933 Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for Lead

http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf

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Summary of Health Effects

An enormous amount of information is available on the health effects of lead on human health. In fact, the toxic effects of lead have been known for centuries, but the discovery in the past few decades that levels of exposure resulting in relatively low levels of lead in blood (e.g., <20 µg/dL) are associated with adverse effects in the developing organism is a matter of great concern. Most of the information gathered in modern times regarding lead toxicity comes from studies of workers from a variety of industries and from studies of adults and children in the general population. The most sensitive targets for lead toxicity are the developing nervous system, the hematological and cardiovascular systems, and the kidney. However, due to the multi-modes of action of lead in biological systems, lead could potentially affect any system or organs in the body.

Studies of lead workers suggest that long-term exposure to lead may be associated with increased mortality due to cerebrovascular disease. The same was found in a study of adults from the general population who were hospitalized for lead poisoning during childhood. Population studies suggest that there is a significant association between bone-lead levels and elevated blood pressure. Blood lead levels (Pb Bs) also have been associated with small elevations in blood pressure. Between the two biomarkers, bone lead appears to be the better predictor. Lead also affects kidney functions; glomerular filtration rate appears to be the function affected at the lowest PbBs. Decreased glomerular filtration rate has been consistently observed in populations with mean PbB <20 µg/dL and two studies have reported effects at PbB <10 µg/dL. Lead may alter glomerular filtration rate by several mechanisms.

Lead has long been known to alter the hematological system by inhibiting the activities of several enzymes involved in heme biosynthesis. Particularly sensitive to lead action is δ-aminolevulinic acid dehydratase (ALAD). Inhibition of ALAD activity

occurs over a wide range of PbBs beginning at <10 µg/dL. The anemia induced by lead is primarily the result of both inhibition of heme synthesis and shortening of erythrocyte lifespan, but lead also can induce inappropriate production of the hormone erythropoietin leading to inadequate maturation of red cell progenitors, which can contribute to the anemia.

A recent study in children 8–10 years of age suggested that lead accelerates skeletal maturation, which might predispose to osteoporosis in later life. Lead also has been associated with increased occurrence of dental caries in children and periodontal bone loss, which is consistent with delayed mineralization in teeth observed in studies in animals. Current mean PbBs in these cohorts were <5 µg/dL; however, the cross-sectional nature of the studies precluded assessment of the exposure history.

Changes in circulating levels of thyroid hormones, particularly serum thyroxine (T4) and thyroid stimulating hormone (TSH), generally occurred in workers having mean PbB ≥40–60 µg/dL. Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone have been observed at PbB ≥30–40 µg/dL. Lead also has been shown to decrease circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D, in children with moderate to high PbB (30–60 µg/dL), but not in children with low to moderate PbB (average lifetime PbB between 4.9 and 23.6 µg/dL, geometric mean, 9.8 µg/dL). Normal levels of vitamin D are important for maintaining calcium homeostasis.

Altered immune parameters have been described in lead workers with PbB in the range of 30–70 µg/dL. Reported effects included changes in some T-cell subpopulations, response to T-cell mitogens, and reduced chemotaxis of polymorphonuclear leukocytes. Several studies of children reported significant associations between PbB and increases in serum IgE levels. IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma. These findings in children along with results from studies in rodents exposed in utero have led some to suggest that lead may be a risk factor for childhood asthma, although a recent relatively large study (4,634 children) found that PbB was less a predictor of asthma than was race.

Exposure to high amounts of lead resulting in PbBs of 100–120 µg/dL in adults or 70–100 µg/dL in children produce encephalopathy, a general term that describes various diseases that affect brain function. Symptoms develop following prolonged exposure and include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death. Lead poisoning in children can leave residual cognitive deficits that can be still detected in adulthood. Neurobehavioral effects including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia have been reported in lead workers with PbBs in the range of 40–80 µg/dL. Also, PbBs between 40 and 80 µg/dL have been associated with neuropsychological effects in lead workers. A recent study of lead workers reported that higher tibia lead was associated with increased prevalence and severity of white matter lesions, as assessed by brain MRI. Studies of older populations with current mean PbBs <10

µg/dL have reported associations between PbB and/or bone lead and poorer performance in neurobehavioral tests. Lead also has been shown to affect nerve conduction velocity and postural balance in workers with PbB in the range of 30–60 µg/dL. Alterations of somatosensory evoked potentials also have been reported in lead workers with mean PbBs in the range of 30–50 µg/dL.

As previously mentioned, one of the major concerns regarding lead toxicity is the cognitive and neurobehavioral deficits that are observed in children exposed to lead. Prospective studies have provided the greatest amount of information. Analyses of these and other studies suggest that an IQ decline of 1– 5 points is associated with an increase in PbB of 10 µg/dL. Of special interest and concern are the results of recent studies that have reported neurobehavioral deficits in children associated with PbBs <10 µg/dL and an apparent lack of threshold down to even the lowest PbBs recorded in these studies. Lead also has caused neurobehavioral alterations in developing animals, and at PbBs similar to those reported in children. Studies in animals, particularly in monkeys, have provided key information for the interpretation of a cognitive basis for IQ changes. Studies of children also have shown associations between PbB and growth, delayed sexual maturation in girls, and decreased erythropoietin production.

Some studies of humans occupationally or environmentally exposed to lead have observed associations between PbB and abortion and preterm delivery in women and alterations in sperm and decreased fertility in men. On the other hand, there are several studies that found no significant association between lead exposure and these end points. At least for the effects in males, the threshold PbB appears to be in the range of 30–40 µg/dL. Studies have shown that lead can affect the association of protamines with DNA in sperm cells from exposed males. Lead does so by competing or reducing zinc in protamine P2 in vivo, which would leave sperm chromatin and DNA open to damage from other exposures.

In vitro mutagenicity studies in microorganisms have yielded mostly negative results for lead, but lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei and by sister chromatid exchanges in peripheral blood cells from lead workers. Studies of cancer in lead workers have been inconclusive. A meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure concluded that there is some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer. The results also showed a weak evidence for an association with kidney cancer and gliomas. In the only study of the general population available, there was suggestive evidence for an increase risk of cancer mortality in women, but not men, with a threshold PbB of 24 µg/dL. This study used data from the Second National Health and Nutrition Survey (NHANES II) Mortality Study. Lead has produced primarily renal tumors in rodents by a mechanism not yet elucidated. Some nongenotoxic mechanisms that have been proposed for lead-induced cancer include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage.

The Department of Health and Human Services (DHHS) has determined that lead and lead com pounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from animal studies. The EPA has determined that lead is a probable human carcinogen based on sufficient evidence from studies in animals and inadequate evidence in humans. The International Agency for Research on Cancer (IARC) has determined that inorganic lead is probably carcinogenic to humans based on sufficient evidence from studies in animals and limited evidence of carcin ogenicity from studies in humans. IARC also determined that organic lead compounds are not classifiable as to their carcinogenicity in humans based on inadequate evidence from studies in humans and animals.

A discussion of the most sensitive end points fo r lead toxicity, neurodevelopmental, cardiovascular/renal, and hematological, is presented below. The reader is referred to Chapter 3, Health Effects, for information on additional effects.

Neurodevelopmental Effects . Lead can impair cognitive function in children and adults, but children are more vulnerable than adults. The increased vulnerability is due in part to the relative importance of exposure pathways (i.e., dust-to-hand-mouth) and differences in toxicokinetics (i.e., absorption of ingested lead). Although the inhalation and oral routes are the main routes of exposure for both adults and children, children are more likely to have contact with contaminated surfaces due to playing on the ground and to hand-to-mouth activities. Furthermore, children absorb a larger fraction of ingested lead than adults. However, perhaps more important is the fact that the developing nervous system is especially susceptible to lead toxicity. During brain development, lead interferes with the trimming and pruning of synapses, migration of neurons, and neuron/glia interactions. Alterations of any of these processes may result in failure to establish appropriate connections between structures and eventually in permanently altered functions. Because different brain areas mat ure at different times, the final outcome of the exposure to lead during development (i.e., in utero vs. pediatric exposure) will vary depending on the time of exposure. This has been demonstrated in studies in animals. The time of exposure-specific response appears to have contributed to the failure to identify a "behavioral signature" of lead exposure in children. Other factors that may affect individual vulnerability are certain genetic polymorphisms, such as that for the vitamin D receptor, the lead-bin ding enzyme ALAD, or the APOE genotype. One important additional factor shown to influence the toxicity of lead is the characteristics of the child's rearing environment, a modifying factor. It has been argued that effect modification is a property of a tr ue association and should be distinguished from confounding. Effect modification can explain inconsistencies in findings, and if it exists, failure to address it will lead to an error in inference. For example, if social class is an effect modifier of the association between PbB and IQ, and differs between two cohorts, the strength of the association based on these two studies will necessarily be different.

Despite the many factors that can potentially work against finding agreement among studies, the prep onderance of the evidence indicates that lead exposure is

associated with decrements in cognitive function. Meta-analyses conducted on cross-sectional studies or a combination of cross-sectional and prospective studies suggest that an IQ decline of 1 –5 points is associated with an increase in PbB of 10 µg/dL. Most importantly, no threshold for the effects of lead on IQ has been identified. This has been confirmed by a series of recent studies in children that found significant inverse associations between cognitive function and PbBs <10 µg/dL. Moreover, these and other studies have shown that the slope of the lead effects on cognitive variables is steeper (the effect is greater) at lower than at higher PbBs (supralinear dose-response relationship). However, there is not complete agreement on the interpretation of the lack of linearity in the dose-response relationship among the scientific community. Some have argued, based on a theoretical statistical analysis, that the supra-linear slope is a required outcome of correlations between data distributions where one is log-normally distributed and the other is normally distributed. Perhaps the strongest evidence for nonlinearity is provided by an international pooled analysis of seven prospective studies (details in Section 3.2.4). After testing several models, these investigators determined that the shape of the dose-response was nonlinear insofar as the quadratic and cubic terms for concurrent PbB were statistically significant ($p<0.001$, $p=0.003$, respectively). Additional support for the steeper slope at low PbB was provided by plotting the individual effects estimates for each of the seven cohorts, adjusted for the same covariates. The plot showed that the studies with the lowest mean PbBs had a steeper slope compared with studies with higher PbBs. Yet further evidence for nonlinearity was presented when the data were divided at two cut-points a priori (maximal PbB above and below 10 µg/dL and above and below 7.5 µg/dL). The investigators then fit separate linear models to the data in each of those ranges and compared the PbB coefficients for the concurrent PbB index. The stratified analyses showed that the effects estimate for children with maximal PbB <7.5 µg/dL was significantly greater ($p=0.015$) than those with a maximal PbB ≥7.5 µg/dL. Similar results were seen at the cut-off point of 10 µg/dL. A reanalysis of the pooled studies found that a log-linear relationship between PbB and IQ was a better fit within the ranges of PbBs in the studies than was a linear relationship ($p<0.009$). Collectively, the results of the pooled analysis and of additional studies provide suggestive evidence of lead effects on cognitive functions in children at PbBs <10 µg/dL and, possibly as low as 5 µg/dL. It should be stressed, however, that the effects of lead on IQ and other neurobehavioral scores are very small compared with the effects of other factors such as parents' IQ, but is also important to stress that lead exposure, unlike most of those other factors, is highly preventable.

The other aspect that has been questioned regarding the nonlinear shape of the dose-response relationship is the apparent lack of a biological mechanism that could produce this result, and this clearly represents a data need. To explain the nonlinear shape of the dose-response, it was proposed that "the initial damage caused by lead may reflect the disruption of different biological mechanisms than the more severe effects of high exposures that result in encephalopathy or frank mental disability. This might explain why, within the range of exposures not producing overt clinical effects, an increase in PbB beyond a certain level might cause little additional impairment in children's cognitive function."

While measurements of IQ are convenient in that they allow comparison across populations of different demographic and cultural characteristics, and help define the extent of the public health issue, they only partially advance our understanding of the problem of lead-induced behavioral toxicity. It is import ant to elucidate the underlying basis of the deficits in IQ as well as the behavioral mechanisms that account for them. It was noted that "the answers are critical not only to further define neurobiological mechanisms associated with learning deficits, but also to determine behavioral or neurochemical therapeutic approaches to alleviate them. " Studies in animals have provided answers to some of these questions. Studies in animals have great utility because the possibility of confounding is reduced with the controlled experimental design and genetic factors. In addition, they address specific domains of cognitive function and allow determination of critical periods of exposure. Results of behavioral tests performed primarily in rats and monkeys exposed to lead have suggested that the impaired performance is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseveration in behaviors that are no longer appropriate. Evaluation of children expose d to lead with different subscales of IQ tests in conjunction with assessments of behavior on teacher's rating scales on young school-age children suggest that increased distractibility, impulsivity, short attention span, and inability to follow simple and complex sequences of directions are associated with increased lead body burden. The similarity between neurobehavioral effects in lead-exposed children and in animals, and the fact that the deficits are observed at similar PbBs should stimulate continued research to elucidate the biochemical and morphological substrates that underlie specific behaviors.

Although the decrement of IQ points in children associated with lead exposure is generally small, lead neurotoxicity may have major implications for publi c health when exposure is considered in terms of large populations and its preventable nature. One study quantified the economic benefits from projected improvements in worker productivity resulting from the reduction in children's exposure to lead in the United States since 1976. Based on data from NHANES (a study designed to provide national estimates of the health and nutritional status of the U.S. civilian noninstitutionalized population aged 2 months and older) and meta-analyses, it was estimated that mean PbBs declined 15.1 µg/dL between 1976 and 1999 and that IQ scores increased between 0.185 and 0.323 points for each 1 µg/dL blood lead concentration. It was further estimated that each IQ point raises worker 's productivity by 1.76–2.38%, and that the economic benefit for each year 's cohort of 3.8 million 2-year-old children ranges from $110 to $319 billion. In another study, using an environmentally attributable fraction model, it was estimated that the present value of economic losses in the United St ates attributable to lead exposure in amounts to $43.4 billion per year in each annual birth cohort. More recently, one study estimated that mild mental retardation and cardiovascular outcomes resulting from exposure to lead amounts to almost 1% of the glo bal burden of disease, with the highest burden in developing regions.

A related and important issue is whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes reportedly altered by

lead. In one study, improvement in cognitive functions was related to decreases in blood lead but not to chelation treatment. In a multi-center study of 780 children, chelation therapy lowered blood lead by a mean of 4.5 µg/dL during the 6 months after initiation of treatment , but it did not improve scores on tests of cognition, behavior, or neuropsychological function in children with PbB below 45 µg/dL. Re-analysis of these data showed that improvement in test scores was associated with greater falls in PbB only in the place bo group. A further evaluation of this cohort showed that chelation therapy lowered blood lead, but produced no benefits in cognitive, behavioral, or neuromotor end points. The conclusion of this series of studies reached by the investigators was that chel ation therapy is not indicated in children with moderate blood lead levels. Thus, it appears that lead abatement must remain the primary approach in the public health management of lead poisoning.

Cardiovascular/Renal Effects . Although lead has been shown to produce various cardiovascular and renal effects in animals, end points of greatest concern for humans at low exposures and low PbB are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistic ally related and, furthermore, can be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease.

Effects on Blood Pressure . 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 va rious dietary factors. Varying approaches and breadth of inclusion of these may account for some of the disparity of results that have been reported. Including confounders in a regression model will attenuate the apparent association between lead exposure and the measured health outcome. 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. Few studies have employed such techniques and, when used, have not found significant associations between PbB and blood pressure.

An additional limitation of blood lead studies, in general, is that PbB may not provide the ideal biomarker for long-term exposure to target tis sues that contribute a hypertensive effect of lead. Bone lead appears to be a better predictor of lead-induced elevations in blood pressure than PbB. In a recent prospective analysis of the Normative Aging Study, higher tibial lead levels, but not PbBs, we re associated with higher systolic blood pressure and abnormalities in electrocardiographic conduction.

Chronic lead exposure increases blood pressure in rats through diverse mechanisms that include alterations in neurohumoral control of peripheral vascul ar resistance, heart rate, and cardiac output (see Section 3.4.2). Studies conducted in animal models provide strong evidence for the plausibility of lead elevating blood pressure in humans. Meta-analyses of the epidemiological findings have found a persis tent 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. 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. A longitudinal study of males, mean age 67 years, found positive associations between systolic blood pressure and bone lead concentrations, and increased risk of hypertension in association with increased bone lead concentration. Based on this study, an increase in patella bone lead from the midpoint of the lowest quintile (12.0 µg/g) to the highest quintile (53.0 µg/g) was associated with a 1.71-fold increase in hypertension risk (rate-ratio, 95%; confidence interval [CI], 1.08–2.71). A case-control study of women, ages >55 years, found increased risk of hypertension in association with increased bone lead concentration. In this study, an increase in patella bone lead from 6 to 31 µg/g was associated with a 1.86-fold (odds ratio [OR], 95%; CI, 1.09–3.19) increase in risk of hypertension. A large-scale cross-sectional analysis of the NHANES III data on males and females, age 40–59 years, found increasing risk for hypertension in association with increasing PbB, with higher risks in postmenopausal women than in premenopausal women. Risks of diastolic hypertension for pre- and postmenopausal women, combined, who were in the highest blood lead quartile (mean, 6.4 µg/dL; range, 3.0–31.1) was predicted to be 3.4-fold higher (OR, 95%; CI, 1.3– 8.7) than that of women in the lowest quartile (mean, 1 µg/dL; range, 0.5–1.6); corresponding risks for postmenopausal women were 8.1 times greater (OR, 95%; CI, 2.6–24.7) (highest vs. lowest quartile). 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. Lead exposures during infancy and childhood (reflected in PbB) have been associated with increased blood pressure and altered responses to acute pressor stresses in childhood. Lead poisoning in childhood has also been associated with hypertension during adulthood in the absence of clinically significant renal disease and discernable elevations in PbB.

Effects in Renal Glomerular Filtration. Classic lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis and related functional deficits, including enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate. In humans, the overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs below 10 µg/dL, enzymuria and proteinuria becoming evident above 30 µg/dL, and severe deficits in function and pathological changes occurring in association with PbB exceeding 50 µg/dL. Thus, the renal effects of greatest concern, at low exposures (i.e., low PbB), are on glomerular filtration.

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 (see Section 3.2.2. Renal Effects). Furthermore, as noted previously, hypertension can be both a confounder in studies of associations between lead exposure and creatinine clearance as well as a covariable with lead exposure. Another important complication

in the assessment of associations between lead exposure and adverse effects on glomerular filtration is the potential confounding effect of decrements in glomerular filtration rate and increased lead body burden. Lead exposure has also been associated with increases in glomerular filtration rate. This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Increases in glomerular filtration rate have been observed in the early phases of development of chronic renal injury in rats. When age and other covariables that might contribute to glomerular disease are factored into the dose-response analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbBs <20 µg/dL, with some studies finding effects at PbBs <10 µg/dL (see Section 3.2.2, Table 3-4). Two studies provide evidence for an effect at lead concentrations below 10 µg/dL. A longitudinal study found a significant relationship between increasing serum creatinine concentration and increasing PbB below 10 µg/dL. A cross-sectional analysis of data from the NHANES III found increased risk of chronic renal disease (defined as severely depressed glomerular filtration rate) in association with PbB <6 µg/dL. 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 PbB relationship with serum concentration of creatinine or creatinine clearance.

Hematological Effects . The adverse hematological effects of lead are mainly the result of its perturbation of the heme biosynthesis pathway. The activity of ALAD, an enzyme occurring early in the heme synthesis pathway, is negatively correlated with PbBs between 5 and 95 µg/dL. Although inhibition of ALAD occurs at very low exposure levels, there is some controversy as to the toxicological significance of a depression in ALAD activity in the absence of a detectable effect on hemoglobin levels. Nevertheless, because the impairment of heme synthesis has a far-ranging impact not limited to the hemopoietic system, there is concern that developing organisms might be particularly susceptible.

A potential consequence of the inhibition of heme synthesis is a decreased formation of mixed function oxidases in the liver resulting in impaired metabolism of endogenous compounds, as well as impaired detoxification of xenobiotics. Mitochondrial cytochrome oxidase is another heme-requiring protein that could be affected by heme synthesis inhibition. In addition, tryptophan pyrrolase, a hepatic heme-requiring enzyme system, is inhibited via the reduction in the free hepatic heme pool. This could ultimately lead to increased levels of the neurotransmitter serotonin in the brain and increased aberrant neurotransmission in serotonergic pathways. Inhibition of heme synthesis also results in increased levels of δ-aminolevulinic acid (ALA), which has a structure similar to that of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and therefore, interferes with GABA neurotransmission. Finally, a prospective study of children with moderate PbB (25–40 µg/dL) and hemoglobin levels within normal limits found that serum

erythropoietin (EPO) was positively associated with PbB at ages 4.5 and 6.5 years, but the magnitude of the association gradually declined from 4.5 to 12 years. EPO is a glycoprotein hormone produced in the kidney that regulates both steady-state a nd accelerated erythrocyte production. This suggested that in nonanemic children with moderate PbB, hyperproduction of EPO is necessary to maintain normal hemoglobin concentrations. The decline in slope with age suggested that the compensatory mechanism gr adually begins to fail due to direct lead-induced inhibition of EPO production or indirectly through toxic effects of lead on the kidney. Inhibition of EPO production may contribute to lead-induced anemia. Anemia occurs at PbBs of ≥20 µg/dL.