HEALTH EFFECTS
WHAT ARE THE HEALTH EFFECTS?

Although much early work focused on the effect of lead on behavior and cognition, lead toxicity can affect all tissues and organs of the body. Lead in humans, as measured in blood, bone or teeth, has been shown to have detrimental effects on the peripheral and central nervous systems, the kidneys, blood pressure, fertility, and child birth (223). As noted earlier, recent evidence suggests that there is no threshold for the deleterious effects of lead, especially for developing fetuses and young children (23,92,107,149).

Although lead experts agree that children are more susceptible to lead poisoning than adults, researchers have begun to pay more attention to the effects of low-level chronic lead exposure in adults. Most recently there has been an outpouring of research on the long-term health impacts of earlier exposures to lead in adulthood. In January 2007, the journal Environmental Health Perspectives featured a cover article titled “The Weight of Lead: Effects Add Up in Adults,” which reviews several of the newest studies that have linked chronic, low level lead exposure to diseases and disorders of the heart, kidneys and brain (260).

The following is a literature review of the some of the more recent research regarding the impacts of lead exposure on human health. This discussion focuses primarily on inorganic lead compounds (lead, its salts, and oxides/sulfides), the predominant forms of lead in the environment. The available data on organic (i.e., alkyl) lead compounds, such as those added to gasoline, suggest that the toxicokinetic profiles and toxicological effects of these compounds are qualitatively and quantitatively different from those of inorganic lead.

TYPES OF HEALTH EFFECTS

Neurological

Children

Many of the health consequences of lead poisoning are difficult to detect at an early age, especially when lead exposure is not suspected. Nevertheless, extremely small amounts of lead can irreversibly disturb brain development and the creation of neural pathways, which begin early during pregnancy and are largely completed around age 7. Thus, early blood-lead screening is recommended for children and pregnant mothers, especially those at high risk for lead exposure, to ensure that any exposure is eliminated as soon as possible.

The developing nervous system is especially susceptible to lead poisoning (7). Several prospective longitudinal epidemiological studies have been initiated in cities across the U.S. and the world to study birth outcomes and the neurodevelopmental effects of lead exposure in children. These studies include cohorts of children and mothers in Boston, Massachusetts; Cincinnati and Cleveland, Ohio; Rochester, New York; Port Pirie and Sydney, Australia; Mexico City, Mexico; and Titova Mitrovica and Pristina, Yugoslavia. In general, the investigators of these studies have followed their cohorts of children from birth to childhood and have extensively documented their lead exposure and BLLs, social and medical history, intellectual attainment, neuromotor function, academic achievement and behavior (13,81). The findings from these studies have (1) consistently found correlations between lead exposure and abnormal cognitive and neurobehavioral development, and (2) consistently shown no threshold for lead’s toxic effects.

In the late 1980s and early 1990s, data from these prospective studies revealed that childhood lead exposure is negatively associated with intellectual performance. The first round of results from the Boston, Cincinnati and Port Pirie studies demonstrated that lead-associated IQ deficits could be detected in the first two years of life (22,83,302). For example, in the lead-smelting town of Port Pirie, South Australia, over 600 children were studied, with BLLs measured before birth (maternal), at birth, at ages of 6 and 15 months, and annually from 2–7 years of age (302). In 1988, Wigg and associates observed an inverse association between the BLL measured at 6 months of age and mental development at 2 years of age (302). In a follow-up study in 1992, Baghurst and associates compared the BLLs and IQ scores of 494 seven-year-old children in the Port Pirie cohort. The findings of the study showed that a BLL increase from 10 µg/dL to 30 µg/dL resulted in a 4–5% loss in IQ points (13). These results were consistent with similar research conducted around the same time elsewhere (25,82). In 1994, Joel Schwartz of the Harvard School of Public Health conducted a meta-analysis of seven longitudinal and cross-sectional studies that studied BLLs and IQ and found that an increase in blood lead from 10 µg/dL to 20 µg/dL was associated with a decrease of 2.6 IQ points (249).

Several recent studies strongly suggest that BLLs less than the current CDC definition of elevated blood lead, i.e., 10 µg/dL, are associated with measurable declines in intelligence and mental development, and that these lead-associated decrements are greater below 10 µg/dL than above (46,161,271) (Figure 5). These findings suggest that the effects are not linear, with greater relative damage occurring at lower lead levels. Canfield and associates used a nonlinear mixed model and demonstrated that IQ declined 7.4 points in children with lifetime BLLs (calculated from seven measurements between 6 months and 5 years) up to 10 µg/dL and more gradually—a
What are the health effects?

Decline of 2.4 points—in children with lifetimes BLL between 10 µg/dL and 30 µg/dL (46). Reinforcing these findings, a meta-analysis by Lanphear and associates showed that, for a given increase in blood lead, intellectual deficits were significantly greater for children with a maximal BLL < 7.5 µg/dL than for those who had a maximal BLL ≥ 7.5 µg/dL (46). These studies provide strong evidence that there is no threshold for the adverse health effects of lead and further suggest that “more U.S. children may be adversely affected by environmental lead than previously estimated” (161).

Currently researchers are also using the longitudinal studies to try to pinpoint the critical periods when lead causes the most neurological damage. NHANES data consistently show that the highest geometric mean BLLs occur in children aged 1–3 years (53). Our study in Galveston similarly showed peak BLLs between 2 and 3 years of age. Bellinger and associates found that slightly elevated BLLs at age 2 years are associated with intellectual and academics performance deficits at age 10 years (25). However, the studies by Canfield and associates (46), Téllez-Rojo and associates (271) and Lanphear and associates (161) suggest that IQ deficits may be strongly affected by longer term exposure as well. This raises interesting questions about on-going external and endogenous exposure, as well as providing some limited evidence to suggest that significantly reducing or eliminating exposure may affect long-term intelligence positively.

These cohort studies and many other studies have shown that low levels of lead exposure also negatively impact learning and academic achievement (158,199,298), psychomotor development (29,77,81,82,271), hearing (250) and a wide array of cognitive functions, such as attention (21,44,65,234), language (95,187), memory (158) and visual-motor integration (12,81,234). Both epidemiological and experimental animals studies have also linked childhood lead exposure to aggressive and delinquent behavior and attention deficit hyperactivity disorder (ADHD) (36,42,60,64,172,175). Some studies have further suggested that these effects persist into later childhood and young adulthood (214,266,275). See “What Are the Costs of Lead Poisoning: Crime” (page 29) for a broader discussion of the effects of lead poisoning on society.

The advancements made in medical technology and the field of neuroscience have aided researchers in better understanding lead-induced neurological pathologies and their underlying mechanisms. For example, in 2006, Yuan and associates used MRI technology to study effects of low-level childhood lead exposure on language areas of the brain (306). The study subjects were 42 young adults who had previously participated in the Cincinnati Lead Study during infancy and childhood. Among the subjects with higher mean childhood BLLs, the researchers found significantly diminished activation of the left frontal cortex and left middle temporal gyrus, which are traditionally areas responsible for speech generation and language processing (306). This study is not only one of the first studies to localize the effects of lead poisoning in the brain, but is also consistent with many other studies that indicate that childhood lead exposure has a significant and persistent impact on the brain.

A good deal of recent research focuses on exposure of the fetus. Several recent studies have found evidence that low levels of prenatal lead exposure, caused in part by mobilization of maternal lead stores from bone during pregnancy, during critical windows of fetal neurodevelopment may play a major role in subsequent deficits. It is known that brain and spinal cord development and the creation of neural pathways begin early during pregnancy. Experimental studies in mice suggest that memory, in particular, may be affected by prenatal lead exposure (75). In humans, Hu and associates studied 146 mother and infant pairs, measuring lead levels in maternal plasma and whole blood during each trimester and in umbilical cord blood at birth (136). When the infants...
were 1 and 2 years of age, the researchers measured the BLLs of the children and administered the Bayley Scales of Infant Development, the most commonly used mental development test for infants (136). The investigators found that first trimester BLLs were stronger predictors of lower Mental Development Index (MDI) scores than the 2nd and 3rd trimester and postnatal BLLs (136). Gomaa and associates similarly found that higher lead levels in maternal trabecular bone (e.g., patella bone), the primary endogenous source of prenatal exposure, are associated with impaired mental development in infants at 2 years of age (113). Increasingly healthcare professionals advocate screening the lead levels of all women or at least high-risk women of child-bearing age. High-risk women include those who are poor, live in substandard housing or near major roadways, are of color, or immigrated from countries where lead is still used in gasoline.

Adults
In 2002, investigators from University of Maryland and John Hopkins University published a study that demonstrated that BLLs ≥ 10 µg/dl in adults were associated with increased risk of cardiovascular disease and all-cause mortality (178). A more recent study found that adults with BLLs as low as 2.0 µg/dl had an increased risk for myocardial infarction and stroke mortality (190). Recent studies have also shown that lead exposure during adulthood may have an adverse impact on the brain, including an increased risk for brain cancer. For example, a study published in 2006 in the International Journal of Cancer found that individuals with high levels of occupational lead exposure were more likely than unexposed workers to die from brain cancer (290).

In the past 15 years, several groups of investigators have studied cohorts of American and Korean lead-exposed workers to determine whether cumulative lead exposure is associated with degenerative effects in the brain (246,248,264). Their studies demonstrate that cognitive function declines as a function of cumulative lead dose. The American cohort included 535 former organolead manufacturing workers from New Jersey who had been free of occupational lead for approximately 16 years and had low BLLs at the start of the study (248). The researchers measured tibia lead with X-ray fluorescence to evaluate cumulative lead dose (see also How Is Lead Exposure Measured?” page 21) and administered a battery of neurobehavioral tests over four years (248). Peak tibia lead was associated with declines in test scores for verbal memory and learning, visual memory, executive ability and manual dexterity. Because a longitudinal decline in test scores was observed over the four years, the investigators concluded that past lead exposure may lead to a progressive decline in cognitive function (248). In a follow-up study, the investigators used magnetic resonance imaging (MRI) to examine the workers’ brains (265). In this study, higher peak tibia lead was associated with a greater number of white matter lesions (WML) and decreased volume of the frontal and parietal lobes, gray matter, and the total brain (265). Currently, Stewart and Schwartz are conducting a second MRI study to see if former lead exposure causes or accelerates on-going changes in brain structure (264).

Additionally, to determine whether the study results of the two occupational cohorts are applicable to the general population, Shih and colleagues conducted a similar study in 985 50–70-year-old Baltimore residents (253). Unlike the two occupational cohorts, this cohort included both sexes, was racially diverse, and was chronically exposed to environmental lead sources, such as leaded gasoline emissions, during the early stages of their lifetimes (253). The researchers observed an association between higher tibia lead levels and decreased cognitive function, which suggested that early episodes of lead exposure may cause persistent changes in the brain in adulthood (253). As a result, both teams of researchers believe that “a significant proportion of what is considered “normal” age-related cognitive decline may, in fact, be due to past exposure to neurotoxicants such as lead” (264).

Occupational exposure to lead has also been linked to a decrease in nerve conduction velocity, a form of peripheral neuropathy. The totality of current data suggests that peripheral neurological damage starts around a mean BLL of 30–40 µg/dL. Recent research is examining the potential effect of early exposure on neurodegenerative diseases such as Alzheimer’s and Parkinson’s Disease (307). Coon and associates recently used a matched case-control study design to examine the potential relationship between Parkinson’s Disease (PD) and lifetime lead exposure (70). They found that PD was elevated by > 2-fold (odds ratio = 2.27 [95% CI: 1.13–4.55]) for individuals in the highest quartile for lifetime lead exposure, relative to the lowest quartile, adjusting for age, sex, race, smoking history, and coffee and alcohol consumption.

Cardiovascular and Renal
Although lead has been shown to produce various cardiovascular and renal effects in animals, the end points of greatest concern for humans at low exposures and low BLLs are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistically
related and, furthermore, can be confounders and covariables in epidemiological studies. Another cardiovascular effect that has been noted in association with higher body burdens of lead is cardiac arrhythmias (32), which may be related to impairment of peripheral nerve conduction.

**Blood Pressure**

The effect of lead on blood pressure has been documented in numerous studies, although some of the findings are equivocal. For example, a meta-analysis by Nawrot and associates that examined the effect of a doubling of blood lead on systolic and diastolic blood pressure in a total of 31 studies and 58,518 subjects found the increase to be small, around 1 mm Hg (209).

A number of investigators, however, claim that BLLs, as used in Nawrot’s analysis, may not provide the most relevant estimate of exposure (62), and more recent studies have included patella and tibia lead levels in their analyses. Tibial lead, for example, has been shown in many studies to be associated with hypertension (132,167,186). There is also some evidence that some subpopulations, including Blacks, pregnant women, those with existing hypertension and postmenopausal women, may be especially affected. In addition, even a small elevation in blood pressure in association with low-level lead exposure has significant public health consequences, given the ubiquity of exposure and the importance of hypertension as a cause of disability and death.

It is unclear whether the blood-pressure effects are a function of cumulative or acute exposure to lead or both. In several studies of occupationally exposed workers, BLLs have correlated with blood pressure but other studies suggest that this may be a function of bone-lead mobilization and/or concomitant elevated plasma levels of lead. Schwartz and associates conducted a cross-sectional analysis of 543 former American lead workers to compare the associations of blood and tibial lead levels with systolic and diastolic blood pressure and hypertension status (247). The investigators found that blood lead, but not tibial lead, was significantly associated with both systolic and diastolic blood pressure, with a 1 µg/dL increase in BLL associated with a 0.50 mm Hg increase in systolic blood pressure and a 0.31 mm Hg increase in diastolic blood pressure (247). The subjects of this study are unique because they had all been chronically exposed to significant levels of lead an average of 18 years previously. At the time of the study, the mean BLL was 4.6 µg/dL, which the investigators believe resulted primarily from mobilization of bone-lead stores. Thus, the results of this study suggest that prior chronic occupational exposure can lead to future elevations in blood pressure (247).

Using the same population of occupationally-exposed workers, Glenn and associates conducted a longitudinal study to determine whether the blood pressure effects were acute or chronic in nature. The investigators measured blood and tibial lead and recorded 3–4 blood pressure measurements taken over a 4-year period (109). They found that both baseline blood lead and year three tibial lead were strong, independent predictors of average annual change in systolic blood pressure. These findings suggest that lead can have persistent effects on systolic blood pressure in adult men. The authors conclude that “continued efforts to reduce lead exposure in the young may contribute to the prevention of age-associated elevations in blood pressure and subsequent cardiovascular disease” (109).

Several major longitudinal studies, including the Normative Aging Study of health in males and the Nurses Health Study in females, have measured blood and bone lead in more recent years. In the Normative Aging Study, after controlling for numerous confounders, an increase in patella lead from the lowest to the highest quintile was associated with a 71% increase in hypertension (62). The observation that risk of hypertension increases in association with increasing patella bone-lead concentrations, but not with tibia or blood lead, is consistent with a similar finding in middle-aged females derived from the Nurses Health Study (151) Korrick and associates found that an increase from the 10th to 90th percentile of patella lead was associated with approximately a 2-fold (95% CI: 1.1, 3.2) increased risk of hypertension. In another study, Nash and associates used NHANES data to study postmenopausal women and found strong associations between BLLs and hypertension. For example, women in the highest quartile of blood lead (4.0–31.1 µg/dL) were more than 8 times more likely to have diastolic hypertension than women in the lowest quartile of exposure (0.5–1.6 µg/dL) (205).

The biologic mechanisms underlying these lead-induced blood pressure effects are attributed to various mechanisms, including: (1) oxidation and inactivation of endogenous nitric oxide (NO) by oxygen radicals; (2) increased sympathetic activity and circulating noradrenaline coupled with decreased vascular and elevated renal beta-adrenergic receptor density; (3) increased angiotensin-converting enzyme activity and plasma renin, angiotensin II and aldosterone levels; (4) heightened kininase I and kininase II activities; (5) inhibition of vascular smooth muscle Na+/K+ ATPase causing a rise in cellular Na+ and Ca2+ stores; and (6) increased endothelin and thromboxane production (16,123,124,217,291-294).
Renal
Hypertension and renal dysfunction are often interconnected, as noted earlier. Lead-induced damage to kidneys in humans has been reported in a number of studies. Adverse symptoms include effects on glomerular filtration evident at BLLs below 20 µg/dL, enzymuria and proteinuria becoming evident above 30 µg/dL, and severe deficits in function and pathological changes occurring in association with BLLs exceeding 50 µg/dL (7). Using a case-control design, Muntner and associates recently studied 55 African Americans with end-stage renal disease (ESRD) and 54 age- and sex-matched African-American controls without renal disease (203). After adjusting for potential confounders, the odds ratio of ESRD associated with a tibia lead ≥ 20 µg/g was 1.55 (95% CI: 0.55, 4.41) (203). In a study of 15,211 subjects from the NHANES-III, elevated serum creatinine and chronic kidney disease were 2.41 and 2.60 times more likely, respectively, in those in the highest quartile of blood lead compared with those in the lowest quartile (202).

Immunological
The immune system has been shown to be one of the more sensitive targets of lead-induced toxicity. Most of what is currently known about the immunotoxic effects of lead has come from animal studies. Immunologic effects that have been reported following exposure to lead include increased susceptibility to viral infection in mice (99,122) and chickens (305); increased susceptibility to bacterial challenge in rats (69) and mice (85,127,152); an increase in autoimmune diseases such as systemic lupus erythematous in mice (137); and increased cancer in mice (145) and hamsters (148).

Experimental studies with three species (mice, rats, and chickens) have shown that exposure to lead produces immune system changes in the fetus at much lower levels than in the adult. Blood-lead levels as low as 5–18 µg/dL have been shown to be immunotoxic in the fetus, whereas levels well above 40 µg/dL are required for comparable effects in adults. Lead-induced immune changes in the fetus can persist long after reduction to background levels (41,80). When pregnant mice were exposed to lead acetate in their drinking water, a substantial amount of lead was transferred transplacentally and lactationally from the mother to offspring (259). Two-week-old neonates exposed to lead via the mother before and/or after birth had significantly higher plasma immunoglobulin E (IgE) levels and lower splenic white blood cell numbers than did age-matched controls. It is not known precisely when during postnatal maturation that fetal hypersensitivity to lead declines to adult levels (80).

Short-term exposure to lead, spanning different portions of embryonic development, can produce different immune outcomes in the juvenile and adult offspring (79,177). The window of hypersusceptibility for lead-induced T-cell alterations has been shown in animal studies to occur in the second half of embryonic development. This period corresponds to the seeding of the thymus with bone marrow-derived precursors followed by thymocyte maturation (80).

It appears that at low lead levels the spectrum of the types of immune cells, factors and antibodies produced may be considerably shifted. In a recent literature review, Dietert and Piepenbrink from Cornell University report that lead at low levels disrupts immunological regulation and causes shifts in functional capacity (80). They believe that these changes in immune regulation and function are responsible for the major immunotoxic effects associated with lead exposure, which include increased production of IgE, modulation of macrophage function, and suppression of the T-helper cell 1 (Th1)-dependent delayed type hypersensitivity response (80). All of these effects may influence host susceptibility to a wide array of diseases, as well as to allergic and autoimmune conditions.

Abnormal antibody production has been documented in studies of children and adults exposed to environmental lead. Lutz and associates conducted a survey of the immune system’s function in a cohort of 279 children aged 9 months to 6 years, with blood-lead levels ranging from 1 to 45 µg/dL (179). A statistically significant relationship between IgE and blood-lead levels was found in this population. As the BLL increased, the IgE level increased. Controlling for variables such as age, race, gender, nutrition and socioeconomic level, the investigators showed that levels of IgE still increased significantly with BLLs. A possible role for ingested lead in allergic immune responses was noted by the authors, since the development of allergic symptoms is often preceded by an increase in IgE (179).

In a study by Sun and associates of Chinese children 3–6 years old, IgG, IgM, and IgE levels in 38 children with BLLs ≥ 10 µg/dL were compared with those in 35 children with BLLs < 10 µg/dL (269). In this study, a significant association between immunoglobulins and BLLs was found only when the cohort was stratified by sex. IgG and IgM were significantly lower and IgE was significantly higher in high-dose females (N = 16) than in control females (N = 17). No significant association between immunoglobulins and BLLs was seen among males. The authors suggest that modulation of sex steroid hormones by developmental exposure to lead may affect the immunoglobulins.

Sarasua and co-workers conducted a more extensive study of 2,041 children and adults from four communities with elevated soil levels of cadmium and lead (N = 1,561) and two communities with non-elevated levels (N = 480). Mean BLLs were 7 µg/dL for participants aged 6–35 months; 6 µg/dL for participants aged 36–71 months; 4 µg/dL for participants aged 6–15 years; and 3.4 µg/dL for participants aged 16–75 years. Parameters monitored included IgA, IgG, IgM, and peripheral blood lymphocyte phenotypes (T cells, B cells, NK cells, and CD4/CD8 subsets). The results of the multivariate analyses indicated no marked differences in any of the immune marker distributions attributed to lead for adults.
or children over 3 years of age. However, in children under 3 years of age, BLLs >15 µg/dL were associated with increases in IgA, IgG, IgM, and circulating B lymphocytes (243). The correlation of increasing IgE levels with increasing BLLs at this early age may be indicative of an increased predisposition to allergies and asthma later in life. These results are also consistent with other studies linking heavy metals with autoimmune disorders (243).

Endocrine and Reproductive
Lead has been reported to decrease steroid sex hormone levels in juvenile rats after uterus exposure to lead acetate (238,301). Effects on thyroid, pituitary and testicular hormones, as a result of lead exposure, have been reported in a number of occupational studies as well as in the general population. High levels of lead exposure are associated with increased rates of miscarriage in pregnant women and impaired sperm production in men (7). A study of 668 pregnant women in Mexico City indicated that even low-to-moderate levels of lead exposure may increase the risk of losing a pregnancy in the first trimester. The authors found a 1.13-fold increase in the risk of spontaneous abortion per every µg/dL increase in blood lead (35). Mean BLLs in “cases” (35 women who aborted before week 21) and “controls” (women whose pregnancies extended beyond week 20) were 12.0 and 10.1 µg/dL, respectively.

Another study compared pregnancies of 531 women living in Port Pirie, a lead smelter community in South Australia, with pregnancies of 171 women in the surrounding rural area and neighboring towns. There was no association found between BLLs and spontaneous abortions; however, 22 of 23 miscarriages and 10 of 11 stillbirths occurred among the Port Pirie residents, with only 1 miscarriage and 1 stillbirth occurring among residents outside Port Pirie (14). Maternal BLLs were actually lower in the cases of stillbirth than in the cases of live birth, but fetal and placental levels were higher in the still births than in the live births. It has been suggested that a reduction in maternal blood-lead during pregnancy may be an indication that lead is being transferred from the mother to the fetus, a condition that could be toxic to the fetus (8,74).

There is some evidence that lead exposure may cause reduced fertility in men when BLLs are above roughly 30-40 µg/dL (7). Studies suggest that lead-induced reductions in sperm concentration may occur in men with mean BLLs > 40 µg/dL but not in men with lower levels.

An analysis of data on BLLs for 4,391 U.S. children, ages 1–7 years, collected in the NHANES-III (1988–1994) showed that increasing BLLs (1–72 µg/dL) were significantly associated with decreasing body stature (length or height) and head circumference, after adjusting for covariates (15).

Cancer
Although there is no conclusive proof that lead causes cancer in humans, a number of recent studies, particularly in animals, suggest some correlation between lead exposure and cancer. Kidney tumors, for example, have developed in rats and mice that were given large doses of some kind of lead compounds. The Department of Health and Human Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from animal studies, and the EPA has determined that lead is a probable human carcinogen. The International Agency for Research on Cancer (IARC) has determined that inorganic lead is probably carcinogenic to humans. IARC determined that organic lead compounds are not classifiable as to their carcinogenicity in humans based on inadequate evidence from studies in humans and in animals.

Almost all of the information regarding lead exposure and cancer in humans is derived from studies of lead workers and involves exposure to inorganic lead, with equivocal results. One recent study of the general public used data from the National Longitudinal Mortality Study (NLMS) to study lead exposure and the risk of brain cancer in a subset of 317,968 individuals for whom occupational information was available (290). After adjusting for the effects of age, gender and several other covariates, brain cancer mortality rates were greater among individuals in jobs potentially involving lead exposure, compared with those in jobs that did not involve exposure to lead (hazard ratio = 1.5; 95% CI = 0.9, 2.3), with indications of a dose-response trend.

Mortality
Most mortality studies concerning lead have been based on occupational exposure. In a study published in 1985, for example, Cooper and associates reported on their study of two cohorts of male lead workers: 4,519 battery plant workers and 2,300 lead production workers, all of whom had been employed for at least one year between January 1, 1946, and December 1970, and who were followed for 34 years (71). Mortality from all causes combined was significantly greater than expected in each cohort, the standardized mortality ratio (SMR) being 107 and 113, respectively. Among the battery plant workers the greater than expected mortality rate resulted in large part from a significant number of
excess deaths from malignant neoplasms (SMR 113), other hypertensive disease (mainly renal) (SMR 320), chronic nephritis (SMR 222), and a group of ill-defined conditions (SMR 355). Among the lead production workers the pattern was similar, with a significant number of excess deaths from hypertensive disease (SMR 475), hypertensive heart disease (SMR 203), chronic nephritis (SMR 265), and ill-defined conditions (SMR 214). There were no excess deaths from malignancies of the kidney, brain, or lymphopoietic system in either cohort. The authors note that it is impossible to relate the observed mortality to levels of lead exposure, in part because of meager quantitative information prior to 1960, although past exposures had been very high. Also, the effects of ethnicity, diet, alcohol, and cigarette smoking could not be ruled out as possible confounding etiologic factors.

Several other occupational studies have found similar results, generally finding a suggestive link between lead exposure and death from cardiovascular or renal disease, and little or equivocal potential associations with other diseases. For example, Fanning reported on a case-control study of 867 deaths between 1926 and 1985 of men who had relatively high occupational lead exposure, compared with 1,206 who died during the same period and whose lead exposure had been low or absent (93). He found a statistically significant excess of deaths from cerebrovascular disease between 1946 and 1965, as well as a decreasing trend in the odds ratios for deaths from this cause between 1926 and 1985, with no difference between the two groups over the past 20 years. Fanning attributes this to the introduction of stricter standards of lead control. Few mortality studies of the general public have been done. In 2002 Lustberg and Silbergeld used data from the NHANES-II, a cross-sectional survey of the U.S. general population conducted from 1976 to 1980 (178). They followed 4,292 individuals aged 30–74 years with BLL data through December 31, 1992. After adjusting for potential confounders, all-cause mortality in individuals with a BLL between 20 and 29 µg/dL was increased by 46%, circulatory mortality by 39%, and cancer mortality by 68%, compared with those with a BLL < 10 µg/dL. They also found that non-White subjects had significantly increased mortality at lower BLLs than did White subjects, and that smoking was associated with higher cancer mortality in those with a BLL of 20–29 µg/dL, compared with those with BLL < 20 µg/dL.

A more recent study found an association between BLLs and increased all-cause and cardiovascular mortality at substantially lower BLLs than previously reported (190). Menke and associates studied 13,946 U.S. adults with BLL data who had participated in the NHANES-III (1988–1994), following the participants for up to 12 years. The mean BLL in study participants was 2.58 µg/dL. In the U.S. 99% of adults have BLLs below 10 µg/dL (204). After adjusting for numerous potential confounders, such as age, race/ethnicity, smoking, income, education, hypertension and weight, the investigators found that those in highest tertile of blood lead (≥ 3.62 µg/dL) were 25% more likely than those in the lowest tertile of lead (< 1.94 µg/dL) to die from all causes (hazard ratio 1.25; 95% CI: 1.04 to 1.51), and 55% more likely to die from cardiovascular causes (hazard ratio 1.55; 95% CI: 1.08 to 2.24). The importance of this study is that it suggests that what were thought to be relatively low levels of lead in adults are associated with significant mortality. Indeed the association between blood lead and cardiovascular mortality was evident at levels as low as 2 µg/dL, a level that 38% of the U.S. adult population exceeded in the 1999–2002 NHANES.

Although deaths due to acute lead poisoning are relatively rare and have declined significantly over the last few decades, they still occur, especially among Blacks in the South. Kaufmann and co-workers reviewed death certificates of approximately 200 lead poisoning-related deaths that occurred between 1979 and 1998 (143). The majority were male (74%), African American (67%), 45 years of age or older (76%), living in the South (70%), and living in cities with a population < 100,000 (73%). Moonshine ingestion was a key source of high-dose fatal lead exposure in these adults.

Other
One of the more important recent findings—as discussed in the previous sections—is that lead not only has profound effects on children, but that early exposure has a lasting effect on adults as well. These exposures in turn can expose children during pregnancy and lactation, and can affect fertility and birth outcome. Occupational “take-home” lead can continue to expose children, and most operations—such as painting bridges with lead-based paint or renovating a lead-contaminated home—increase environmental loads nearby and expose children and adults to elevated levels of lead. Thus there is a major effort to significantly reduce occupational exposure and the use of all nonessential lead, and to determine the most appropriate biomarkers of lead exposure to better quantify its effects. For adults, measurement of bone lead appears necessary. Schwartz and Hu argue strongly that OSHA must lower its occupational standards, which were put in place based on data from the 1970s. They argue that the current standard of a BLL of 40 µg/dL over a working lifetime leads to an unacceptable cumulative dose, something that OSHA was not measuring.

“Although deaths due to acute lead poisoning are relatively rare and have declined significantly over the last few decades, they still occur, especially among Blacks in the South.”
recent paper by Rezende and associates describes several homeostasis have been found to also affect lead toxicity. A is not surprising then that genetic variations that affect calcium nutritional deficiency, osteoporosis or normal aging process. It for calcium ions in homeostatic processes. Lead in the blood and re-enter the blood during pregnancy, lactation, periods of transport mechanisms. Likewise, by the same mechanisms as for calcium, accumulated lead may be mobilized from bone and to compete with calcium for common binding sites and is able to leave and accumulate in bone because it is able to compete with calcium for binding sites, inhibiting enzyme activity or altering the transport of essential cations such as calcium. At the subcellular level, the mitochondria appear to be a key target for the toxic effects of lead in many tissues. Mitochondria are the cellular powerhouse that converts food to energy, and are also involved in controlling the intercellular movement of calcium. Lead has been shown to selectively accumulate in the mitochondria and there is evidence that it causes structural injury to this organelle and thereby impairs its basic functioning and may increase the rate of cell death. By affecting cellular viability and communication, lead disrupts multiple processes and can lead to structural abnormalities, including failure of neurons to properly differentiate and migrate in the brain, and failure of key “pruning” activities in the brain that are necessary for establishing functional pathways for memory and other processes. In experimental studies, lead has been shown to change the dendrite numbers and branching patterns in neurons in the hippocampus and cortical areas of the brain (146). Trope and associates used magnetic resonance spectroscopy (MRS) to monitor brain metabolism in lead-exposed and nonlead-exposed individuals. The found significantly reduced levels of N-acetylaspartate/creatine and phosphocreatine ratios in frontal gray matter compared with the nonlead-exposed controls (277). Although much is still poorly understood about the biological mechanisms by which lead damages the brain and other organs and processes, some of the better understood mechanisms are discussed below.

Substitution for Essential Metals
One key mechanism of lead toxicity is its ability to substitute for calcium ions in homoeostatic processes. Lead in the blood is able to leave and accumulate in bone because it is able to compete with calcium for common binding sites and transport mechanisms. Likewise, by the same mechanisms as for calcium, accumulated lead may be mobilized from bone and re-enter the blood during pregnancy, lactation, periods of nutritional deficiency, osteoporosis or normal aging process. It is not surprising then that genetic variations that affect calcium homeostasis have been found to also affect lead toxicity. A recent paper by Rezende and associates describes several polymorphisms in the gene for Vitamin D receptor that affect circulating levels of lead in the blood and/or plasma (231). Small differences in the ionic characteristics of lead vs. calcium (e.g., greater radius and electronegativity), which result in tighter binding by lead, is another basis for lead’s toxicity (104). For example, lead has been shown to bind tighter and be more potent than calcium as an activator of calmodulin, synaptoagmin 1 and protein kinase C. Thus, numerous cell systems normally regulated by these proteins are disrupted in the presence of lead. In neurons, activation of calcium channels by lead produces abnormal increases in the cytoplasmic calcium concentration which, in turn, triggers potentially toxic signaling processes including neurotransmitter releases (144,270).

Lead also successfully competes with zinc. For example, because both zinc and lead form stable bonds with sulfur, lead has a high affinity for zinc-binding sites that contain sulfhydryl groups, such as those in the amino acid cysteine (110). However, lead will often bind more tightly than zinc to these sulfur-rich binding sites, allowing it to out-compete zinc. This has been observed in studies involving the zinc-dependent enzyme ALAD (88), which contains a Cys3 catalytic zinc site; GATA proteins (105), and various cysteine-rich zinc-finger proteins (224). Several mechanisms by which lead substitution can lead to structural or functional changes in the brain or elsewhere are discussed in the next section.

Changes in the Function of Metal-Binding Proteins
Much attention has been given to how the interactions between lead and metal-binding proteins, described above, change the intended structures and functions of proteins. These changes can have a dramatic effect on the biochemical processes in the body. Based on the diverse functions of essential metals in the body, potentially affected processes include metal transport, energy metabolism, apoptosis, ionic conduction, cell adhesion, inter-and intracellular signaling, enzymatic functions and pathways, protein maturation and genetic regulation (104). There is an enormous amount of research in the molecular mechanisms of lead toxicity. Here we report on several recent studies describing key mechanisms by which lead affects key biologic functions.

ALAD
Lead inhibits three enzymes in the heme biosynthesis pathway: delta-aminolevulinic acid dehydratase (ALAD), coproporphyrinogen oxidase and ferrochelatase. However, it has its greatest effect on ALAD (299). Activated by zinc binding, ALAD catalyzes the second step of the heme biosynthesis pathway. Under normal conditions, ALAD catalyzes the condensation of two molecules of 5-aminolevulinic acid (ALA) into one molecule of porphobilinogen (PBG), a precursor of heme. When BLLs exceed 20 µg/dL, ALAD activity is inhibited by approximately 50 percent (223). This reduction in heme
Oxidative stress is behind many of the adverse health effects associated with lead exposure. Evidence indicates that multiple mechanisms are most likely involved. A review by Ercal and associates describes how “redox-active” metals, such as iron, copper and chromium, undergo redox-cycling whereas “redox-inactive” metals, such as lead, cadmium and mercury, deplete major antioxidants in the cells, particularly thiol-containing antioxidants and enzymes (87). Both mechanisms may increase production of reactive oxygen species (ROS), such as hydroxyl radical (HO-), superoxide radical (O2-.) or hydrogen peroxide (H2O2), and overwhelm intrinsic cellular antioxidant defenses, leading to a number of problems due to oxidative cell and tissue damage.

Bechara and associates have proposed the involvement of accumulated ALA and ALA-generated oxygen radicals in the oxidative stress associated with lead poisoning (20). Their reasons include (1) ALA undergoes transition metal-catalyzed oxidation to give the reactive free radical species; (2) ALA induces iron release from ferritin, lipid peroxidation of cardioliipin-rich vesicles, single strand breaks in plasmid DNA, and guanosine oxidation in calf thymus DNA; (3) ALA causes Ca(2+)-mediated rat liver mitochondria permeabilization; (4) rats chronically treated with ALA exhibit increased glycolytic metabolism; (5) brain extracts of ALA-treated rats reveal increased levels of thiobarbituric acid reactive substances, direct chemiluminescence intensity, carbonyl proteins, ferritin, and “free iron” and gamma-aminobutyric acid-receptor dissociation constant; and (6) lead-exposed workers present with augmented erythrocytic levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase (20).

An important antioxidant target of lead is the tripeptide glutathione (GSH). GSH is a nonenzymatic antioxidant that protects cells against oxidative stress by direct interaction of its sulfhydryl group with ROS or by serving as a cofactor in the enzymatic detoxification reactions for ROS (124). Lead-binding to the sulfhydryl group interferes with this antioxidant activity. Furthermore, under normal conditions, another enzyme, glutathione reductase (GR), reduces the oxidized form of GSH, glutathione disulfide (GSSG), back to GSH thereby supporting the antioxidant defense system. A disulfide in the active site of GR is another likely target for lead binding, leading to an even greater decrease in GSH:GSSG ratios that ultimately render cells more susceptible to oxidative damage (124). Moreover, other enzymes involved in antioxidant defense mechanisms that would normally help protect against the GSH:GSSG imbalance also become inactivated due to direct binding of the lead to the enzymes. For example, glutathione peroxidase, catalase, and super oxide dismutase are metalloproteins that serve antioxidant functions by enzymatically detoxifying peroxides, H2O2 and O2-, respectively. The binding sites for essential metals in these proteins are targets for lead binding. Upon binding by lead, normal anti-oxidation defenses may be overwhelmed (87,124).

**WHAT ARE THE HEALTH EFFECTS?**

production may be responsible for the diverse health consequences associated with lead toxicity, including anemia (223). Even at very low levels, lead displaces zinc because ALAD’s Cys3 binding site has a 25-fold higher affinity for lead than zinc (111). Presumably, lead binding inactivates ALAD by steric obstruction or by its inability to function as a Lewis acid in catalysis (299). Furthermore, inhibition of ALAD activity results in the breakdown in the feedback inhibition mechanism of ALA synthesis and the subsequent build up of ALA in the plasma and urine (144). As discussed in the following section, the accumulation of ALA is believed to be responsible for oxidative stress and cell damage. Additionally, ALA resembles the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and studies by Brennan and Cantrill have shown that ALA may act as a GABA receptor agonist in the nervous system (37). Thus, high concentrations of ALA may be responsible for a number of the neurotoxic symptoms associated with lead poisoning.

**Lead and Zinc Finger Domains**

Zinc-finger domains, which are found in many transcription factors and regulatory proteins, are another likely molecular target of lead. Zinc-finger domains have two to four cysteine residues and require zinc binding in order to acquire a configuration that permits proper binding to DNA. Recent experiments using synthetic zinc fingers have shown that, although lead binds tightly to the structural zinc sites, it does not stabilize the correct fold of the peptides (224). Scientists believe that this destabilization effect is caused by difference in coordination preferences between lead and zinc in sulfur-rich sites; lead binds in a three coordinate mode, which is fundamentally different from the four coordinate mode of zinc binding (181). Consequently, lead binding may interfere with proper DNA binding and gene expression. Indeed, a study by Hanas and associates revealed that exposure of transcription factor IIIA (TFIIIA), which contains a Cys2His2 zinc-finger domain, to high levels of lead results in DNA-binding inhibition (126). Similarly, Ghering and associates recently found considerable evidence to show that GATA proteins, which are transcription factors involved in neurological and urogential development, are also inhibited by lead. The scientists reported that upon addition of lead, GATA exhibited a decreased ability to bind DNA and subsequently activate transcription (105). Thus, these experiments suggest that lead binding to zinc-finger domains is one of the molecular mechanisms of lead-induced developmental problems.

**Oxidative Stress**

Lead exposure promotes the generation of superoxide and hydrogen peroxide in human endothelial cells and vascular smooth muscle cells. This is believed to contribute to lead-associated hypertension and cardiovascular disease (217). Oxidative stress is behind many of the adverse health effects