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REVIEW

Neurotoxicity and Biomarkers of Lead Exposure: a Review

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Abstract Appropriate selection and measurement of lead biomarkers of exposure are critically important for health care management purposes, public health decision making, and primary prevention synthesis. Lead is one of the neurotoxicants that seems to be involved in the etiology of psychologies. Biomarkers are generally classified into three groups: biomarkers of exposure, effect, and susceptibility. The main body compartments that store lead are the blood, soft tissues, and bone; the half-life of lead in these tissues is measured in weeks for blood, months for soft tissues, and years for bone. Within the brain, lead-induced damage in the prefrontal cerebral cortex, hippocampus, and cerebellum can lead to a variety of neurological disorders, such as brain damage, mental retardation, behavioral problems, nerve damage, and possibly Alzheimer's disease, Parkinson's disease, and schizophrenia. This paper presents an overview of biomarkers of lead exposure and discusses the neurotoxic effects of lead with regard to children and adults.

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IN some countries, there are many complex sources of lead exposure (mining activities, pollution from leaded gasoline remaining in the atmosphere and industrial emissions, cosmetics, etc.).¹ Routes of

exposure to lead include contaminated air, water, soil, food, and consumer products. Occupational exposure is a common cause of lead poisoning in adults. According to estimates made by the National Institute of Occupational Safety and Health (NIOSH), more than 3 million workers in the United States are potentially exposed to lead in the workplace. One of the largest threats to children is lead paint that exists in many homes, especially older ones;

thus children in older housing with chipping paint are at greater risk. Prevention of lead exposure can range from individual efforts (e.g. removing lead-containing items such as piping or blinds from the home) to nationwide policies (e.g. laws that ban lead in products or reduce allowable levels in water or soil).

A remarkable explosion in the literature about the health effects of lead has occurred since the dissemination of US Occupational Safety and Health Administration lead standards in 1993 stating that workers can attain blood lead levels up to 40 $\mu\text{g}/\text{dL}$ for their working lifetime.^{2, 3} Since then, many longitudinal studies have provided evidence that cumulative lead dose causes cognitive dysfunction or decline.⁴ The neurotoxic effects of lead in workers can be induced at blood lead (BPb) levels below 18 $\mu\text{g}/\text{dL}$, somewhat higher than the critical level of lead neurotoxicity in children (5 $\mu\text{g}/\text{dL}$).⁵ Adverse health effects caused by lead exposure include intellectual and behavioral deficits in children, including hyperactivity; deficits in fine motor function, hand-eye coordination, and reaction time; and lowered performance on intelligence tests. Recent evidence has revealed other important health effects of lead exposure, such as hypertension and other cardiovascular outcomes,⁶ renal disease.⁷ Chronic lead exposure in adults can also lead to decreased fertility, cataracts, nerve disorders, muscle and joint pain, and memory or concentration problems. Extreme lead exposure can cause a variety of neurologic disorders, such as lack of muscular coordination, convulsions, and coma. As lead affects several enzymatic processes responsible for heme synthesis, the hematologic system is also a highly sensitive target for lead toxicity.

BIOMARKERS AND BIOLOGICAL MONITORING OF LEAD EXPOSURE

Biological monitoring has been defined as the measurement and assessment of agents or their metabolites either in tissues, secretions, excreta, expired air or any combination of these to evaluate exposure and health risks compared with an appropriate reference.⁸⁻¹⁰ The term biological marker is a general term used for a system that specifically measures an interaction between a biological system and a chemical, physical, or biological environmental agent. Biological monitoring techniques are useful for risk assessment of toxic agents in the field of environmental health. Biomarkers are generally classified into three groups: biomarkers of exposure, effect, and susceptibility. A variety of biomarkers are available to monitor human exposure to lead. Appropriate selection and measurement of lead biomarkers of exposure are critically important for health care management purposes, public

health decision making, and primary prevention synthesis. Although different biologic tissues and fluids (breast milk lead, blood, urine, bone, tooth, hair, and nail) have been used to test for lead exposure, no biomarker of bioavailable lead has been generally accepted.

The main body compartments that store lead are the blood, soft tissues, and bone; the half-life of lead in these tissues is measured in weeks for blood, months for soft tissues, and years for bone.¹¹ Lead in the bones, teeth, hair, and nails is bound tightly and not available to other tissues, and is generally thought not harmful.¹² In adults, 94% of absorbed lead is deposited in the bones and teeth, but children only store 70% in this manner, a fact which may partially account for the more serious health effects on children.¹³ The estimated half-life of lead in bone is 20 to 30 years, and bone can introduce lead into the bloodstream long after the initial exposure is gone.¹⁴ The half-life of lead in the blood in men is about 40 days, but it may be longer in children and pregnant women, whose bones are undergoing remodeling, which allows the lead to be continuously re-introduced into the bloodstream.¹³ Also, if lead exposure takes place over years, clearance is much slower, partly due to the re-release of lead from bone.¹⁵ Many other tissues store lead, but those with the highest concentrations (other than blood, bone, and teeth) are the brain, spleen, kidneys, liver, and lungs.¹⁶

In a study of the environmental, dietary, demographic, and activity variables associated with biomarkers of lead exposure, BPb was found to be associated with: 1, housedust concentrations of lead; 2, the duration of time spent working in a closed workshop; 3, low-income people often live in old housing with lead paint and the year in which the subject moved into the residence.¹⁷ An important weakness of BPb is its poor response to changes in exposure at high levels.¹⁸ Other currently available biomarkers of internal lead dose have not yet been accepted by the scientific community as a reliable substitute for BPb measurement.¹⁹ Nevertheless, in certain cases bone or teeth (for past exposures), feces (for current gastrointestinal exposure), or urine (for organic lead) are sometimes more useful than blood. As the plasma fraction is rapidly exchangeable in the blood, the toxic effects of lead are assumed to be primarily associated with plasma lead (PPb). Although PPb should be more germane than BPb to lead exposure and distribution, little is known about the association between PPb and clinical outcome. The determination of PPb is problematic because erythrocyte hemolysis can shift the metal into the plasma and artificially increase PPb levels. Many researchers accept that a cumulative lead exposure integrated over many years, in bone for example, rather than a single BPb measurement of lead dose may be

the most important determinant of some forms of toxicity. Bone Pb (BnPb) accounts for > 94% of the adult body burden of lead (70% in children).²⁰⁻²² Hernandez-Avila and colleagues²³ reported a strong association between BnPb levels and serum lead levels of adults exposed to lead. The findings of this study indicated the potential role of the skeleton as an important source of endogenous labile lead that may not be adequately discerned through the measurement of BPb levels. The most informative recent epidemiologic studies of the impact of lead on health are those that could derive estimates of both recent (BPb) and cumulative (BnPb) exposure for each participant. In a recent review of studies measuring both BPb and BnPb at exposure levels encountered after environmental exposure, the associations between the biomarkers of cumulative dose (mainly in tibia) and cognitive function in adults were stronger and more consistent than were the associations with BPb levels.⁷ Patella (kneecap) lead, representing a pool that may capture aspects of both current bioavailable and cumulative lead dose thus offering advantages over tibia or BPb, was used by Wright *et al*²⁴ to determine whether lead-exposure biomarkers are associated with declines in cognitive test scores in older persons. The researchers found that among subjects in the lowest quartile of patella lead levels, Mini-Mental Status Exam (MMSE) scores decreased by 0.03 points per year ($CI = -0.07$ to 0.005), whereas in the highest quartile, the MMSE score decreased by 0.13 points per year ($CI = -0.19$ to -0.07). Similar interactions were found between BPb levels and age. Increased levels of BnPb and BPb were found inversely associated with cognitive performance among older men, suggesting that lead exposure might accelerate age-associated cognitive decline.

In comparison to bone, teeth accumulate lead over the long term. The intrinsic importance of teeth as historical records of lead exposure has been recognized, tested and discussed for several decades. From the seminal papers of Rabinowitz to the more recent works of studies by Robbins *et al*,^{25, 26} research has revealed the value of dental enamel and dentine as biological indicators of exposure. Central of many of these studies has been the aim to develop a blood lead biomarker as an alternative to blood lead measurements (BPb). The latter are still the most reliable indicator of recent lead exposure, both for screening and for bio-monitoring purposes. As succinctly stated by Barbosa *et al*,²⁷ it appears impossible to differentiate between low-level chronic Pb exposure and a high-level short Pb exposure based on a single BPb measurement. By contrast, deciduous teeth are easy to collect (i.e. require non-invasive procedures), chemically stable and in theory provide a continuous record from in utero to several

years after birth. Unfortunately, previous work has not had the desired degree of control over the temporal relationship between blood sampling and that part of the tooth corresponding to the exact time of sampling. This failure has been exacerbated by the different analytical tools employed, as a result of which, published tooth data have proven hard to interpret.²⁸ Recent studies have sought to resolve this problem using the neonatal line as a fixed point in time.²⁹ Whilst advancing our understanding, there remain issues to address concerning the processes governing the incorporation of lead into dental tissues and the stability of lead once incorporated.

The collection of urine lead (UPb) is favored for long-term biomonitoring, especially for occupational exposures. UPb originates from PPb that is filtered at the glomerular level and excreted through the kidneys. According to certain authors³⁰ UPb levels adjusted for glomerular filtration rate can serve as a proxy for PPb. Fukui *et al*³¹ concluded that the correlation of UPb with BPb among workers occupationally exposed to lead was close enough to suggest that UPb can be a good alternative to BPb on a group basis, but not close enough to allow UPb to predict BPb on an individual basis.

Although lead excreted in hair has been suggested for the assessment of lead exposure,³² an extensive debate ensues about hair lead (HPb) as a biomarker (discussed in [27]). Hair is a biological specimen that is easily and non-invasively collected with minimal cost and is easily stored and transported to the laboratory for analysis. Such advantages should make hair an attractive biomonitoring substrate, at least superficially. Similar to hair, nails have many superficial advantages as a lead exposure biomarker, especially as specimen collection is noninvasive and simple and specimens are very stable after collection, not requiring special storage conditions. Nail lead (NPb) is considered to reflect long-term exposure because this compartment remains isolated from other metabolic activities in the body.³³ Because toenails are less affected than fingernails by exogenous environmental contamination, toenails have been preferred for lead-exposure studies. The lead concentration in nails depends on the age of the subject,³⁴ but apparently not on the subject's gender.³⁵ Saliva is a convenient source and therefore a potential substitute for blood as a biomarker for lead exposure.³⁶ Nevertheless, saliva has not been generally accepted as a reliable biomarker of lead exposure because of conflicting and unreliable saliva lead (SPb) measurements. Early research suggested an association between SPb levels and BPb and PPb levels.^{37, 38} Subsequently, data from a study by Thaweboon *et al*³⁹ compared BPb and SPb in an area highly contaminated from lead mining, Thailand. The geometric mean for the BPb content was $24.03 \mu\text{g/dL}$ (range 11.80 - $46.60 \mu\text{g/dL}$) whereas the SPb content was

5.69 $\mu\text{g}/\text{dL}$ (range 1.82-25.28 $\mu\text{g}/\text{dL}$), suggesting that saliva is not suitable material for biological monitoring with respect to lead exposure. Similarly, Barbosa and coworkers⁴⁰ evaluated the use of parotid SPb levels as a surrogate of BPb or PPb levels to diagnose lead exposure. Age or gender did not affect SPb levels or the SPb:PPb ratio. Only a weak correlation was found between Log SPb and Log BPb ($r=0.277$, $P<0.008$), and between Log SPb and Log PPb ($r=0.280$, $P=0.006$), suggesting that SPb cannot be used as a biomarker to diagnose lead exposure or as a surrogate of PPb levels, at least for low to moderately lead-exposed populations. A later study by this group²⁹ did show a clear relation between SPb and environmental contamination by lead. The authors suggested that further studies on SPb should be undertaken to investigate the usefulness of saliva as a biomarker of lead exposure, particularly in children.

Some study has shown that human milk could be a feasible biological matrix for use as a biomarker for lead exposure, with the goal of evaluating the risk to children's health using a noninvasive biological procedure. The WHO has reported that 2–5 $\mu\text{g}/\text{L}$ of Pb may exist in the breast milk 3 months postpartum under normal conditions based on its research conducted in 1989 in five countries (Sweden, Hungary, Zaire, The Philippines, Guatemala and Nigeria).⁴¹ Pb levels in breast milk vary widely around the world (0.5-126.6 $\mu\text{g}/\text{L}$).⁴²⁻⁵³ The difference in the breast milk levels may depend on various factors such as the time of sampling (morning or night), the time of lactation (colostrum/transient/mature milk or fore-milk/hind-milk), the method of sampling (pump or manual), maternal factors (parity and maternal Pb burden), as well as environmental factors (place of residence and exposure level/duration). However, such variations also reflect several other factors (methods of analysis and contamination of the samples) that might interfere in the final results.⁵⁴⁻⁵⁷ Some studies conducted in Turkey have reported that the breast milk Pb levels range from 2.3 to 21.7 $\mu\text{g}/\text{L}$.⁵⁸⁻⁶¹ Recently, in a study reported from Iran, the mean and SD of lead concentration in human milk was 10.39 and 4.72 $\mu\text{g}/\text{L}$, respectively.⁶² The results of some studies show that smoking habits increased lead concentration in milk significantly.⁶³ The differences found between different countries might also be due to different assays employed.

EFFECTS OF LEAD ON BRAIN FUNCTION AND DEVELOPMENT

Lead, a known toxic element, is a public health problem due to its adverse effects, mainly those affecting the central nervous system (CNS) in the most vulnerable populations, such as pregnant and lactating women and

children. In the absence of a safe exposure limit of children to lead and because of its ability to accumulate in the body for a long time, a great interest in the evaluation of the adverse effects of this metal in low concentrations has emerged.⁶⁴⁻⁶⁷ New research provides additional evidence of the effects of early lead exposure persisting into late childhood, manifested by poor cognitive outcomes and school achievement. As the main target for lead toxicity is the CNS, the brain is the organ most studied in lead toxicity.

Lead exposure damages cells in the hippocampus, a part of the brain involved in memory. Hippocampi in the lead-exposed rats show structural damage such as irregular nuclei and denaturation of myelin (DNS) compared to controls (top).⁶⁸ Lead interferes with the release of neurotransmitters, chemicals used by neurons to send signals to other cells.⁶⁹ It interferes with the release of glutamate, a neurotransmitter important in many functions including learning, by blocking N-methyl-D-aspartic acid (NMDA) receptors. The targeting of NMDA receptors is thought to be one of the main causes for lead's toxicity to neurons.⁷⁰ A report found that in addition to inhibiting the NMDA receptor, lead exposure decreased the amount of the gene for the receptor in part of the brain.⁷¹ In addition, lead has been found in animal studies to cause programmed cell death in brain cells.⁷⁰

A child's BPb measurement is estimated to account for 2% to 4% of variance in neurodevelopment measures (approximately 4% to 8% of the explained variance).^{72, 73} Agency for Toxic Substances and Disease Registry (ATSDR) cautions, however, that when studying the effects of lead on child development, the influence of multiple factors like treatment by parents or other adult caregivers should be taken into account. A child's family and personal psychosocial experiences are strongly associated with performance on neurodevelopment measures and account for a greater proportion of the explained variance in these measures than BPb levels. Many studies have examined the effects of lead on children's development outcomes covering varying ages at which BPb was measured and varying ages over which BPb levels were averaged. Statistically significant associations have been identified between average BPb levels over a specific period (for example, 0-5 years) and various adverse health outcomes; other studies have reported statistically significant associations with a single lead measurement at a specific age (for example, prenatal, 24 months, 6.5 years) or with a peak measurement. In contrast to adults, central nervous system effects are more prominent than peripheral effects in the developing nervous system.⁷⁴ The developmental effects of lead occur during a critical time window (age < 2 years of age).

Although the toxic effects of high levels of lead have been well documented for centuries, of great concern is the relative recent discovery that low levels of BPb ($<10 \mu\text{g/dL}$) are associated with adverse effects in the developing organism. In 1991, Centers for Disease Control and Prevention (CDC) in the US declared that a BPb level of $10 \mu\text{g/dL}$ should prompt public health actions,⁷⁵ while concurrently recognizing that although useful as a risk management tool, $10 \mu\text{g/dL}$ BPb should not be interpreted as a threshold for toxicity. Indeed, no threshold has yet been identified. Subsequently, low-level exposure to lead during early childhood was shown to be inversely associated with neuropsychological development through the first 7 years of life.⁵⁷ In 2007, the CDC⁷⁶ summarized the findings of a review of clinical interpretation and management of blood lead levels (BLLs) $<10 \mu\text{g/dL}$ conducted by CDC's Advisory Committee on Childhood Lead Poisoning Prevention and concluded that research conducted since 1991 has strengthened the evidence that children's physical and mental development can be affected at BLLs $<10 \mu\text{g/dL}$.

IN UTERO LEAD EXPOSURE

Lead is readily transferred to the fetus through the placenta.⁷⁷ In the absence of placental barrier efficacy, the fetus would be exposed to lead in a concentration very close to that of the mother. Fetus vulnerability can occur even if the mother's exposure had ceased many years earlier.^{78,79} Lead interferes with signal transmission at the synapse and with cellular adhesion molecules, causing disruption in cell migration during critical times in the nervous system development.⁸⁰ Other adverse effects related to prenatal lead exposure have also been reported, such as reproductive effects, conduct disorder in children, cardiovascular functioning, and genomic methylation of DNA.⁸¹⁻⁸⁴ Prenatal lead exposure not only can affect various organ systems of the mother, but also would provide a plumbeous environment for the fetus and newborns and may affect the fetus in a number of detrimental ways because it can cross the placenta freely.^{85,86} Elevated BPb levels during pregnancy are associated with an increased risk of preterm births, spontaneous abortion, and other anomalies.⁸⁷⁻⁸⁹ Therefore, it is particularly important to reduce lead exposure of pregnant women for aristogenesis. Lead exposure is the inherent accompaniment of economy development and is inevitable for human being. The BLLs and susceptibility to lead toxicity of pregnant women can be influenced by many factors such as environmental exposure, life styles, diet habits, and nutritional status. Moreover, the increase in lead level in breast milk with increasing maternal BPb levels represents an additional

risk to the newborn infant.⁹⁰

Prenatal lead exposure, assessed using umbilical cord blood lead (UCPb) as a biomarker, has long been known to impair the cognitive development of the infant. Strong evidence on the early developmental effects of exposure to lead was first provided by Bellinger and colleagues.⁹¹ Scores from the Bayley Scales of Infant Development (BSID) revealed that high cord blood levels were associated with lower covariance-adjusted scores on the Mental Development Index (MDI) but not on the Psychomotor Development Index (PDI). The level of BPb at 6 months of age was not associated with scores on either MDI or PDI, consistent with the hypothesis that low levels of lead are delivered transplacentally and are toxic to infants. In a later study covering 6 and 12 months of age,⁹² the lead concentration of capillary blood measured at both ages showed that MDI scores, adjusted for confounding, were inversely related to infants' UCPb level. As the scores were not significantly related to postnatal BPb levels at either age, the prenatal exposure to lead level was deemed to be associated with less favorable development through the first year of life.

In a prospective longitudinal cohort study of 249 children from birth to two years of age. Bellinger *et al*⁹³ assessed the relation between prenatal and postnatal exposure to low levels of lead and early cognitive development. The development of children with UCPb was assessed semiannually, beginning at the age of 6 months, with the MDI (mean $\pm$ SD, 100 ± 16). Infants in the high-prenatal-exposure group scored lower than those in the other two groups at all ages, and as before, the scores were not related to the infants' postnatal BPb levels.

A nonlinear relation between the first trimester of pregnancy BPb and the MDI at age 24 months was reported.⁹⁴ The results of the analyses showed that both maternal PPb and whole BPb levels during the first trimester (but not in the second or third trimester) were significant predictors ($P<0.05$) of poorer postnatal MDI scores. Additionally, the effect of first-trimester maternal PPb was substantially greater than the effects of second- and third- trimester PPb. On the other hand, another study excluding the first trimester showed that the intelligence quotient (IQ) of 6-10 year old children decreased significantly ($P<0.0029$, 95% CI = -6.45 to -1.36) with increasing natural-log third trimester BPb, but not with BPb at other times during pregnancy or postnatal BPb measurements.⁹⁵

Although a causal association between lead exposure and impaired cognitive functioning was most likely in early studies, the potential for residual confounding, particularly by social factors, made the strength and shape (linear or nonlinear) of this association across. A direct link exists

between low-level lead exposure during early development and deficits in neurobehavioral-cognitive performance evident late in childhood through adolescence.⁹⁶ Strong evidence for an association between low BPb levels and intellectual impairment in children, especially for those having maximal measured BPb levels of $<10\text{ }\mu\text{g/dL}$, emerged from a pooled analysis of 1333 children followed from birth or infancy until 5–10 years of age.⁹⁷ Of these, 18% had a maximal BPb concentration of $<10\text{ }\mu\text{g/dL}$ and 8% had a maximal blood lead concentration of $<7.5\text{ }\mu\text{g/dL}$. After adjustment for covariates, an inverse relation was found between BPb concentration and the full-scale IQ score. A log linear model revealed a 6.9 IQ point decrement (95% $CI=4.2-9.4$) associated with an increase in concurrent BPb levels from 2.4 to $30\text{ }\mu\text{g/dL}$. The respective estimated IQ point decrements associated with an increase in BPb from 2.4 to $10\text{ }\mu\text{g/dL}$, 10 to $20\text{ }\mu\text{g/dL}$, and 20 to $30\text{ }\mu\text{g/dL}$ were 3.9 (95% $CI=2.4-5.3$), 1.9 (95% $CI=1.2-2.6$), and 1.1 (95% $CI=0.7-1.5$). For a given increase in BPb, the lead-associated intellectual decrement for children with a maximal BPb level $<7.5\text{ }\mu\text{g/dL}$ was significantly greater than that observed for those with a maximal blood lead level $\geq 7.5\text{ }\mu\text{g/dL}$ ($P=0.015$). Téllez-Rojo *et al*⁹⁸ also studied the longitudinal associations between low concentrations of BPb and neurobehavioral development in environmentally exposed children in Mexico City in 294 children having a BPb $<10\text{ }\mu\text{g/dL}$ at both 12 and 24 months of age, with a gestation ≥ 37 weeks and a birth weight $>2000\text{ g}$. The MDI and PDI of the BSID II translated into Spanish were used for the evaluation. Also included in the multivariate models were maternal age and IQ and children's gender and birth weight. The finding of inverse associations between 24-month BPb level and concurrent MDI and PDI scores on the BSID II indicated that children's neurodevelopment is inversely related to their BPb levels in the range of $<10\text{ }\mu\text{g/dL}$, providing further evidence that $10\text{ }\mu\text{g/dL}$ should not be viewed as a biological threshold for lead neurotoxicity.

An association was found between prenatal and childhood BPb concentrations and criminal arrests in early adulthood. Between 1979 and 1984, Wright *et al*⁹⁹ recruited pregnant women living in poor areas of Cincinnati, which had a high concentration of older, lead contaminated housing, into the Cincinnati Lead Study. The researchers measured the women's BPb concentrations during pregnancy, as an indication of the prenatal lead exposure of the offspring, and the child's BPb levels regularly until the children were six and half years old. The authors then obtained information from the local criminal justice records on how many times each of the 250 offspring had been arrested between becoming 18 years old and the end of October 2005. Increased BPb

levels before birth and during early childhood were associated with higher rates of arrest for any reason and for violent crimes. For example, for every $5\text{ }\mu\text{g/dL}$ increase in BPb levels at six years of age the risk of being arrested for a violent crime as a young adult increased by almost 50% ($RR=1.48$) (see Hwang⁷⁰).

NEUROTOXICITY OF LEAD IN ADULTS

A early study by Stokes and colleagues¹⁰⁰ evaluated young adults (mean age 24.3 years) 20 years after lead exposure as children. The exposed group grew up around a lead smelter which was operated without emission-reducing devices. The average BLL for children in this area was $50\text{ }\mu\text{g/dL}$ in 1974 and $39.6\text{ }\mu\text{g/dL}$ in 1975. The BPb level ($49.3\text{ }\mu\text{g/dL}$) was known for only 25% of the exposed group. At the time of evaluation both groups had low BLLs. The exposed group performed significantly worse on each test of cognitive functioning as well as on tests of fine motor functioning and postural stability. The neuropsychological functioning of a group of adults 50 years after hospitalization for lead poisoning at the age of 4 years or younger was evaluated in a study by White and colleagues.¹⁰¹ Each individual in the exposed group had a history of lead exposure. When tested, the lead-exposed group had poorer performance on tasks of abstract reasoning, cognitive flexibility, verbal memory, verbal fluency, and fine motor speed. In the late 1970s, Tonge *et al*¹⁰² found microscopically a significant correlation between cerebellar calcification and raised BnBp lead levels in 10% to 15% of autopsies. A decade later Reyes and colleagues¹⁰³ described CT findings of cerebral and cerebellar calcification in three adults with known lead exposure for ≥ 30 years and elevated SPb levels at admission ($54-72\text{ }\mu\text{g/dL}$; normal range, $0-30\text{ }\mu\text{g/dL}$). Punctiform, curvilinear, speck-like, and diffuse calcification patterns were found in the subcortical area, basal ganglia, vermis, and cerebellum. All three patients showed nonspecific neurologic symptoms of dementia, loss of visual acuity, and peripheral neuropathy. Schroter and colleagues¹⁰⁴ reported a case of a 59-year old potter in Germany who presented lead neuropathy after 37 years of occupational exposure. The patient had a 25-year history of normochromic normocytic anemia with moderate basophilic stippling. The patient also reported history of 3 short psychotic episodes. Cranial CT showed extensive, bilateral, symmetrical calcification in the cerebellar hemispheres and minor calcification in the subcortical area of the cerebral hemispheres and basal ganglia. T2-weighted MRI showed high signal intensity in the periventricular white matter, basal ganglia, insula, posterior thalamus, and pons. Most research on lead exposure has focused on deficits in memory and learning. A large body of evidence

shows, however, that lead also influences other behaviors such as mood (depression), anxiety, and violence/aggression. Observations of the relations between early lead-exposure and neuropsychological abnormalities have been carried out throughout the course of life. Chronic lead exposure has been linked to the development of neurodegenerative diseases such as Alzheimer's and Parkinson's disease (reviewed by Brubaker *et al*¹⁰⁵). Alzheimer's disease is characterized by the formation between neurons of waxy plaques consisting predominantly of β -amyloid protein, and lead increases the expression of the amyloid precursor protein. Schizophrenia is also a candidate due to its features that closely resemble the behavior deficits linked to lead exposure.¹⁰⁶ Opler *et al*¹⁰⁷ conducted a study of prenatal lead exposure and schizophrenia using the biomarker of exposure δ -aminolevulinic acid in archived maternal serum samples collected from subjects enrolled in the Childhood Health and Development Study (1959-1966) based in Oakland, California. The authors found a possible association between prenatal Pb exposure and the development of schizophrenia in later life. Although several limitations constrained generalizability in a second study in 2008 by the same group, the results provided further evidence for the role of early environmental exposures in the development of adult-onset psychiatric disorders.

Recent studies showed that lead poisoning can cause nerve damage to the sense organs and nerves controlling the body, leading to neurodegenerative diseases like Alzheimer's and Parkinson's disease,¹⁰⁸ hearing and vision impairment, schizophrenia, and impaired cognitive function. Which cognitive domains are affected has only begun to be explored in detail. Weisskopf *et al*¹⁰⁹ found that low-level cumulative exposure to lead in nonoccupational settings can adversely affect cognitive function, particularly in the visuospatial/visuomotor domain. Bleecker *et al*¹¹⁰ administered the Rey Auditory Verbal Learning Test (RAVLT), a test of verbal learning and memory, to 256 English speaking lead smelter workers (mean age of 41 ± 9.4 years and employment duration of 17 ± 8.1 years). The findings of study are consistent with other investigations that have found that early exposure to lead is associated with long-term and apparently irreversible effects on behavioral, cognitive, and neuroradiological endpoints in adults.¹⁰⁸ Lead exposure variables, based on up to 25 years of prior BPb data, included a mean current BPb of 28 ± 8.8 $\mu\text{g/dL}$, working lifetime time weighted average blood lead (TWA) of 39 ± 12.3 $\mu\text{g/dL}$, and a working lifetime integrated blood lead index (IBL) of 728 (434.4) $\mu\text{g-y/dL}$. The results indicated that BPb was not associated with any of the RAVLT variables, but TWA and IBL contributed significantly to the explanation of variance of measures of encoding/storage and retrieval but not immediate memory span, attention, and

learning. Thus, lead exposure over years but not current BPb interfered with the organization and recall of previously learned verbal material. Associations between PbB and/or BnPB and poorer performance in neurobehavioral tests have been reported in older populations having a current mean BPb < 10 $\mu\text{g/dL}$.

CONCLUSIONS

Lead pervades almost every organ and system in the human body, but the main target for lead toxicity is the CNS, both in adults and in children. Blood is the most common tissue used as a biomarker of lead exposure although many other tissues and body fluids including breast milk lead, bone, hair, nail, saliva, tooth, urine, and umbilical cord blood have been considered. Lead is more toxic in young and unborn children than in older children and adults. In children, they are at high risk for lead poisoning because their smaller bodies are in a continuous state of growth and development. Lead poisoning has been associated with brain damage, mental retardation, behavioral problems, developmental delays, violence, and death at high levels of exposure. The metal has also been related to the damage of sense organs and nerves controlling the body, impaired cognitive function, as well as hearing and vision impairment in adults.

REFERENCES

1. Agency for Toxic Substances and Disease Registry (ATSDR). Hazardous Substance Release and Health Effects Database (HazDat). Atlanta: Centers for Disease Control and Prevention; 2006. p. 83-4.
2. U.S. Department of Labor. Occupational Safety & Health Administrations (OSHA) Lead. 1910.1025. Washington, DC: OSHA, 2006 [2013-01-22]. Available from: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10030
3. Guidotti TL, Ragain L. Protecting children from toxic exposure: Three strategies. *Pediatr Clin North Am* 2007; 54: 227-35.
4. Shih R, Hu H, Weisskopf MG, et al. Cumulative lead dose and cognitive function in adults: A review of studies that measured both blood lead and bone lead. *Environ Health Perspect* 2007; 115: 483-92.
5. Murata K, Iwata T, Dakeishi M, et al. Lead toxicity: Does the critical level of lead resulting in adverse effects differ between adults and children? *J Occup Health* 2009; 51: 1-12.
6. Lustberg M, Silbergeld E. Blood lead levels and mortality. *Arch Intern Med* 2002; 162: 2443-9.
7. Weaver VM, Jaar BG, Schwartz BS, et al. Associations among

- lead dose biomarkers, uric acid, and renal function in Korean lead workers. *Environ Health Perspect* 2005; 113: 36-42.
8. Berlin A, Yodaiken RE, Henman BA. International Seminar on the Assessment of Toxic Agents at the Workplace. Roles of Ambient and Biological Monitoring. Luxembourg, 8-12 December, 1980. *Int Arch Occup Environ Health* 1982; 50: 197-207.
9. DeSilva PE. Determination of lead in plasma and studies of its relationship to lead in erythrocytes. *Br J Ind Med* 1981; 38: 209-17.
10. Schütz A, Bergdahl IA, Ekholm A, et al. Measurement by ICP-MS of lead in plasma and whole blood of lead workers and controls. *Occup Environ Med* 1996; 53: 736-40.
11. Karri SK, Saper RB, Kales SN. Lead encephalopathy due to traditional medicines. *Curr Drug Saf* 2008; 3: 54-9.
12. White LD, Cory-Slechta DA, Gilbert ME, et al. New and evolving concepts in the neurotoxicology of lead. *Toxicol Appl Pharmacol* 2007; 225: 1-27.
13. Barbosa Jr, Tanus-Santos JE, Gerlach RF, et al. A critical review of biomarkers used for monitoring human exposure to lead: Advantages, limitations, and future needs. *Environ Health Perspect* 2005; 113: 1669-74.
14. Patrick L. Lead toxicity, a review of the literature. Part 1: Exposure, evaluation, and treatment. *Altern Med Rev* 2006; 11: 2-22.
15. Hu H, Shih R, Rothenberg S, et al. The epidemiology of lead toxicity in adults: Measuring dose and consideration of other methodologic issues. *Environ Health Perspect* 2007; 115: 455-62.
16. Timbrell JA. Biochemical mechanisms of toxicity: Specific examples. *Principles of Biochemical Toxicology*. 4th ed. London: Informa Healthcare; 2008.
17. Roy A, Georgopoulos PG, Ouyang M, et al. Environmental, dietary, demographic, and activity variables associated with biomarkers of exposure. *Expo Anal Environ Epidemiol* 2003; 13: 417-26.
18. Bergdahl IA, Skerfving S. Biomonitoring of lead exposure—alternatives to blood. *J Toxicol Environ Health A* 2008; 71: 1235-43.
19. Verseick J, Cornelius R. Trace elements in human plasma and serum. Boca Raton: CRC Press; 1989.
20. Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: Conceptual paradigms. *Environ Health Perspect* 1998; 106: 1-8.
21. O'Flaherty EJ. Physiologically based models for bone-seeking elements V: Lead absorption and disposition in childhood. *Toxicol Appl Pharmacol* 1995; 131: 297-308.
22. Landrigan PJ, Todd AC. Direct measurement of lead in bone—a promising biomarker. *JAMA* 1994; 271: 239-40.
23. Hernandez-Avila M, Smith D, Meneses F, et al. The influence of bone and blood lead on plasma lead levels in environmentally exposed adults. *Environ Health Perspect* 1998; 106: 473-7.
24. Wright RO, Tsaih SW, Schwartz J, et al. Lead exposure biomarkers and mini-mental status exam scores in older men. *Epidemiology* 2003; 14: 713-8.
25. Arora M, Hare D, Austin C, et al. Spatial distribution of manganese in enamel and coronal dentine of human primary teeth. *Sci Total Environ* 2011; 409: 1315-9.
26. Robbins N, Robbins ZF, Zhang J, et al. Shulze Childhood lead exposure and uptake in teeth in the Cleveland area during the era of leaded gasoline. *Sci Total Environ* 2010; 408: 4118-27.
27. Barbosa F Jr, Tanus-Santos JE, Gerlach RF, et al. A critical review of biomarkers used for monitoring human exposure to lead: Advantages, limitations, and future needs. *Environ Health Perspect* 2005; 113: 1669-74.
28. Arora M, Arora BJ, Kennedy S, et al. Spatial distribution of lead in human primary teeth as a biomarker of pre- and neonatal lead exposure. *Sci Total Environ* 2006; 371: 55-62.
29. Costa de Almeida GR, Umbelino de Freitas C, Barbosa FJ. Lead in saliva from lead-exposed and unexposed children. *Sci Total Environ* 2009; 407: 1547-50.
30. Tsaih SW, Schwartz J, Lee ML, et al. The independent contribution of bone and erythrocyte lead to urinary lead among middle-aged and elderly men: The normative aging study. *Environ Health Perspect* 1999; 107: 391-6.
31. Fukui Y, Miki M, Ukai H, et al. Urinary lead as a possible surrogate of blood lead among workers occupationally exposed to lead. *Int Arch Occup Environ Health* 1999; 72: 516-20.
32. Schumacher M, Domingo JL, Llobet JM. Corbella lead in children's hair, as related to exposure in Tarragona province, Spain. *Sci Total Environ* 1991; 104: 167-77.
33. Takagi Y, Matsuda S, Imai S, et al. Survey of trace elements in human nails: an international comparison. *Bull Environ Contam Toxicol* 1988; 41: 690-5.
34. Nowak B, Chmielnicka J. Relationship of lead and cadmium to essential elements in hair, teeth, and nails and of environmentally exposed people. *Ecotoxicol Environ Saf* 2000; 46: 265-74.
35. Rodushkin I, Axelsson M. Application of double focusing sector field ICP-MS for multielemental characterization of human hair and nails. Part II: A study of the inhabitants of northern Sweden. *Sci Total Environ* 2000; 262: 21-36.
36. Silbergeld EK. New approaches to monitoring environmental neurotoxins. *Ann NY Acad Sci* 1993; 694: 62-71.
37. Omokhodion FO, Crockford GW. Lead in sweat and its relationship to salivary and urinary levels in normal healthy

- subjects. *Sci Total Environ* 1991; 103: 113-22.
38. Pan AY. Lead levels in saliva and in blood. *J Toxicol Environ Health* 1981; 7: 273-80.
39. Thaweboon S, Thaweboon B, Veerapradist W. Lead in saliva and its relationship to blood in the residents of Klity Village in Thailand. *Southeast Asian J Trop Med Public Health* 2005; 36: 1576-9.
40. Barbosa F Jr, Corrêa Rodrigues MH, Buzalaf MR, et al. Evaluation of the use of salivary lead levels as a surrogate of blood lead or plasma lead levels in lead exposed subjects. *Arch Toxicol* 2006; 80: 633-7.
41. WHO. Minor and trace elements in human milk. Geneva: World Health Organization; 1989.
42. Al-Saleh I, Shinwari N, Mashhour A. Heavy metal concentrations in the breast milk of Saudi women. *Biol Trace Elem Res* 2003; 96: 21-37.
43. Guidi B, Ronchi S, Ori E, et al. Lead concentrations in breast milk of women living in urban areas compared with women living in rural areas. *Pediatr Med Chir* 1992; 14: 611-6.
44. Gulson BL, Mizon KJ, Palmer JM, et al. Longitudinal study of daily intake and excretion of lead in newly born infants. *Environ Res* 2001; 85: 232-45.
45. Gundacker C, Pietschnig B, Wittmann KJ, et al. Smoking, cereal consumption, and supplementation affect cadmium content in breast milk. *J Expo Sci Environ Epidemiol* 2007; 17: 39-46.
46. Frković A, Kras M, Alebić-Juretić A. Lead and cadmium content in human milk from the Northern Adriatic area of Croatia. *Bull Environ Contam Toxicol* 1997; 58: 16-21.
47. Hallén IP, Jorhem L, Lagerkvist BJ, et al. Lead and cadmium levels in human milk and blood. *Sci Total Environ* 1995; 166: 149-55.
48. Honda R, Tawara K, Nishijo M, et al. Cadmium exposure and trace elements in human breast milk. *Toxicology* 2003; 186: 255-9.
49. Leotsinidis M, Alexopoulos A, Kostopoulou-Farri E. Toxic and essential trace elements in human milk from Greek lactating women: Association with dietary habits and other factors. *Chemosphere* 2005; 61: 238-47.
50. Namihira D, Saldivar L, Pustilnik N, et al. Lead in human blood and milk from nursing women living near a smelter in Mexico City. *J Toxicol Environ Health* 1993; 38: 225-32.
51. Radisch B, Luck W, Nau H. Cadmium concentrations in milk and blood of smoking mothers. *Toxicol Lett* 1987; 36: 147-52.
52. Saleh MA, Ragab AA, Kamel A, et al. Regional distribution of lead in human milk from Egypt. *Chemosphere* 1996; 32: 1859-67.
53. Souad C, Farida Z, Narda L, et al. Trace element level in infant hair and diet, and in the local environment of the Moroccan city of Marrakech. *Sci Total Environ* 2006; 370: 337-42.
54. Sternowsky HJ, Wessolowski R. Lead and cadmium in breast milk. Higher levels in urban vs. rural mothers during the first 3 months of lactation. *Arch Toxicol* 1985; 57: 41-5.
55. Ursinyova M, Masanova V. Cadmium, lead and mercury in human milk from Slovakia. *Food Addit Contam* 2005; 22: 579-89.
56. Casey CE, Smith A, Zhang P. Microminerals in human and animal milk. In: Jensen RC, editor. *Handbook of milk composition*. San Diego: Academic Press, Inc.; 1995. p. 622-74.
57. Ettinger AS, Téllez-Rojo MM, Amarasiriwardena C, et al. Levels of lead in breast milk and their relation to maternal blood and bone lead levels at one month postpartum. *Environ Health Perspect* 2004; 112: 926-31.
58. Örün E, Yalçın SS, Aykut O. Breast milk lead and cadmium levels from suburban areas of Ankara. *Sci Total Environ* 2011; 409: 2467-72.
59. Turan S, Saygi S, Kiliç Z, et al. Determination of heavy metal contents in human colostrum samples by electrothermal atomic absorption spectrophotometry. *J Trop Pediatr* 2001; 47: 81-5.
60. Kirel B, Akşit MA, Bulut H. Blood lead levels of maternal-cord pairs, children and adults who live in a central urban area in Turkey. *Turk J Pediatr* 2005; 47: 125-31.
61. Dursun A. The levels of Pb, Hg, Cd in cord blood, breast milk, and newborn hair. Ankara: Hacettepe University; 2008.
62. Goudarzi MA, Parsaei P, Nayeypour F, et al. Determination of mercury, cadmium and lead in human milk in Iran. *Toxicol Ind Health* 2012; 25: 1-4.
63. Gundacker C, Pietschnig B, Wittmann KJ, et al. Human milk mercury and lead levels in Vienna. *Adv Exp Med Biol* 2008; 8: 387-8.
64. Schnaas L, Rothenberg SJ, Flores MF, et al. Reduced intellectual development in children with prenatal lead exposure. *Environ Health Perspect* 2006; 114: 791-9.
65. Anfield RL, Henderson CR, Cory-Slechta DA, et al. Intellectual impairment in children with blood lead concentrations below 10 microgram per deciliter. *N Engl J Med* 2005; 348: 1517-26.
66. Lanphear BP, Hornung R, Khoury J. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. *Environ Health Perspect* 2003; 13: 894-9.
67. Gulson BL, Mizon KJ, Korsch MJ, et al. Mobilization of lead from human bone tissue during pregnancy and lactation—a summary of long-term research. *Sci Total Environ* 2003; 303: 79-104.
68. Xu J, Yan HC, Yang B. Effects of lead exposure on hippo-

- campal metabotropic glutamate receptor subtype 3 and 7 in developmental rats. *J Negat Results Biomed* 2009; 8: 5.
69. Finkelstein Y, Markowitz ME, Rosen JF. Low-level lead-induced neurotoxicity in children: An update on central nervous system effects. *Brain Res Rev* 1998; 27: 168-76.
70. Hwang L. Environmental stressors and violence: Lead and polychlorinated biphenyls. *Rev Environ Health* 2007; 22: 313-28.
71. Needleman H. Lead poisoning. *Ann Rev Med* 2004; 55: 209-22.
72. Centers for Disease Control and Prevention (CDC). Managing elevated blood lead levels among young children: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. Atlanta: US Department of Health and Human Services, CDC; 2002.
73. Needleman H, Gatsonis C. Low-level lead exposure and the IQ of children. *JAMA* 1990; 263: 673-8.
74. National Research Council. Measuring lead exposure in infants, children, and other sensitive populations. Washington: National Academy Press; 1993.
75. Centers for Disease Control and Prevention (CDC). Preventing lead poisoning in young children. Atlanta: US Department of Health and Human Services, CDC; 1991.
76. Binns HJ, Campbell C, Brown MJ. Interpreting and managing blood lead levels of less than 10 microg/dL in children and reducing childhood exposure to lead: Recommendations of the Centers for Disease Control and Prevention Advisory Committee on Childhood Lead Poisoning Prevention. *Pediatrics* 2007; 120: 1285-98.
77. Rossipal E, Krachler M, Li F, et al. Investigation of the transport of trace elements across barriers in humans: Studies of placental and mammary transfer. *Acta Paediatr* 2000; 89: 1190-5.
78. Bellinger D. Teratogen update: lead and pregnancy. *Birth Defects Res A Clin Mol Teratol* 2005; 73: 409-20.
79. Hu H, Téllez-Rojo MM, Bellinger D. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. *Environ Health Perspect* 2006; 114: 1730-5.
80. Jones AL. Emerging aspects of assessing lead poisoning in childhood. *Emerg Health Threats J* 2009; 2: 3-7.
81. Chen PC, Pan IJ, Wang JD. Parental exposure to lead and small for gestational age births. *Am J Ind Med* 2006; 49: 417-22.
82. Braun JM, Froehlich TE, Daniels JL. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. *Environ Health Perspect* 2008; 116: 956-62.
83. Gump BB, Stewart P, Reihman J. Prenatal and early childhood blood lead levels and cardiovascular functioning in 9 (1/2) year old children. *Neurotoxicol Teratol* 2005; 27: 655-65.
84. Herman DS, Geraldine M, Venkatesh T. Evaluation, diagnosis, and treatment of lead poisoning in a patient with occupational lead exposure: A case presentation. *J Occup Med Toxicol* 2007; 2: 71-8.
85. Goyer RA. Transplacental transport of lead. *Environ Health Perspect* 1990; 89: 101-5.
86. Wan BJ, Zhang Y, Tian CY, et al. Blood lead dynamics of lead-exposed pregnant women and its effects on fetus development. *Biomed Environ Sci* 1996; 9: 41-5.
87. Hertz-Picciotto I. The evidence that lead increases the risk for spontaneous abortion. *Am J Ind Med* 2000; 38: 300-9.
88. Borja-Aburto VH, Hertz-Picciotto I, Rojas Lopez M, et al. Blood lead levels measured prospectively and risk of spontaneous abortion. *Am J Epidemiol* 1999; 150: 590-7.
89. Gardella C. Lead exposure in pregnancy: A review of the literature and argument for routine prenatal screening. *Obstet Gynecol Surv* 2001; 56: 231-8.
90. Li PJ, Sheng YZ, Wang QY, et al. Transfer of lead via placenta and breast milk in human. *Biomed Environ Sci* 2000; 13: 85-9.
91. Bellinger DC, Needleman HL, Leviton A, et al. Early sensory-motor development and prenatal exposure to lead. *Neurobehav Toxicol Teratol* 1984; 6: 387-402.
92. Bellinger D, Leviton A, Needleman HL, et al. Low-level lead exposure and infant development in the first year. *Neurobehav Toxicol Teratol* 1986; 8: 151-61.
93. Bellinger D, Leviton A, Waternaux C, et al. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med* 1987; 316: 1037-43.
94. Hu H, Téllez-Rojo MM, Bellinger D, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. *Environ Health Perspect* 2006; 114: 1730-5.
95. Schnaas L, Rothenberg SJ, Flores MF. Reduced intellectual development in children with prenatal lead exposure. *Environ Health Perspect* 2006; 114: 791-7.
96. Rosen JF. Health effects of lead at low exposure levels. *Am J Dis Child* 1992; 146: 1278-81.
97. Lanphear BP, Hornung R, Khoury J, et al. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. *Environ Health Perspect* 2005; 113: 894-9.
98. Téllez-Rojo MM, Bellinger DC, Arroyo-Quiroz C, et al. Longitudinal associations between blood lead concentrations lower than 10 microg/dL and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* 2006; 118: e323-30.
99. Wright JP, Dietrich KN, Ri MD, et al. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med* 2008; 5: e101.

100. Stokes L, Letz R, Gerr F, et al. Neurotoxicity in young adults years after childhood exposure to lead: The Bunker Hill experience. *Occup Environ Med* 1998; 55: 507-16.
101. White RF, Diamond R, Proctor S, et al. Residual cognitive deficits 50 years after lead poisoning during childhood. *Br J Ind Med* 1993; 50: 613-22.
102. Tonge JI, Burry AF, Saal JR. Cerebellar calcification: A possible marker of lead poisoning. *Pathology* 1977; 9: 289-300.
103. Reyes PF, Gonzalez CF, Zalewska MK, et al. Intracranial calcification in adults with chronic lead exposure. *AJR Am J Roentgenol* 1986; 146: 267-70.
104. Schröter C, Schröter H, Huffman G. Neurologic and psychiatric manifestations of lead poisoning in adults. *Fortschr Neurol Psychiat* 1991; 59: 413-24.
105. Brubaker CJ, Schmithorst VJ, Haynes EN, et al. Altered myelination and axonal integrity in adults with childhood lead exposure: A diffusion tensor imaging study. *Neurotoxicology* 2009; 30: 867-75.
106. Jones B. Schizophrenia: Into the next millennium. *Can J Psychiat* 1993; 38: 567-9.
107. Opler MG, Buka SL, Groeger J, et al. Prenatal exposure to lead, delta-aminolevulinic acid, and schizophrenia: Further evidence. *Environ Health Perspect* 2008; 116: 1586-90.
108. Monnet-Tschudi F, Zurich MG, Boschat C, et al. Involvement of environmental mercury and lead in the etiology of neurodegenerative diseases. *Rev Environ Health* 2006; 21: 105-17.
109. Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. *Epidemiology* 2007; 18: 59-66.
110. Bleecker ML, Ford DP, Lindgren KN, et al. Differential effects of lead exposure on components of verbal memory. *Occup Environ Med* 2005; 62: 181-7.