (2004) conducted a cross-sectional evaluation of intellectual function in 201 children 10 years of age whose parents were part of a larger cohort in Bangladesh. Intellectual function was measured using tests drawn from the Wechsler Intelligence Scale for Children; results were assessed by summing related items into Verbal, Performance, and Full-Scale raw scores. The mean arsenic concentration in the water was 0.118 mg/L. The children were divided into four exposure groups, representing <5.5, 5.6–50, 50–176, or 177–790 μg As/L drinking water. After adjustment for confounding factors, a dose-related inverse effect of arsenic exposure was seen on both Performance and Full-Scale subset scores; for both end points, exposure to ≥50 μg/L resulted in statistically significant differences ($p<0.05$) relative to the lowest exposure group (<5.5 μg/L). In a later report, the same group of investigators examined 301 6-year-old children from the same area (Wasserman et al. 2007). In this case, the children were categorized into the following quartiles based on water arsenic concentration: 0.1–20.9, 21–77.9, 78–184.9, and 185–864 μg/L. After adjustment for water Mn, blood lead, and sociodemographic features known to contribute to intellectual function, water arsenic was significantly negatively associated with both Performance and Processing speed raw scores. Analyses of the dose-response showed that compared to the first quartile, those in the second and third categories had significantly lower Performance raw scores ($p<0.03$ and $p=0.05$, respectively). Those in the fourth category had marginally significantly lower Full-Scale and Processing Speed raw scores. It should be mentioned, however, that in general, arsenic in the water explained <1% of the variance in test

scores. Water arsenic made no contribution to IQ outcomes. A study of 351 children age 5–15 years from West Bengal, India, found significant associations between urinary arsenic concentrations and reductions in scores of tests of vocabulary, object assembly, and picture completion; the magnitude of the reductions varied between 12 and 21% (von Ehrenstein et al. 2007). In this cohort, the average lifetime peak arsenic concentration in well water was 0.147 mg/L. However, no clear pattern was found for increasing categories of peak arsenic water concentrations since birth and children's scores in the various neurobehavioral tests conducted. Furthermore, using peak arsenic as a continuous variable in the regression models also did not support an adverse effect on the tests results. Exposure to arsenic *in utero* also did not suggest an association with the tests scores. Von Ehrestein et al. (2007) concluded that the study provided little evidence for an effect of long-term arsenic concentrations in drinking water and that the lack of findings with past exposures via drinking water may be due to incomplete assessment of past exposure, particularly exposure originating from food. Wasserman's results are consistent with those of ecological studies in children in Taiwan (Tsai et al. 2003) and in China (Wang et al. 2007). In the former, adolescents exposed to low (0.0017–0.0018 mg As/kg/day; n=20) levels of inorganic arsenic in the drinking water showed decreased performance in the switching attention task, while children in the high exposure group (0.0034–0.0042 mg As/kg/day; n=29) showed decreased performance in both the switching attention task and in tests of pattern memory, relative to unexposed controls (n=60). In the study in China (age 8– 12 years), 87 children whose mean arsenic concentration in the drinking water was 0.190 mg/L had a mean IQ score of 95 compared with 101 for children (n=253) with 0.142 mg/L arsenic in the water and 105 for control children (n=196) with 0.002 mg/L arsenic in the drinking water (Wang et al. 2007). The differences in IQ scores between the two exposure groups and the control group were statistically significant. Neurological effects have also been observed in animal studies.

Reproductive Effects ***Inorganic Arsenicals.*** Exposure to arsenic in drinking water has been associated with adverse reproductive outcomes in some studies. For example, a study of 96 women in Bangladesh who had been drinking water containing ≥0.10 mg As/L (approximately 0.008 mg As/kg/day) for 5–10 years reported a significant increase in spontaneous abortions (p=0.008), stillbirth (p=0.046), and preterm birth (p=0.018) compared to a nonexposed group (Ahmad et al. 2001). Similar results were reported by Milton et al. (2005) who found a significant association between concentrations of arsenic in the water >0.05 mg/L (approximately 0.006 mg As/kg/day) and spontaneous abortion (odds ratio [OR]=2.5; 95% CI=1.5–4.3) in a study of 533 women, also from Bangladesh. A study of 202 women from West Bengal, India, reported that exposure to arsenic concentrations of arsenic ≥0.2 mg/L in drinking water (approximately 0.02 mg As/kg/day) during pregnancy were associated with a 6-fold increased risk of stillbirth (OR=6.1; 95% CI=1.54–24.0) after adjustment for confounders (von Ehrenstein et al. 2006). No association was found between arsenic exposure and risk of spontaneous abortion (OR=1.01; 95% CI=0.73–10.8). An earlier study of 286 women in the United States also found no significant association between arsenic in the drinking water (0.0016 mg/L; approximately 0.00005 mg As/kg/day) and spontaneous abortion (OR=1.7; 95% CI=0.7–4.2) (Aschengrau et al. 1989). Lugo et al. (1969) reported a case of a 17-year-old mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at week 30 of pregnancy. Twenty-four hours after ingestion of approximately 30 mL of arsenic trioxide (0.39 mg As/kg), she was admitted for treatment of acute renal failure. She went into labor and delivered a live female

infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated and she died at 11 hours of age.

Toxicological Profile for Cadmium

Information on health effects of oral exposure to cadmium in humans is derived mainly from studies of residents living in cadmium-polluted areas. Cadmium exposure in these populations is often estimated by blood or urinary cadmium levels. Exposure in these cases occurs primarily through the diet, but smokers in these cohorts are also exposed to cadmium by inhalation. When evaluating oral exposure studies, smoking was treated as a confounding variable rather than an exposure route because of the large number of toxic compounds (in addition to cadmium) present in cigarette smoke, and because the primary concern is effects attributable to cadmium.

Cardiovascular Effects. Studies regarding cardiovascular effects in humans after oral exposure to cadmium have primarily investigated relationships between blood pressure and biomarkers of cadmium exposure such as cadmium levels in blood, urine, or other tissues. Smoking is an important confounding factor, because of the higher blood, urine, and tissue cadmium levels of smokers and the known cardiovascular toxicity of cigarette smoking. Case-control and cohort epidemiologic studies that adequately control for smoking have typically found no association between body cadmium levels (primarily reflecting dietary exposure) and hypertension (Beevers et al. 1980; Cummins et al. 1980; Ewers et al. 1985; Lazebnik et al. 1989; Shiwen et al. 1990); however, some studies have found positive correlations (Geiger et al. 1989; Tulley and Lehmann 1982) or negative correlations (Kagamimori et al. 1986; Staessen et al. 1984). Similar conflicting findings have been reported in studies analyzing death rates from cardiovascular disease among populations with dietary cadmium exposure (Inskip et al. 1982; Shigematsu 1984). Disorders of the cardiac conduction system, lower blood pressure, and decreased frequency of cardiac ischemic changes were found among elderly women with past high dietary exposure to cadmium (Kagamimori et al. 1986). Rhythmic disturbances, including ventricular fibrillation, were seen in an individual who had ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

Several studies conducting cross-sectional analysis on data from the National Health and Nutrition Examination Surveys (NHANES), investigated associations between blood and urine cadmium levels and cardiovascular effects (Everett and Frithsen 2008; Navas-Acien et al. 2005; Tellez-Plaza et al. 2008). Urinary cadmium levels were found to be strongly associated with peripheral arterial disease (PAD, defined as blood pressure ankle brachial index <0.0 in at least one leg) in analysis conducted on 728 participants (at least 40 years of age) in the NHANES 1999–2000 study (Navas-Acien et al. 2005). Individuals with PAD had a 36% higher mean urine cadmium level than individuals without PAD. This study also found that individuals with PAD had 49% higher urinary tungsten levels and urinary antimony levels exceeding 0.1 μg/L. Another study found a modest increase in systolic or diastolic blood pressure associated with increasing blood cadmium levels (geometric mean blood cadmium levels among all participants was 0.4 μg/L); no associations with blood pressure and urinary cadmium levels were found (Tellez-Plaza et al. 2008). The association between blood cadmium levels and blood pressure was stronger in

participants who never smoked than in former smokers or current smokers. There were no associations between hypertension and cadmium levels in blood or urine. In the third study, analysis on 4,912 participants (45–79 years old) in the NHANES 1988–1994 survey found a significant association between urinary cadmium levels and myocardial infarction in women, but not men (Everett and Frithsen 2008). After adjusting for numerous risk factors including smoking, race, and family history, a significant increase in the risk of myocardial infarction was observed in women with urinary cadmium levels of ≥0.88 μg/g creatinine.

Gastrointestinal Effects. Numerous human and animal studies indicate that oral exposure to cadmium in high concentrations causes severe irritation to the gastrointestinal epithelium (Andersen et al. 1988; Frant and Kleeman 1941). Common symptoms in humans following ingestion of food or beverages containing high concentrations of cadmium include nausea, vomiting, salivation, abdominal pain, cramps, and diarrhea (Baker and Hafner 1961; Buckler et al. 1986; Frant and Kleeman 1941; Nordberg et al. 1973; Shipman 1986; Wisniewska-Knypl et al. 1971). Although exact doses have not been measured, gastrointestinal symptoms have been caused in children by 16 mg/L cadmium in soft drinks (Nordberg et al. 1973) and 13 mg/L cadmium in popsicles (Frant and Kleeman 1941). Assuming an intake of 0.15 L (Nordberg et al. 1973) and a body weight of 35 kg, the emetic dose is 0.07 mg/kg. Although few studies have specifically examined gastrointestinal effects of longer-term cadmium exposure, no surveys of environmentally exposed populations have reported gastrointestinal symptoms (Morgan and Simms 1988; Roels et al. 1981a; Shigematsu 1984).

Hematological Effects. Oral cadmium exposure reduces gastrointestinal uptake of iron, which can result in anemia if dietary intake of iron is low. Anemia has been found in some instances among humans with chronic dietary exposure to cadmium (Kagamimori et al. 1986), but other studies have found no significant relationship between dietary cadmium exposure and anemia in humans (Roels et al. 1981a; Shiwen et al. 1990). Hypoproteinemia and hypoalbuminemia were reported in a male who ingested 25 mg/kg cadmium as cadmium iodide (Wisniewska-Knypl et al. 1971).

Musculoskeletal Effects. Osteomalacia, osteoporosis, bone fractures, and decreased bone mineral density have been observed in several populations exposed to elevated levels of cadmium in the diet. Bone effects were first reported in residents in the Jinzu River Basin, a cadmium-contaminated area in Japan. The disease termed Itai-Itai or "ouch-ouch" disease most often affected women with several risk factors such as poor nutrition, multiparity, and post-menopausal status (Shigematsu 1984). The disease was characterized by multiple fractures of the long bones, osteomalacia, and osteoporosis in combination with proteinuria (Järup et al. 1998b; Nordberg et al. 1997). Other Japanese populations with dietary cadmium exposure have also been found to have elevated osteoporosis and osteomalacia in both men and women (Kido et al. 1989b). Kagamimori et al. (1986) evaluated elderly Japanese women with heavy cadmium exposure from ingesting polluted drinking water, rice, and fish during World Wars I and II; and continued low-grade cadmium exposure from agricultural produce. Of 56 cases of Itai-Itai disease, 26 were accompanied by osteomalacia and 26 were without osteomalacia. Another study found that the degree of loss of bone density is correlated with urinary excretion of β2-microglobulin, an index of renal injury (Kido et al. 1990a). The bone effects observed in Itai-Itai disease and in other studies of Japanese populations exposed to high levels of cadmium in rice

are primarily due to kidney damage, which results from a progressive disturbance in renal metabolism of vitamin D to its biologically active form (Nogawa et al. 1987, 1990) and an increased urinary excretion of calcium (Buchet et al. 1990). These results suggest that bone changes may be secondary to disruption in kidney of vitamin D metabolism and resulting imbalances in calcium absorption and excretion. A recent study of women living in the Jinzu River basin found that bone turnover, particularly bone formation, was influenced by renal tubular function (Aoshima et al. 2003). However, it is possible that some bone effects are not mediated via the kidney.

Bone effects have also been observed in communities outside of Japan and in populations exposed to low levels of cadmium. In a study of Swedish women environmentally exposed to cadmium, a significant negative relationship between urinary cadmium levels and bone mineral density was observed (Åkesson et al. 2005); the mean urinary cadmium level of the population was 0.52 μg/L. In Swedish residents living in an area with known cadmium pollution from battery manufacturing facilities, significant associations were noted between blood cadmium levels and bone mineral density and between urinary cadmium levels and risk of fractures and osteoporosis. There were significant decreases in bone mineral density in environmentally exposed subjects older than 60 years of age with blood cadmium levels of ≥0.56 μg/L (Alfvén et al. 2002a). Increases in the risk of bone fractures were observed in subjects (approximately 10% of all subjects examined had environmental and occupational exposure to cadmium) older than 50 years of age with urinary cadmium levels >2 μg/g creatinine; no significant associations were found in subjects under 50 years of age (Alfvén et al. 2004). Another study of this population found significant increases in the risk of osteoporosis among men >60 years of age with urinary cadmium levels ≥5 μg/g creatinine; however, an increased risk of osteoporosis was not observed in women (Alfvén et al. 2000). A Belgian study in which residents living near zinc smelters found a 2-fold increase in cadmium exposure (as assessed via urinary cadmium levels) was associated with a decrease in proximal and distal forearm bone density of approximately 0.1 g/cm2 among post-menopausal women (Staessen et al. 1999). For women with urinary cadmium levels >1 μg/day, the incidence of bone fracture was 13.5 per 1,000 person-years. Another study of a subset of the women living near a zinc smelters (Schutte et al. 2008) provides suggestive evidence that cadmium has a direct osteotoxic effect. Significant associations between urinary cadmium levels and the levels of two pyridinium crosslinks of collagen (urinary levels of hydroxylysylpyridinoline and lysylpyridinoline), proximal forearm bone mineral density, and serum parathyroid hormone levels were found. In almost all of the examined women, urinary levels of retinol binding protein were below the cut-off level of 338 μg/day, suggesting no cadmium-induced effect on renal tubular function. Similar results have been observed in several studies of residents living in areas of China with moderate or high cadmium pollution levels (Jin et al. 2004b; Nordberg et al. 2002; Wang et al. 2003; Zhu et al. 2004). There were significant increases in the prevalence of low forearm bone mineral density in post-menopausal women with urinary cadmium levels >20 μg/g creatinine and in men, premenopausal women, and post-menopausal women with blood cadmium levels >20 μg/L (Nordberg et al. 2002). An increase in bone fractures was observed in males and females over the age of 40 years living in the area of high cadmium exposure (mean urinary cadmium levels in the area were 9.20 and 12.86 μg/g creatinine in the males and females, respectively) (Wang et al. 2003). A significant dose-response relationship between urinary cadmium levels and the prevalence of osteoporosis was

observed (Jin et al. 2004b; Wang et al. 2003; Zhu et al. 2004); the Jin et al. (2004b) study found that 23 of the 31 subjects with osteoporosis also exhibited signs of renal dysfunction.

Renal Effects. Numerous studies indicate that the kidney is the primary target organ of cadmium toxicity following extended oral exposure, with effects similar to those seen following inhalation exposure. Most of the data involves chronic exposure to cadmium; two case reports involving acute exposure to large doses of cadmium also found kidney effects. In two fatal cases of oral cadmium poisoning, anuria was present in one individual who ingested 25 mg/kg cadmium as cadmium iodide. Damage to the kidneys was reported at autopsy, but was not further specified (Wisniewska-Knypl et al. 1971). The kidneys were reported as normal at autopsy in an individual who died 2 days after ingesting 1,840 mg/kg cadmium (Buckler et al. 1986).

Several studies have found associations between increased mortality and renal dysfunction in residents living in cadmium polluted areas. Significant increases in SMRs were found in residents living in cadmium polluted areas of Japan with elevated levels of biomarkers of renal dysfunction (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006). Among the studies that examined cause of death, significant increases in deaths from renal diseases were found in the residents that were categorized as biomarker-positive (urinary levels of the renal biomarker was higher than the cut-off value); the cut-off values used were β2-microglobulin ≥1,000 μg/g creatinine (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Nakagawa et al. 1993; Nishijo et al. 2004a, 2006) or retinol binding protein ≥4 mg/L (Nishijo et al. 1995). Other studies have found that mortality increased in proportion to the renal biomarker level (β2-microglobulin, protein, or glucose) (Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 2004a, 2006). Increases in mortality from renal diseases have also been observed among populations living in cadmium polluted areas of Belgium (Lauwerys and De Wals 1981) and England (Inskip et al. 1982); however, statistical analysis was not reported in the Belgium study and the increase in renal disease was not statistically significant in the other study.

Elevated levels of several biomarkers of renal dysfunction and/or associations between cadmium burden and these biomarkers have been found in studies of populations living in cadmium non-polluted areas of Japan (Ezaki et al. 2003; Ikeda et al. 1999; Suwazono et al. 2000; Oo et al. 2000; Uno et al. 2005; Yamanaka et al. 1998), Belgium (Buchet et al. 1990; Roels et al. 1981a), and the United States (Noonan et al. 2002) and in populations living in cadmium polluted areas of China (Cai et al. 1990, 1992, 1998; Jin et al. 2002, 2004a, 2004c; Nordberg et al. 1997; Wu et al. 2001), Japan (Cai et al. 2001; Hayano et al. 1996; Ishizaki et al. 1989; Izuno et al. 2000; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002b; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Osawa et al. 2001; Watanabe et al. 2002), Thailand (Teeyakasem et al. 2007), Sweden (Järup et al. 2000; Olsson et al. 2002), and Poland (Trzcinka-Ochocka et al. 2004). Most of these studies did not estimate cadmium intake; rather, exposure was characterized based on the levels of cadmium in rice, blood, or urine. The oral route is assumed to be the primary route of exposure, although the inhalation route, particularly in smokers, may have contributed to the overall cadmium body

burden. The epidemiology data are summarized in Table 3-7 and brief discussions of the better designed studies providing valuable dose-response data follows.

Buchet et al. (1990) examined 1,699 non-occupationally exposed males and females (aged 20–80 years) living in Belgium. Urinary cadmium levels significantly correlated with urinary β2-microglobulin, retinol binding protein, NAG, amino acid, and calcium levels; the partial r2 values were 0.0036, 0.0210, 0.0684, 0.0160, and 0.0168, respectively. The probability that individuals would have abnormal values for the renal biomarkers (defined as >95th percentile for subjects without diabetes or urinary tract diseases and who did not regularly take analgesics) was estimated using logistic regression models with adjustments for age, gender, smoking, disease, and use of analgesics. It was estimated that >10% of β2-microglobulin, retinol binding protein, amino acid, and calcium values would be abnormal when 24-hour urinary cadmium levels were >3.05, 2.87, 2.74, 4.29, or 1.92 μg/24 hour, respectively.

Järup et al. (2000) examined 1,021 individuals living near a nickel-cadmium battery plant in Sweden for at least 5 years (n=799) or employed as battery workers (n=222). The mean urinary cadmium levels were 0.81 and 0.65 μg/g creatinine in males and females, respectively. Urinary cadmium levels were significantly associated with urinary human complex-forming glycoprotein (pHC; also referred to as α1-microglobulin) levels, after adjustment for age. The relationship remained statistically significant after removal of the cadmium workers from the analysis. The prevalence of abnormal pHC values (defined as exceeding the 95th percentile in a Swedish reference population; >7.1 and 5.3 mg/g creatinine for males and females, respectively) was estimated to increase by 10% at urinary cadmium levels of 1 μg/g creatinine. The European Chemicals Bureau (2007) recalculated the probability of HC proteinuria (using the raw data from Järup and associates) to account for the differences in age of the reference population (mean of 40 years) and study population (mean of 53 years). Based on these recalculations, the urinary cadmium level associated with a 10% increased probability of abnormal pHC values (20% total probability) was 2.62 μg/g creatinine for the total population. In the environmental exposed subgroup, a urinary cadmium level of 0.5 μg/g creatinine was associated with a 13% probability (doubling of the probability in reference population) of abnormal pHC values.

Noonan et al. (2002) examined residents in Pennsylvania living near a defunct zinc smelting facility (geometric mean urinary cadmium level of 0.14 μg/g creatinine) and a reference community located 10 miles from the facility (geometric mean urinary cadmium levels of 0.12 μg/g creatinine). The data from the two communities were pooled because there were no differences in urinary cadmium levels between them. β2-microglobulin, NAG, alanine aminopeptidase (AAP), and albumin levels were measured as biomarkers of renal dysfunction. The geometric mean urinary cadmium levels were 0.07 and 0.08 μg/g creatinine in 88 males and 71 females aged 6–17 years and 0.24 and 0.23 μg/g creatinine in 71 males and 80 females aged ≥18 years. No significant correlations between urinary cadmium levels and renal biomarkers were observed in the children, after adjustment for creatinine, age, and gender. In adults, significant correlations (after adjustment for creatinine, age, gender, smoking, and self-reported diabetes or thyroid disease) between urinary cadmium and NAG (partial correlation coefficient of 0.20, 95% CI of 0.05–0.36) and AAP (partial correlation coefficient of 0.21 and 95% CI of 0.05–0.36) were observed. Significant dose-effect relationships were also found for these two

biomarkers. Urinary cadmium levels were not significantly associated with elevated levels of β2-microglobulin or albumin.

Nogawa et al. (1980) examined 878 males and 972 females aged ≥50 years living in the Kakehashi River basin in Japan; the Kakehashi River, cadmium polluted from an upstream mine, was used to irrigate rice fields. β2-Microglobulin measured in morning urine samples was used as a biomarker of renal dysfunction and cadmium intake was estimated from rice samples collected in 1974. Cadmium levels in rice were considered to be representative of cadmium intake because over 70% of the total cadmium intake has been shown to come from rice. Cadmium in the rice ranged from 0.10 to 0.69 μg/g. β2-Microglobulin levels were significantly higher in the study population compared to a reference population of 113 males and 161 females living in a nearby area. A significant dose-related association between total cadmium intake and prevalence of abnormal β2-microglobulin values (defined as β2-microglobulin levels of ≥1,000 μg/g creatinine) was found. The total cadmium intake, which resulted in a prevalence of abnormal β2-microglobulin levels equal to the control group, was 1,678 mg in males (prevalence in controls was 6.0%) and 1,763 mg in females (prevalence in controls was 5.0%). A further analysis of the exposed subjects (Hochi et al. 1995) found that the prevalence of abnormal β2-microglobulin levels (using a cut-off level of 1,000 μg/g creatinine) exceeded the prevalence in the reference population when cadmium intake was ≥2 g and the subjects were divided into subgroups by age. The prevalence of abnormal β2-microglobulin levels at a given cadmium intake increased with age.

Yamanaka et al. (1998) examined 558 males and 743 females aged ≥50 years living in a cadmium nonpolluted area in Japan. Urinary cadmium level was used as a biomarker of exposure and urinary β2-microglobulin, total protein, and NAG as biomarkers of renal dysfunction. The geometric mean urinary cadmium levels were 1.3 and 1.3 μg/g creatinine in males and females, respectively. Significant correlations (after adjustment for age) between urinary cadmium levels and total protein, β2-microglobulin, and NAG were found. Abnormal levels of renal biomarkers were defined as exceeding the 84% upper limit value calculated from a referent group of 2,778 non-exposed individuals; the cut-off values were 124.8 and 120.8 mg/g creatinine for total protein in males and females, 492 and 403 μg/g creatinine for β2-microglobulin, and 8.0 and 8.5 U/g creatinine for NAG. Dose-response relationships between urinary cadmium levels and prevalence of abnormal levels of β2-microglobulin, total protein, and NAG were found. The odds ratios (95% CI) were 6.589 (3.383–12.833), 3.065 (1.700–5.526), and 1.887 (1.090–3.268) for protein, β2-microglobulin, and NAG in males and 17.486 (7.520–40.660), 5.625 (3.032–10.435), and 2.313 (1.399–3.824) for protein, β2-microglobulin, and NAG in females.

Another study of residents living in a cadmium non-polluted area of Japan examined 346 males and 529 females from one area (area A) and 222 males and 413 females in another area (area B); all subjects were ≥50 years of age and were not occupationally exposed to heavy metals (Oo et al. 2000). The geometric mean urinary cadmium levels were 2.2 and 2.8 μg/L in males and females in area A and 3.4 and 3.9 μg/L in area B. Significant correlations (with adjustment for age) were found between urinary cadmium and urinary levels of protein, β2-microglobulin (not significant in males in area B) and NAG levels. A significant association between urinary cadmium levels and the prevalence (cut-off levels from same referent population as Yamanaka et al. 1998) of abnormal levels of urinary protein (cut-off level of 113.8 and 96.8 μg/L in males and

females), β2-microglobulin (378 and 275 μg/L) (only significant in females in area A), and NAG (8.0 and 7.2 μg/L). The odds ratios (95% CI) for an increase in prevalence of abnormal renal biomarkers were 8.810 (3.401–22.819) and 11.282 (3.301–38.362) for protein in males in areas A and B, respectively, 8.234 (3.696–18.343) and 23.901 (8.897–64.210) for protein in females in areas A and B; 2.558 (1.246–5.248) for β2-microglobulin in females in area A; 47.944 (14.193–161.954) and 9.940 (3.153–31.340) for NAG in males in areas A and B; and 72.945 (21.873–243.263) and 25.374 (9.452–68.117) for NAG in females in areas A and B.

In a re-examination of the populations studied by Yamanaka et al. (1998) and Oo et al. (2000), Suwazono et al. (2000) measured cadmium levels in blood and urine and urinary levels of total protein, β2-microglobulin, and NAG in 1,105 males and 1,648 females over the age of 50 years. The geometric mean concentrations of cadmium in urine were 1.8 and 2.4 μg/g creatinine in males and females, respectively, and blood cadmium levels were 2.0 and 1.8 ng/g in males and females. After adjustment for age, significant associations between urinary cadmium levels and urinary protein and β2-microglobulin in males and females were found. Additionally, blood cadmium levels were significantly associated with urinary protein and NAG levels in males and urinary protein, β2-microglobulin, and NAG levels in females. Cut-off levels (defined as the 84% upper limit values from 424 male and 1,611 female nonsmoking subjects) of 157.4 and 158.5 mg/g creatinine for protein in males and females, respectively, 507 and 400 μg/g creatinine for β2-microglobulin in males and females, respectively, and 8.2 and 8.5 μg/g creatinine for NAG in males and females, respectively, were used to evaluate the prevalence of abnormal levels of renal biomarkers. Logistic regression analysis demonstrated significant associations between urinary cadmium levels and increased prevalence of abnormal levels of total protein (odds ratio of 3.923, 95% CI of 2.2028–7.590) and β2-microglobulin (odds ratio of 2.259, 95% CI of 1.372–3.717) in males; in females, significant associations were found for total protein (odds ratio of 7.763; 95% CI of 4.231–14.243), β2-microglobulin (odds ratio of 2.259, 95% CI of 1.879–4.281), and NAG (odds ratio of 1.882, 95% CI of 1.311–2.702). For blood cadmium levels, the only significant association found was for an increased prevalence of abnormal total protein levels in females (odds ratio of 3.490, 95% CI of 1.661– 7.331).

Jin et al. (2002) examined three populations living various distances from a nonferrous metal smelter. The geometric mean levels of urinary cadmium were 11.18 and 12.86 μg/g creatinine in males (n=294) and females (n=171) in the highly polluted area, 3.55 and 4.45 μg/g creatinine in males (n=243) and females (n=162) in the moderately polluted area, and 1.83 and 1.79 μg/g creatinine in males (n=253) and females (n=155) in the control area. Significant correlations were found between urinary (and blood) cadmium levels and renal biomarkers (β2-microglobulin, retinol binding protein, and albumin). Cut-off values for β2-microglobulin, retinol binding protein, and albumin of 300 μg/g creatinine, 300 μg/g creatinine, and 15 mg/g creatinine, respectively, were used to assess possible dose-response relationships (no additional information was provided); although 300 μg/g creatinine was reported as the cut-off values for β2-microglobulin, subsequent analysis of this data set (Jin et al. 2004c) reported a cut-off value of 800 μg/g creatinine. Significant dose-response relationships between urinary (and blood) cadmium and the prevalence of abnormal levels of renal markers of kidney dysfunction were found.

Unlike the studies discussed above, Hellström et al. (2001) used the incidence of renal replacement therapy (dialysis or kidney transplantation) as an indicator of renal dysfunction, in particular, end-stage renal disease. Residents of Kalmar County, Sweden were divided into four exposure groups: high exposure (workers at cadmium battery production facility), moderate (residents living within 2 km of the cadmium battery facility), low (residents living between 2 and 10 km of the facility), and no exposure (residents living at least 10 km from the facility); all subjects were 20–79 years of age. The Mentel- Haenszel rate ratio (MH-RR) for renal replacement therapy in the cadmium exposed group was 1.8 (95% CI 1.3–2.3); among the environmentally exposed group, the MH-RR was 1.7 (95% CI 1.3–2.3). The age SRRs were 1.9 (95% CI 1.3–2.5) and 1.9 (95% CI 1.2–2.6) for subjects in the moderate exposure group aged 20–79 years or 40–79 years, respectively. The trend for increasing MH-RR with increasing exposure was statistically significant. The age SRRs were not significantly elevated in the low exposure group. The investigators noted that the causes of end stage renal disease were similar in the cadmium exposed and unexposed groups. When only primary renal diseases (excludes renal failure secondary to diabetes or vascular or systemic diseases) were considered, the MH-RR was 1.7 (95% CI 1.1–2.6) for all cadmium exposed individuals and 2.1 (95% CI 1.4–3.2) for cadmium exposed individuals aged 40– 79 years. Although urinary cadmium levels were not assessed in this study, other studies in this area found mean urinary cadmium levels of 1.0 and 0.46 μg/g creatinine in residents living within 0.5 and 0.5– 1 km, respectively, of the battery facility (Järup et al. 1995a) and 0.38 and 0.55 μg/g creatinine in men and women, respectively, living in the contaminated area (Alfvén et al. 2000).

Although there is strong evidence to suggest a relationship between urinary cadmium excretion and excretion of renal biomarkers (particularly low molecular weight proteins such as β2-microglobulin, pHC, and retinol binding protein), there is less agreement about the significance of the early renal changes and the threshold urinary cadmium levels associated with renal damage. Several studies monitoring populations following a decrease in cadmium exposure have attempted to address the question of the reversibility of early renal changes. In Japan, cadmium-contaminated soil used in rice paddies was replaced resulting in decreasing urinary cadmium levels in residents consuming rice grown in these fields (Cai et al. 2001; Iwata et al. 1993; Kobayashi et al. 2008). Although, cadmium exposure decreased over the same time period, the levels of renal biomarkers increased (Cai et al. 2001; Iwata et al. 1993; Kido et al. 1988; Kobayashi et al. 2008) and the prevalence of abnormal values remained higher compared to the reference population (Cai et al. 2001). Although significant decreases in urinary cadmium levels were observed over time, cadmium burdens still remained high; urinary cadmium levels at the later time periods were 6.03–9.6 μg/g creatinine (Cai et al. 2001; Iwata et al. 1993; Kido et al. 1988). Kobayashi et al. (2008) found significant correlations (after adjustment for age) between the amount of time since soil replacement and increases in urinary levels of retinol binding protein, total protein, and glucose (males only). In contrast, a follow-up study of a portion of the population examined by Buchet et al. (1990) found small, but statistically significant, decreases in urinary cadmium levels and urinary levels of β2-microglobulin, NAG, and retinol binding protein (Hotz et al. 1999). Urinary cadmium levels in this study (0.6–0.9 μg/g creatinine at baseline and 0.5–0.8 μg/g creatinine at follow-up) were much lower than levels in the Japanese studies. Although the data are inconclusive, there is some indication of reversibility of renal damage associated with exposure to low levels of cadmium following a substantial decrease in cadmium intake.

Neurological Effects A few studies have reported an association between environmental cadmium exposure and neuropsychological functioning. These studies used hair cadmium as an index of exposure (see Section 3.8.1 for a discussion of the limitations of using hair as an indicator of exposure). End points that were affected included verbal IQ in rural Maryland children (Thatcher et al. 1982), acting-out and distractibility in rural Wyoming children (Marlowe et al. 1985), and disruptive behavior in Navy recruits (Struempler et al. 1985). The usefulness of the data from these studies is limited because of the potential confounding effects of lead exposure; lack of control for other possible confounders including home environment, caregiving, and parental IQ levels; and an inadequate quantification of cadmium exposure.

Reproductive Effects. Several studies have examined the possible association between increased cadmium exposure and male reproductive toxicity; however, most studies focused on sex steroid hormone levels and the results appear to be inconsistent. Akinloye et al. (2006) found significant associations between increasing blood cadmium levels and increasing levels of serum luteinizing hormone, follicle stimulating hormone, prolactin, and testosterone among infertile men (sperm counts <20 million/cm3 or no spermatozoa in semen). A significant association between increased blood cadmium levels and increased serum testosterone was also found in a group of workers with slight to moderate lead exposure (Teli.man et al. 2000); however, neither study controlled for smoking. A study by Jurasovi. et al. (2004) found significant associations between blood cadmium levels and increased serum estradiol, follicle stimulating hormone, and testosterone levels in infertile men after adjusting for age, smoking, alcohol consumption, and biomarkers of lead, copper, zinc, and selenium. In contrast, a study of Chinese men living in areas with high levels of cadmium in rice did not find significant correlations between urinary or blood cadmium levels.and serum testosterone, follicle stimulating hormone, or luteininzing hormone levels after adjusting for BMI, age, smoking, and alcohol consumption (Zeng et al. 2004a). However, they did find that the prevalence of abnormally elevated serum testosterone levels (>95th percentile for controls) increased with exposure to cadmium. Using NHANES III data, Menke et al. (2008) found significant associations between urinary cadmium levels and serum testosterone and estradiol levels, but the associations were no longer significant after adjusting from smoking status and serum cotinine levels. Differences in study populations (e.g., infertile men, background cadmium exposure, high cadmium dietary exposure) and confounding factors (e.g., smoking, lead exposure) limit the interpretation of these results.

Three studies examined the possible association between cadmium exposure and sperm quality. In infertile men, increasing serum cadmium levels were significantly associated with abnormal sperm morphology and decreased sperm counts, sperm motility, and sperm viability (Akinloye et al. 2006). Another study found significant associations between blood cadmium levels and abnormal sperm morphology and decreased sperm motility in workers with slight to moderate lead exposure (Teli.man et al. 2000). As noted previously, neither study adjusted for smoking. No significant correlations between blood cadmium levels and sperm quality were observed in infertile men with or without adjustment for smoking (Jurasovi. et al. 2004). Among men exposed to high levels of environmental cadmium, blood cadmium levels were significantly higher in men with abnormal digital rectal examinations of the prostate and trend analysis

showed a dose-response relationship between cadmium exposure and the prevalence of abnormal prostate specific antigen (Zeng et al. 2004b).

Toxicological Profile for Lead

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 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.

Due to the extent of the lead database, it is impossible to cite all, or even most, of the studies on a specific topic. We 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 this section 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.

Death

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 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 μg/dL had 46% increased all-cause mortality, 39% increased circulatory mortality, and 68% increased cancer mortality compared with those with PbB <10 μg/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 μg/dL compared with those with PbB <20 μg/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 μg/dL, the relative risks of mortality from all causes for those with PbB 5–9 and ≥10 μg/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.

Systemic Effects

Cardiovascular 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 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).

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 metaanalysis 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 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 sinusitus. 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 middleaged 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 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).

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 calcaneous bone lead concentration (OR, 1.86; 95% CI, 1.04–3.32). A 10 μg/g increase in calcaneous 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—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 μg/dL and the mean tibia bone lead concentration was 14.7 μg/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.

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 selfreported 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 μg/dL (range, <1–14 μg/dL). Mean bone lead concentrations were: tibia, 13.3 μg/g and patella, 17.3 μg/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 μg/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 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 sinusitus. 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 ≥96 mmHg. The mean PbBs in cases and controls were 6.9 μg/dL (4.3, SD) and 6.1 μg/dL (4.0, SD), respectively. Mean bone lead concentrations in cases and controls were: tibia, 23.7 μg/g (14.0, SD) and 20.9 μg/g (11.4, SD), respectively; and patella, 35.1 μg/g (19.5, SD) and 31.1 μg/g (18.3, SD), respectively. Risk of hypertension (OR) was assessed using a logistic regression model. Covariateadjusted 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 μg/g) to the mid-point of the highest quintile (37 μg/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) 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, ±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, 0.19–1.44, $p < 0.05$); 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 μg/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 μg/dL) to highest (4.0–31.1 μg/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.

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 ìg/dL, 27%; 12.4–16.6 ìg/dL, 45%; 18.6–22.8 ìg/dL, 19%; and >24.9 ìg/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, 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 ìg/dL in males and 2.6 ìg/dL in females. Based on multivariate linear regression (with log-transformed PbB), increasing covariateadjusted 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 ìg/dL (SD±2.3) and tibia lead was 18.8 ìg/g (SD±12.4). Increasing PbB (but not tibia lead) was significantly associated (linear regression model) with increasing covariate-adjusted systolic (â, 0.99 mm Hg per ìg/dL; 95% CI, 0.47–1.51; p<0.01) and diastolic blood pressure (â, 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 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 ìg/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 (ìg/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 ig/dL) compared to the lower bone lead groups (2–2.4 ig/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 ig/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).

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 (preexposure) to 37 μg/dL at the 0.01 mg/m3 exposure level. ALAD decreased to approximately 80% of 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 preexposure 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).

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 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. 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 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.

Musculoskeletal Effects. 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, socioeconomic 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) 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.

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 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.

Hepatic Effects. In children, exposure to lead has been shown to inhibit formation of the hemecontaining 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 (≥500 μg/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.

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/.

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 doseresponse analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbB <20 μg/dL. In the Kim et al. (1996a) and Muntner et al. (2003) studies, a 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, 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 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 (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.

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 sinusitus. 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 ig/dL (range, <4–26 ig/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. Covariates 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 (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 nondiabetics (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 m2 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 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-glutamyltransferase 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) 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.

Neurological Effects

In studies where adults were exposed occupationally to lead, a number of neurobehavioral parameters were reportedly affected at high lead levels. 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 μg/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 μg/dL and the geometric and arithmetic means were 2.5 and 3.3 μg/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 μg/dL (range, 3.7–20.4 μg/dL), whereas the mean in the exposed groups was 41.1 μg/dL (range, 24.0–72 μg/dL). The groups exposed to lead in the occupational studies consistently 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 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 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 of the eight parameters measured. The same was observed when only workers with PbB ≥40 μg/dL were included in the analysis, but no significant association was found among workers with PbB <40 μg/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 μg/dL (range, 17–186 μg/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 μg/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 μg/dL (range, 6.4–64.5 μg/dL) among the workers and 6.3 μg/dL (range, 3.1–10.9 μg/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 μg/dL) (Yokoyama et al. 1997). Also, an increase in sway with the eyes 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 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.

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 *f*Êg/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 *f*Êg/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 *f*Êg/dL) did not differ from controls. PbB in the referent group averaged 21 *f*Êg/dL, which is high for so-called gcontrols. h 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 via drinking water. The geometric mean PbB of the study population was 11.5 *f*Êg/dL, with a range of 3.3.34 µg/dL and ten children had PbB >25 *f*Êg/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 doseeffect relationship extending from the mean PbB of the highest lead groups (22.1 *f*Êg/dL) down through the mean PbB of the lowest-lead group (5.6 *f*Êg/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 fs 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 fs 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 fs 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 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 *f*Êg/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 *f*Êg/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. Futhermore, 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 fs 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 *f*Êg/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 *f*Êg/dL, the inverse relationship was significant for arithmetic skills, reading skills, and nonverbal reasoning; when restricted to <5.0 *f*Êg/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 *f*Êg/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 *f*Êg/dL) and the lowest at the age of 6 months (3.4 *f*Êg/dL). The mean PbB at 5 years of age was 6.0 *f*Êg/dL. After adjustment for covariables, an increase in lifetime average PbB of 1 μg/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 *f*Êg/dL, an increase in the lifetime average PbB of 1 μg/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 μg/dL was associated with a decline of 8.0 points in IQ, whereas, an increase from 10 to 30 μg/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 μg/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 teacherreported 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 μg/dL were no more likely to be significant than analyses dichotomizing exposure at 5 *f*Êg/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.

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 Torreon, Mexico. Their ages ranged from 6.2 to 8.5 years and their mean PbB was 11.4 μg/dL (SD }6.1 *f*Êg/dL). Fifty-one percent of the children had PbBs .10 *f*Êg/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 fs 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 *f*Êg/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, Tellez-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 BDID 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 fs gender and birth weight. Adjusting for covariates, children fs 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 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.0.01) among children with PbBs <10 μg/dL than in children with PbBs >10 *f*Êg/dL. Moreover, for MDI scores, the slope of the association was steeper over the range up to 5 μg/dL than between 5 and 10 *f*Êg/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 µg/dL (5th.95th percentiles, 4.1.34.8 *f*Êg/dL), while the concurrent mean PbB was 9.7 µg/dL (5th.95th percentiles, 2.5.33.2 *f*Êg/dL); 244 children (18%) had PbBs that never exceeded 10 *f*Êg/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 fs 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 *f*Êg/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 µg/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 *f*Êg/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 µg/dL was significantly greater than the coefficient for the 1,230 children with maximal PbB .7.5 µg/dL (linear *f*À=-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 µg/dL was not significantly greater than that for 1,089 children who had maximal PbB .10 *f*Êg/dL. Potential limitations 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 fs PbB at 24 months, sex, weight, and height. Potential confounders included in the analyses were child fs 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 μg/dL (SD }3.2 *f*Êg/dL) to 7.3 μg/dL (SD }4.3 *f*Êg/dL); plasma lead during pregnancy ranged between 0.014 and 0.016 *f*Êg/dL. Mean PbB in the cord, at 12 months, and 24 months were 6.2 μg/dL (SD }3.9 *f*Êg/dL), 5.2 μg/dL (SD }3.4 *f*Êg/dL), and 4.8 μg/dL (SD }3.8 *f*Êg/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 μg/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 Tellez-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, 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 *f*Êg/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 *f*Êg/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 fs 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 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 *f*Êg/dL), middle (15.20 *f*Êg/dL), and high (>20 *f*Êg/dL). Outcomes examined in the followup included measures of intelligence at ages 2 (MDI of the Bayley Scales), 4 (McCarthy Scales of Children 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 test score; and HOME score. The geometric mean PbB in children in K. Mitrovica increased from 22.4 *f*Êg/dL, at birth, to 39.9 *f*Êg/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 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 *f*Êg/dL, and current PbB up to 5.6 *f*Êg/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 *f*Êg/dL. On the basis of cord PbBs, the children were divided into low-dose (<3 *f*Êg/dL; mean, 1.8 *f*Êg/dL), medium-dose (6.7 *f*Êg/dL; mean, 6.5 *f*Êg/dL), and high-dose (.10 *f*Êg/dL; mean, 14.6 *f*Êg/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 *f*Êg/dL) than children in higher socioeconomic groups. The early postnatal PbBs (range, 10.25 *f*Êg/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 *f*Êg/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 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 *f*Êg/dL); umbilical cord, 6.3 μg/dL (range, 1. 28 *f*Êg/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 fs 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 *f*Êg/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 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 *f*Êg/dL; range, 1. 11.3 *f*Êg/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 μg/dL (range, 2.7.11.8 *f*Êg/dL) for 185 maternal samples and 5.8 μg/dL (range, 2.6.14.7 *f*Êg/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 μg/dL and ranged up to only 14.7 *f*Êg/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 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 *f*Êg/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 Prpi.-Maji. et al. (2000). In the former five studies, the mean PbB was between 10 and 16 *f*Êg/dL, whereas in the Minder et al. (1998) and Prpi.-Maji. et al. (2000) studies, the mean PbBs were 4.4 μg/dL (range, 0.8.16 *f*Êg/dL) and 7.1μg/dL (range, 2.4. 14.2 *f*Êg/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 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 ìg/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 ìg/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 ìg/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 ìg/dL or of tooth lead from 5 to 10 ìg/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 ìg/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 ìg/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 ìg/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 for a PbB increase from 5 to 20

ìg/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 doseeffect 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 ìg/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 ìg/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 ìg/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.

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 nondelinquent 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 ìg/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 ìg/dL, 79% >15 ìg/dL, and 99% >10 ìg/dL. As adolescents, the mean PbB was 2.8 ìg/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 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 Unites States. The estimated air lead concentrations across all counties ranged from 0 to 0.17 ìg/m3. 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.

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 ƒÊg/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 ƒÊg/dL, respectively. Data from past blood lead surveillance indicated a mean childhood PbB of approximately 45 ƒÊg/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 ƒÊg/dL) (Otto et al. 1985). The current mean PbB was 14 µg/dL (range, 6.59 ƒÊg/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 ƒÊg/dL; range, 1.31 ƒÊg/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 ƒÊg/dL. Rothenberg et al. (2000) hypothesized that the negative linear term was 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 leadrelated 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 ƒÊg/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 ƒÊg/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 ƒÊg/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 ƒÊg/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 *f*Êg/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 *f*Êg/dL, n=14) and 53 μg/dL (10.110 *f*Êg/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 *f*Êg/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.

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 another section.

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 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 μg/dL of blood lead (Sanin et al. 2001). The mean infant (at 1 month) and maternal PbBs (1 month postpartum) were 5.6 and 9.7 *f*Êg/dL, respectively; mean umbilical cord lead was 6.8 *f*Êg/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 μg/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 *f*Êg/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 µg/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 *f*Êg/dL; range, 1.27 *f*Êg/dL) was related to lower birth weight (Dietrich et al. 1989). PbBs .10 µg/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 *f*Êg/dL, PbB showed no significant association with low birth weight, preterm delivery, Apgar scores, or small-forgestational 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 *f*Êg/dL, PbBs had a negative impact on birth weight and child fs 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 (Falcon et al. 2003).

Analyses of data for 2,695 children .7 years old from the NHANES II study indicated that PbB (range, 4. 35 *f*Êg/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 *f*Êg/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 µg/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 µg/dL were related with decreased stature (Frisancho and Ryan 1991). The mean PbB in males and females was 10.6 and 9.3 *f*Êg/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 µg/dL range) were 1.2 cm shorter than children with PbBs below the median. Angle and Kuntzelman (1989) also reported reduced rates of height and weight from birth to 36 months in children with PbB of .30 *f*Êg/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 μg/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 *f*Êg/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.

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 *f*Êg/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 *f*Êg/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 fs socioeconomic status. According to the investigators, the results suggested that chronic lead exposure during childhood may result in obesity that persists into adulthood.

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 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.

Toxicological Profile for Selenium.

Much of the selenium released to the environment comes from the burning of coal and other fossil fuels, and from other industrial processes such as the production of rubber. Most of the available toxicity information for oral exposures to selenium compounds comes from domestic or experimental animal exposures to selenite, selenate, selenium sulfides (mixed), and organic selenium compounds (selenocystine, selenomethionine). As indicated previously, we will only present data from human studies.

Some epidemiological studies report data from populations exposed to selenium in the food chain in areas with high selenium levels in soil. It is likely that selenite, selenate, and the selenium found in food and in dietary supplements comprise the majority of selenium compounds to which oral, off-site selenium exposures will occur at or near hazardous waste sites. Aside from the variation in effective dose, the health effects from exposure to selenate, selenite, and dietary selenium are not expected to differ greatly. However, oral exposures to many other compounds of selenium could occur (primarily through soil or edible plant ingestion) if those compounds were deposited at the site, or if local environmental conditions greatly favor transformation to those forms. Heavy metal selenides, aluminum selenide, tungsten diselenides, and cadmium selenide are used in industry and may end up in waste sites. Mobilization of selenium, typically as selenate in water run-off, has the potential to impact nearby plants and animals, thus potentially exposing people through eating game meat, local plants, and agricultural or livestock food products from the area.

Systemic Effects

Gastrointestinal Effects. In humans, gastrointestinal distress, including nausea, vomiting, diarrhea, and abdominal pain, has been reported following ingestion of aqueous sodium selenate

(Civil and McDonald 1978; Gasmi et al. 1997; Helzlsouer et al. 1985; Koppel et al. 1986; Sioris et al. 1980). Two studies provided an estimate of dose. In a case report by Civil and McDonald (1978), diarrhea was observed in a 15-year-old girl about 45 minutes after she swallowed sheep drench containing selenate at a dose of about 22 mg selenium/kg. This effect was observed despite the induction of vomiting shortly after the exposure. In a second case report of a suicide attempt, a 56-year-old man reported that vomiting, diarrhea, and abdominal pain occurred 1 hour after he ingested approximately 11 mg/kg selenium as sodium selenite (Gasmi et al. 1997). Postmortem examinations following two deaths from selenium ingestion revealed dilation of the stomach and small intestine (Carter 1966) and erosive changes of the gastrointestinal tract (Koppel et al. 1986). High (unspecified) levels of dietary selenium compounds have been implicated as causing gastrointestinal disturbances in chronically exposed humans (Smith et al. 1936), but such symptoms are not specific to selenium intoxication.

Endocrine Effects. An examination of thyroid hormone levels in lactating women residing in areas of Venezuela with high levels of selenium in the soil (selenium intake ranged from 250 to 980 μg per day as estimated from selenium content of breast milk) revealed a significant decrease in serum T3 levels, as compared with women having normal selenium intakes (90–350 μg/day), but these hormone levels remained within the normal range (Brätter and Negretti De Brätter 1996). Additionally, a significant inverse correlation for selenium and serum T3 concentration was found using the Spearman Rank test. The study authors noted that the effect of selenium on T3 levels became significant at dietary intake levels of 350–450 μg/day. No significant alterations in serum T4 or TSH levels or correlations with selenium intake were found.

Dermal Effects. Jensen et al. (1984) described both marked alopecia and the deformity and loss of fingernails in a woman who had consumed a selenium supplement containing 31 mg total selenium (in the form of sodium selenite and elemental selenium) per tablet for 77 days. The woman consumed one tablet each day in addition to vitamin supplements (vitamins C, A, D, E, B complex) and a mineral supplement "labeled as containing all 72 trace elements in undefined quantities." In epidemiological studies of populations chronically exposed to high levels of selenium in food and water, investigators have reported discoloration of skin, pathological deformity and loss of nails, loss of hair, and excessive tooth decay and discoloration (Smith et al. 1936; Yang et al. 1983, 1989a, 1989b). The 1989 studies by Yang et al. follow up their original 1983 study of Chinese populations living in areas classified as having low-, medium-, and high-selenium exposure based on local soils and food supplies. The average and standard error of selenium intakes in the low-, medium-, and high-intake regions were 0.0012±0.00009, 0.0037±0.0004, and 0.025±0.001 mg/kg/day, respectively. The whole blood (average ± standard error) concentrations of selenium in the low-, medium-, and high-intake regions were 0.16±0.00, 0.35±0.02, and 1.51±0.05 mg/L, respectively. The estimated daily dietary selenium intake required to produce these symptoms in an area of China characterized by endemic selenosis was at least 0.016 mg selenium/kg/day (Yang et al. 1989a). This corresponds to a blood concentration of 1.054 mg/L and an estimated daily intake of 0.91 mg/day, assuming a 55-kg Chinese man or woman and using the regression analysis provided by Yang et al. (1989b). The NOAEL from the highest intake population not affected by nail disease is 0.015 mg selenium/kg/day, which corresponds to a blood concentration of 0.97 mg/L. Foods that contributed the greatest levels of selenium were smoked pork, coal-dried corn, chestnuts, pumpkin seeds, dried fruits, and garlic.

It has been noted that the selenosis problem in China began when coal with high levels of selenium was burned as the main source of fuel (Whanger 1989). Food was cooked and dried over the open flame, adding selenium to the food. In addition, the people breathed large amounts of smoke, but the contribution of volatilized selenium to the total dose of selenium has not been adequately characterized (Whanger 1989). Coal was also burned on the fields as a fertilizer source. Environmental selenium concentrations in the low-, medium-, and high-intake regions were 0.37–0.48, 0.73–5.66, and 7.06–12.08 mg/kg in soil, and 370, 1,720, and 12,270 µg/L in water, respectively (Yang et al. 1989b).

Neurological Effects

Following acute oral exposure to selenium compounds in humans, aches and pains and irritability (Civil and McDonald 1978), as well as chills and tremors (Sioris et al. 1980) have been reported. The dizziness associated with selenium inhalation exposure has not been documented after selenium ingestion.

In a 1964 study, Rosenfeld and Beath reported listlessness, a general lack of mental alertness, and other symptoms of selenosis in a family exposed for approximately 3 months to well water containing 9 mg selenium/L (0.26 mg selenium/kg/day from drinking water). All of the symptoms resolved after use of the seleniferous water was discontinued. Because Rosenfeld and Beath (1964) did not estimate the family's exposure to dietary selenium, it is not possible to identify the total daily selenium dose associated with the symptoms of selenosis in this family.

Reproductive Effects

Selenium levels in blood plasma began to change within 3 days of starting the low- and high-selenium diets and progressively continued throughout the study (Hawkes and Turek 2001). By week 17, mean plasma selenium concentrations had increased by 109% in the high-selenium group and decreased by 38.5% in the low-selenium group. A similar pattern of changes occurred in seminal plasma selenium, although selenium levels in sperm did not change significantly in either group. Mean sperm motility was significantly different in the low-selenium subjects and high-selenium groups at week 13, but not at weeks 8 or 17. The fraction of motile sperm increased an average of 10% in the low-selenium group by week 13, and was essentially the same as the baseline value at week 17. Sperm motility decreased an average of 32% in the high-selenium group at week 13, and ended 17% lower than baseline value at week 17. ANOVA showed a significant main effect of dietary selenium on sperm motility, as well as a significant selenium x time interaction, indicating that the group responses diverged over time. Baseline and ending motile sperm fractions in the high-selenium group were 0.588±0.161 and 0.488±0.193, respectively; ≥50% motility is considered normal (FDA 1993). The decrease in sperm motility in the high-selenium group cannot be clearly attributed to selenium because the effect was not consistent over the duration of exposure, is unlikely to be adverse because it is at the low end of the normal range, and is not accompanied by any significant changes in other indices of sperm movement (progression or forward velocity), or sperm numbers or morphology. Additionally, there were no effects of selenium on serum levels of reproductive hormones, and changes in thyroid hormones, which could affect sperm function, were not outside normal ranges.

A nonsignificant increase in spontaneous abortions (relative risk [RR]=1.73; 95% CI=0.62–4.80) was reported among births in the municipality of Reggio Emilia, Italy, where women had been exposed to drinking water containing 7–9 ug/L levels of selenium (as selenate, reported estimated intake 10– 20 ug/day) between 1972 and 1988 (Vinceti et al. 2000a). This study is limited by a level of selenium in water that is not considered high, lack of data on selenium status, and insufficient information on confounding variables. Selenium deficiency has been implicated as a risk factor for recurrent miscarriage in humans (Al-Kunani et al. 2001; Barrington et al. 1996, 1997; Güvenc et al. 2002; Kumar et al. 2002).