DOI: 10.1093/brain/awg014 *Brain* (2003), **126,** 5–19

REVIEW ARTICLE

Lead neurotoxicity in children: basic mechanisms and clinical correlates

Theodore I. Lidsky[1] and Jay S. Schneider[2]

[1]*Center for Trace Element Studies and Environmental Neurotoxicology, NYS Institute for Basic Research in Developmental Disabilities, Staten Island, NY and* [2]*Department of Pathology, Anatomy and Cell Biology and Department of Neurology, Thomas Jefferson University Medical School, Philadelphia, PA, USA*

Correspondence to: Theodore I. Lidsky, Center for Trace Element Studies and Environmental Neurotoxicology, NYS Institute for Basic Research in Developmental Disabilities, Staten Island, NY 10314, USA
E-mail: tlidsky@monmouth.com

Summary

Lead has been recognized as a poison for millennia and has been the focus of public health regulation in much of the developed world for the better part of the past century. The nature of regulation has evolved in response to increasing information provided by vigorous scientific investigation of lead's effects. In recognition of the particular sensitivity of the developing brain to lead's pernicious effects, much of this legislation has been addressed to the prevention of childhood lead poisoning. The present review discusses the current state of knowledge concerning the effects of lead on the cognitive development of children. Addressed are the reasons for the child's exquisite sensitivity, the behavioural effects of lead, how these effects are best measured, and the long-term outlook for the poisoned child. Of particular importance are the accumulating data suggesting that there are toxicological effects with behavioural concomitants at exceedingly low levels of exposure. In addition, there is also evidence that certain genetic and environmental factors can increase the detrimental effects of lead on neural development, thereby rendering certain children more vulnerable to lead neurotoxicity. The public health implications of these findings are discussed.

Keywords: lead poisoning; neurotoxicity; children; toxic mechanisms; toxic threshold

Abbreviations: ALA = δ-aminolevulinic acid; BBB = blood–brain barrier; PKC = protein kinase C; SES = socioeconomic status; VDR = vitamin D receptor

Introduction

Lead is one of the oldest-established poisons. Knowledge of its general toxic effects stretches back three millennia and knowledge of its effects in children over 100 years. However, lead exposure continues to be a major public health problem, particularly in urban centres in the USA and also in Third World nations (Tong *et al*., 2000). As a result, research into the toxic effects of lead continues and the last decade has been particularly fruitful in providing new information on the manifold influences of this metal. The present review concerns some of these recent developments in the study of the basic mechanisms of lead neurotoxicity and of childhood lead poisoning. Public health policy concerning lead has evolved steadily in response to increasing scientific information. The present paper suggests that recently published findings point to the need for additional changes in the regulation of lead exposure.

Toxic mechanisms

The direct neurotoxic actions of lead include apoptosis, excitotoxicity, influences on neurotransmitter storage and release processes, mitochondria, second messengers, cerebrovascular endothelial cells, and both astroglia and oligodendroglia. Although all of lead's toxic effects cannot be tied together by a single unifying mechanism, lead's ability to substitute for calcium [and perhaps zinc (Bressler and Goldstein, 1991)] is a factor common to many of its toxic

actions. For example, lead's ability to pass through the blood–brain barrier (BBB) is due in large part to its ability to substitute for calcium ions (Ca^{2+}). Experiments with metabolic inhibitors suggest that back-transport of lead via the Ca-ATPase pump plays an important role in this process (Bradbury and Deane, 1993). More direct evidence for the role of the Ca-ATPase pump in the transport of lead into the brain has been provided by *in vitro* studies of brain capillary endothelial cells, the primary constituent of the BBB (Kerper and Hinkle, 1997*a*, *b*).

Lead's uptake by excitable cells is also due in large part to its interactions with cellular mechanisms that, under ordinary conditions, perform calcium-mediated functions. Uptake of lead by pituitary GH3, glial C6 and HEK293 cells is increased by depletion of stored calcium (Kerper and Hinkle, 1997*b*). Lead enters astroglia and neurons via voltage-sensitive calcium channels (Kerper and Hinkle, 1997*b*; Legare *et al*., 1998), the predominant channel subtype depending on the specific type of cell (Audesirk and Audesirk, 1993).

Lead and neuronal death

Apoptosis (programmed cell death) can be induced by a variety of stimuli. Apoptosis occurs when a cell activates an internally encoded suicide programme as a response to either intrinsic or extrinsic signals. One of the better characterized apoptotic cascade pathways has mitochondrial dysfunction as its initiator. Mitochondrial dysfunction initiated by the opening of the mitochondrial transition pore leads to mitochondrial depolarization, release of cytochrome C, activation of a variety of caspases and cleavage of downstream death effector proteins, and ultimately results in apoptotic cell death. While a variety of stimuli can trigger opening of the mitochondrial transition pore and cause apoptosis, a sustained intracellular increase in Ca^{2+} is one of the better-known triggers; accumulation of lead is another. Lead disrupts calcium homeostasis, causing a marked accumulation of calcium in lead-exposed cells (Bressler and Goldstein, 1991; Bressler *et al*., 1999). Lead, in nanomolar concentrations, also induces mitochondrial release of calcium (Silbergeld, 1992), thus initiating apoptosis.

Lead-induced apoptosis has been particularly well studied in the retina. Exposure to low to moderate pathophysiologically relevant concentrations (10 nM to 1 μM) of lead ions (Pb^{2+}) induced apoptosis in rod and bipolar cells both in cell culture (He *et al*., 2000) and in developing and adult rats (Fox *et al*., 1997). [To put this in perspective lead exposure in people is typically expressed as the number of micrograms of lead in 100 ml of blood (μg/dl). The threshold of lead poisoning in children set by the Centers for Disease Control is 10 μg/dl, which is equivalent to 0.48 μM.] Exposure to low to moderate levels of lead during development (0–21 days), resulting in blood lead levels of 19–60 μg/dl at 21 days of age, produced selective loss of rod and bipolar cells, the dying cells exhibiting signs of apoptosis. Similar results were obtained from adult rats exposed to low to moderate lead levels for 6 weeks. In all cases, the degree of cell death was age- and dose-dependent, the developing retina being particularly sensitive to lead exposure. Lead-induced retinal degeneration also appeared to be related to rod-specific effects of Pb^{2+} and Ca^{2+} on rod mitochondria, suggesting that Pb^{2+} and Ca^{2+} bind to the internal metal-binding site of the mitochondrial transition pore, subsequently open the transition pore, and initiate the cytochrome C–caspase activation cascade leading to apoptosis. These effects of lead on retinal cell apoptosis may have particular functional significance, since long-term visual system deficits occur in humans, monkeys and rats following low to moderate developmental exposure to lead (20–60 μg/dl) (Fox *et al*., 1997).

Lead accumulates in and damages mitochondria (Anderson *et al*., 1996), the organelles mediating cellular energy metabolism. Haem biosynthesis, a function of normal mitochondrial activity, is affected by lead, with disruptive effects on synaptic transmission in the brain (see below, Indirect neurotoxic effects of lead). However, decreased mitochondrial functioning also can transform ordinarily benign synaptic transmission mediated by glutamate into neuron-killing excitotoxicity (Beal *et al*., 1993). In addition to killing brain cells via excitotoxicity and apoptosis, lead also causes toxic effects by oxidative stress and by either directly- or indirectly-produced lipid peroxidation. Lead alters lipid metabolism, inhibits superoxide dismutase and enhances lipid peroxidation in the brains of developing rats (Shukla *et al*., 1987; Antonio, 1999; Villeda-Hernandez *et al*., 2001).

Chronic administration of low doses of lead to rats, at levels similar to environmental exposure in people, affects various parameters of energy metabolism in adult brain nerve endings (Rafalowska *et al*., 1996). After acute lead exposure that approximated occupational exposure (mean blood lead level 97.2 μg/dl), oxygen consumption was increased in brain synaptosomes and levels of ATP, creatine phosphate and creatine kinase were elevated, while the activity of sodium–potassium-ATPase was decreased (Struzynska *et al*., 1997).

Effects on intraneuronal regulatory mechanisms

Lead substitutes for calcium in affecting the activity of second messengers. Calmodulin, activated by calcium, stimulates several protein kinases, cyclic AMP and phosphodiesterase, and affects potassium channels (Bressler *et al*., 1999). Lead at nanomolar concentrations substitutes for calcium in activating calmodulin and at higher concentrations appears to reduce activity (Kern and Audesirk, 2000). Lead's activating effects on calmodulin perturb intracellular calcium homeostasis (Ferguson *et al*., 2000), an effect with potential disruptive influences on the multiplicity of calcium-mediated processes intrinsic to normal cellular activity.

Protein kinase C (PKC), also affected by lead, participates in many important cellular functions, including proliferation and differentiation. In addition, PKC is also involved in long-term potentiation, a form of neuronal plasticity that may be

involved in memory and learning (Bressler and Goldstein, 1991). In *in vitro* studies, acute administration of picomolar concentrations of lead activates PKC, an action normally induced by nanomolar concentrations of calcium (Bressler *et al*., 1999). However, chronic lead administration *in vivo* (mean blood lead level 31.9 μg/dl) reduces hippocampal PKC expression (Nihei *et al*., 2001).

Effects on neurotransmission

Lead suppresses activity-associated Ca^{2+}-dependent release of acetylcholine, dopamine and amino acid neurotransmitters (Lasley *et al*., 1999; Devoto *et al*., 2001), but also increases basal release (Bressler and Goldstein, 1991). While the mechanism(s) for these effects is not known, lead affects presynaptic Ca^{2+} channels involved in transmitter release (Nachshen, 1984; Audesirk, 1993) and, as discussed by Bouton and colleagues (Bouton *et al*., 2001), by activating PKC, lead increases the pool of releasable vesicles (Gillis *et al*., 1996). Lead also has a variety of effects on synaptic mechanisms and structures. For example, synaptosomes from rats exposed to lead for 3 months after weaning have fewer synaptic vesicles and damaged mitochondria (Jablonska *et al*., 1994). Synaptosomal sodium–potassium ATPase was increased by lead (Regunathan and Sundaresan, 1985) while calcium ATPase was inhibited (Bettaiya *et al*., 1996). Lead also disrupts the activity of synaptotagmin I, a protein localized in the synaptic terminal that appears to be important for transmitter release (Bouton *et al*., 2001).

In addition to affecting neurotransmitter storage and release, lead also alters neurotransmitter receptors. One important target of lead's disruptive influences is the glutamate receptor. Increases in AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor density after 2 weeks of chronic exposure are followed by pronounced decreases after 8 months of exposure (McCoy *et al*., 1997). The density of NMDA (*N*-methyl-D-aspartate) receptors in adult rats is increased by chronic lead exposure beginning at parturition and continuing until adulthood (Lasley *et al*., 2001). Hippocampal long-term potentiation in adult rats, which is dependent on normal glutamatergic functioning, is also disrupted by chronic developmental lead administration (Gilbert *et al*., 1996).

Lead also has disruptive effects on dopamine systems. In mesencephalic dopamine cells in culture, lead causes necrosis and, in a smaller proportion of cells, apoptosis. With continued exposure, lead in concentrations as low as 0.3 μM (the equivalent of 6.25 μg/dl) increases the number of dead cells and reduces dopamine uptake (Scortegagna and Hanbauer, 1997). Rat pups exposed postnatally by lactation from dams drinking water containing lead acetate have changes in dopamine receptor functioning. After weaning at 21 days, D_1 and D_2 receptors increased in the striatum and nucleus accumbens. At 60 days of age in rats with high levels of exposure (blood lead levels >50 μg/dl), D_1 receptors remained increased in the striatum but decreased in the nucleus accumbens. In animals with lower levels of exposure, D_1 receptors did not differ significantly from those in controls. In contrast, with blood lead levels from 10 to 20 μg/dl, but not higher, D_2 receptors in the striatum decreased while those in the nucleus accumbens increased. The authors concluded: 'These findings suggest a preferential vulnerability of D_2 receptors to lower lead exposure concentrations and underscore the importance of lead exposure level and brain region to resulting receptor changes.' (Widzowski *et al*., 1994).

Effects on glia

Lead's toxic influences are also exerted on oligodendroglia and astroglia, the former being far more vulnerable (Tang *et al*., 1996). Oligodendroglia progenitors *in vitro* are more sensitive than cultures of mature oligodendrocytes (Deng *et al*., 2001). Lead exposure delays the differentiation of glial progenitors (Deng *et al*., 2001) and, *in vivo*, causes hypomyelination and demyelination (Coria *et al*., 1984).

A number of studies suggest that astroglia may serve as lead sinks in the mature and developing brain (for review see Tiffany-Castiglioni *et al*., 1989). Brain astrocytes appear to take up and sequester lead in non-mitochondrial sites, potentially protecting not only their own respiratory processes but also those of the more vulnerable neurons (Lindahl *et al*., 1999). Immature astroglia, but not neurons, sequester lead preferentially, and this difference originates from the intrinsic cellular properties of these different cell types (Lindahl *et al*., 1999). Tiffany-Castiglioni and colleagues also showed that astrocytes *in vitro* accumulate lead at levels much higher than the levels measured in the culture medium and that younger astrocytes accumulate and retain more lead than older astrocytes (Tiffany-Castiglioni *et al*., 1989). However, the ability of astrocytes to accumulate lead probably develops at least in part in response to maturation of their interactions with neuronal cells (Lindahl *et al*., 1999). While the astrocytic accumulation of lead may serve initially to protect neurons from the toxic effects of this metal, this glial store of lead may constitute a reservoir for the continuous release of lead into the brain and may ultimately contribute to the damage of nearby neurons (Holtzman *et al*., 1987). In addition, astrocytes modulate synaptic activity and potential excitotoxicity by taking up glutamate after its release and converting it to glutamine in the presence of the glial-specific enzyme glutamine synthetase (Norenberg and Martinez-Hernandez, 1979). Lead (0.25–1.0 μM lead acetate) added to cultures for 7–21 days resulted in a dose- and time-dependent reduction in glutamine synthetase activity (Sierra and Tiffany-Castiglioni, 1991), suggesting that astroglial function is vulnerable to low levels of lead exposure.

Oligodendroglia respond directly and indirectly to lead in ways that could impair brain function. After 3 months of exposure (mean blood lead level, 38.2 μg/dl; mean brain level, 0.03 μg/g), myelin from brains of lead-poisoned rats was morphologically abnormal. Oligodendrocytes from the

Table 1 *Mechanisms of lead toxicity*

Competition with and substitution for calcium
Disruption of calcium homeostasis
Stimulation of release of calcium from mitochondria
Opening of mitochondrial transition pore
Direct damage to mitochondria and mitochondrial membranes
Inhibition of anti-oxidative enzymes (e.g. superoxide dismutase)
Alteration of lipid metabolism
Substitution for zinc in various zinc-mediated processes
Accumulation in brain by astrocytes
Sequestration and mobilization of lead from bone stores
Long half-life in brain (2 years) and slow release from sites of accumulation

Table 2 *Effects of lead toxicity*

Apoptosis
Excitotoxicity
Decreased cellular energy metabolism
Impaired haem biosynthesis and anaemia
Oxidative stress
Lipid peroxidation
Altered activity of second messenger systems
Altered neurotransmitter release
Altered neurotransmitter receptor density
Impaired development and function of oligodendrocytes
Abnormal myelin formation
Abnormal neurotrophic factor expression
Abnormal dendritic branching patterns
Disruption of the blood–brain barrier
Disruption of thyroid hormone transport into the brain
Altered regulation of gene transcription
Lowered IQ
Impaired neuropsychological functioning
Impaired academic achievement

same brains also appeared grossly abnormal (Dabrowska-Bouta *et al*., 1999). Since a significant amount of CNS myelination takes place in the first 2 months of life, it is possible that the destruction of the myelin sheaths observed in lead-exposed rats could be secondary to lead-induced damage to oligodendrocytes. However, direct effects of lead on proteins cannot be ignored. Acute lead exposure has been shown to decrease the activity of CNPase, an enzyme preferentially located in myelin and shown to be an integral protein for myelin synthesis during development (Dabrowska-Bouta *et al*., 2000). Lead exposure also causes delayed maturation of oligodendroglia in lead-exposed animals (for review see Tiffany-Castiglioni *et al*., 1989), in addition to the direct toxic effects of lead on Schwann cells in the peripheral nervous system (Dyck *et al*., 1977).

Indirect neurotoxic effects

Lead, at levels at least as low as 10 μg/dl, disrupts haem synthesis, thereby increasing levels of the precursor δ-aminolevulinic acid (ALA). ALA suppresses GABA-mediated neurotransmission by inhibiting its release and also possibly by competing with GABA at receptors (Anderson *et al*., 1996). Lead also can produce anaemia, both by interfering with haem synthesis and by decreasing iron absorption from the gut (Anderson *et al*., 1996). Severe iron deficiency and iron deficiency anaemia are associated with impaired cognitive and neuropsychological development (Bruner *et al*., 1996; Grantham-McGregor and Ani, 2001).

At high lead concentrations (>4 μM), leading to acute encephalopathy, the BBB is damaged, resulting in oedema and, if unchecked, brain ischaemia (Silbergeld, 1992). However, at lower concentrations, lead also disrupts normal BBB functioning, resulting in regionally specific increases in permeability to plasma proteins without producing oedema (Sundström *et al*., 1985; Moorhouse *et al*., 1988; Dyatlov *et al*., 1998). In *in vitro* studies of brain capillary endothelial cells, lead accumulates in the same intramitochondrial areas as calcium, an effect the authors suggest 'may be associated with lead-induced disruptions in intracellular calcium metabolism and transepithelial transport processes' (Silbergeld *et al*., 1980).

Another indirect effect of lead on the brain is via disruption of thyroid hormone transport into the brain. Thyroid hormones are critical to the normal development of the brain, severe deficiencies causing mental retardation. The choroid plexus, where transthyretin is synthesized, 'accumulates lead (Pb) to an extraordinary degree following Pb exposure', resulting in decreases in transthyretin levels (Zheng *et al*., 2001).

Silbergeld, in considering the concatenation of lead's toxic effects (Tables 1 and 2), suggests that there are 'at least two distinct forms of lead neurotoxicity' that 'may occur at the same time within an organism at a given exposure, but the long-term consequences are likely to differ. Basically, I propose that lead exerts neurotoxic effects in the following distinct ways: first, as a neurodevelopmental toxicant, interfering with the hard wiring and differentiation of the CNS; and second, as a neuropharmacological toxicant, interfering with ionic mechanisms of neurotransmission' (Silbergeld, 1992). Certainly, the effects of lead on second messengers, transmitter release, transport of thyroid hormone and other actions described previously would alter normal neuronal development as seen in, for example, volumetric changes in the developing hippocampus (Slomianka *et al*., 1989), morphological changes in the developing cortex (Wilson *et al*., 2000) of lead-exposed rats and altered dendritic branching of cerebellar Purkinje cells in postnatally exposed kittens (Patrick and Anderson, 2000).

Lead's ability to substitute for zinc, mentioned previously, affords another avenue by which lead can act as a neurodevelopmental toxicant. By displacing zinc, lead can alter the regulation of genetic transcription through sequence-specific DNA-binding zinc finger protein or zinc binding sites in receptor channels (Reddy and Zawia, 2000). Lead accumulates in cell nuclei and associates with nuclear proteins and

chromatin (Hitzfeld and Taylor, 1989). The presence of lead in the nucleus could result in adverse effects on gene function if lead ions at low concentration are capable of having deleterious effects on gene regulatory proteins (Hanas *et al*., 1999). Lead has been shown to interfere selectively with the DNA-binding properties of Sp1 and TFIIIA, at micromolar concentrations (2.5 μM), by acting at the zinc binding site of these proteins (Zawia *et al*., 1998; Hanas *et al*., 1999). Some of the many genes under Sp1 control are ornithine decarboxylase, myelin basic protein, NMDAR1 subunit and metallothionein (Crumpton *et al*., 2001). Although different TFIIIA-type zinc finger proteins exist and their precise functions are not known, their nucleic acid binding potential suggests that they have roles in regulating gene expression, signal transduction, cell growth and differentiation, and/or chromosome structure (Hanas *et al*., 1999). There is also a very strong association between Sp1 expression and cellular differentiation, particularly with differentiation of oligodendrocytes in the brain. Other studies have shown that the developmental profile of another zinc finger protein, Egr-1 (the product of an early growth response gene), which is functionally involved in cell proliferation and differentiation in the brain, is also altered by lead exposure (Reddy and Zawia, 2000).

The development of the brain involves two different but interrelated organizational periods. 'The first period begins at conception and includes the major histogenetic events, such as neurulation, proliferation, migration and differentiation. It has been proposed that these events may be controlled by genetic and epigenetic events, which give rise to neural structures that are amenable to external influence. The second period is a time of reorganization in the human cortex. These events occur during gestation and continue postnatally, possibly through the second decade of life. This stage is characterized by dendritic and axonal growth, synapse production, neuronal and synaptic pruning, and changes in neurotransmitter sensitivity' (Webb *et al*., 2001). In cultured hippocampal neurons, lead, in concentrations as low as 100 nM, inhibited neurite outgrowth (Kern and Audesirk, 1995). Synaptic pruning, the process by which the rich overproduction of synaptic connections that characterizes early development is shaped by experience and learning-dependent synaptic activity to eliminate redundant connections, also seems to be particularly sensitive to lead's effects. The density of dendritic spines was significantly elevated on the dendrites of cerebellar Purkinje cells from kittens postnatally exposed to low levels of lead (<10 μg/dl) (Patrick and Anderson, 2000). Fifty days of lead exposure (0.25 μg/g tissue brain levels), beginning on postnatal day 1, produced time-dependent interference in the expression of a variety of glial-related genes (i.e. myelin basic protein and glial fibrillary acidic protein) involved in the developmental regulation of cerebellar growth and maturation (Zawia and Harry, 1996). Decreases in the width, granule cell density and dendritic arborization of the cerebellar molecular layer have been reported after lead exposure (Lorton and Anderson, 1986).

The architecture of cortical processing units is also affected by lead's developmental influences. In the rat brain, a specialized columnar organized area of the somatosensory cortex, called the barrel field, receives input from the vibrissae via a highly ordered polysynaptic pathway through the brainstem and thalamus. The precise growth and regression of dendrites in this cortical region sharpen the boundaries of the barrel field as the animal matures. Rats exposed to lead from birth to day 10 (blood lead levels between 19 and 31 μg/dl) showed a significant decrease in the size of the cortical columns, the basic functional unit of the somatosensory cortex, in the barrel field during development (Wilson *et al*., 2000). In these animals, lead exposure limited the arborizations of thalamocortical axons and reduced the area of the barrel fields.

The effects of lead on the development of the nervous system establish the basis for cognitive impairments in lead-exposed children, while specific effects on glutamatergic transmission, which is critically involved in both development and neuronal plasticity, presage impairments in learning and memory. Disruption of dopaminergic functioning, which is normally involved in not only motor control but also attention, memory and executive functioning (Brown *et al*., 1997), can produce a host of behavioural problems, including attention deficit hyperactivity disorder, as well as cognitive impairments. Review of the clinical literature (see below) amply demonstrates that the unfortunate expectations based on the preceding consideration of lead's toxic effects are fulfilled by the findings from studies of neuropsychological functioning in lead-exposed children.

Lead and pregnancy

Lead as a neurotoxin can carry a lethal legacy. Young women who live in lead-contaminated housing or who were lead-poisoned themselves as youngsters can pass lead on to their unborn fetuses. There is a strong correlation between maternal and umbilical cord blood lead levels, indicating the transfer of lead from mother to fetus (Gardella, 2001). Lead accumulates and is stored in bone for decades and these bone lead stores may pose a threat to women of reproductive age long after their exposure to lead has ended. In some studies, the contributions from endogenous (bone) and exogenous (environmental) sources on maternal blood lead levels were about equal (Chuang *et al*., 2001). Others suggest that skeletal lead stores are the dominant contributor to blood lead during pregnancy and the postpartum period (Gulson *et al*., 1999). In addition to transfer of lead prenatally, lead levels in breast milk also increase with the lead level in maternal blood, posing an additional risk to the neonate (Li *et al*., 2000). High calcium intake (>2000 mg/day) may attenuate pregnancy-induced increases in maternal blood lead concentrations by decreasing maternal bone resorption or

demineralization during pregnancy and the subsequent release of lead from the bone (Johnson, 2001). The mobilization of bone lead stores in pregnant and post-partum women is particularly troublesome in view of work in children indicating that deleterious effects on cognitive development occur with placental blood lead levels below 10 μg/dl (Bellinger, 2000).

Effects of lead in children

The toxicokinetics of lead is complex (Leggett, 1993; Cory-Schlecta and Schaumburg, 2000). The primary routes of lead absorption are via respiration and ingestion; cutaneous absorption is negligible. Absorbed lead is cleared by the kidneys in the urine and unabsorbed lead is eliminated in the faeces. Absorbed lead is carried throughout the body by the blood, wherein the major burden (95%) is carried by erythrocytes and the remainder—the part that is most accessible to other tissues—in the plasma. Lead enters all tissues of the body, following the distribution of calcium. The half-life of lead in blood approximates that of the erythrocyte (~35 days), while in the brain it is ~2 years and in bone decades. For this reason, the blood lead level, the most common variable used to establish the degree of exposure in studies of childhood lead poisoning, is primarily an indicator of recent exposure. However, in spite of the short half-life of lead in the blood, circulating lead levels can remain elevated for relatively long periods as the result of the mobilization of internal stores (Roberts *et al*., 2001).

Children are particularly sensitive to the effects of lead for several reasons (Leggett, 1993; Cory-Schlecta and Schaumburg, 2000). A greater proportion of ingested lead is absorbed from the gastrointestinal tract of children than of adults. In addition, a greater proportion of systemically circulating lead gains access to the brain of children, especially those 5 years of age or younger, than of adults. Finally, the developing nervous system is far more vulnerable to lead's toxic effects than the mature brain.

The symptoms of severe lead poisoning in children initially include lethargy, abdominal cramps, anorexia and irritability. Over a period of weeks, or days in children younger than 2 years of age, there is progression to vomiting, clumsiness and ataxia, then to alternating periods of hyperirritability and stupor, and finally coma and seizures. Children who survive are either severely compromised cognitively or frankly mentally retarded. This syndrome is typically associated with a blood lead level of 70 μg/dl, although it can occur in some children at 50 μg/dl (Adams and Victor, 1993; Cory-Schlecta and Schaumburg, 2000).

Lower blood levels of lead, while not typically associated with potentially fatal encephalopathy, are also neurotoxic in children and have lasting effects on neurobehavioural functioning, as described elsewhere in this review. Lead poisoning from these lower levels of exposure is far more common and is particularly insidious because of its lack of diagnostically definitive physical signs. Some children complain of stomach pains and loss of appetite and may or may not have anaemia. However, such symptoms are not present in all poisoned children, or even the majority, and in any case do not point unequivocally to lead as the culprit. Such poisoning, often termed 'asymptomatic' because of the lack of clear physical symptoms, is unfortunately not 'asymptomatic' with respect to its effects on brain functioning.

Considerable efforts have been directed at measuring the cognitive effects of lead exposure at levels below those that produce overt signs of encephalopathy. The major goal of much of this work has been to describe the nature of lead's effects on cognition and to determine what levels of lead exposure are presumptively safe. The seminal work in this area was done by H. L. Needleman and his colleagues (Needleman *et al*., 1979). Since lead-poisoned children are often economically disadvantaged and live in poor communities served by inadequate schools, studies of their cognitive functioning can be affected by numerous confounds. However, the studies of Needleman and colleagues focused on white, English-speaking children from working class to upper middle class backgrounds. On the basis of extrapolation from lead levels in deciduous teeth to blood lead levels, the range of exposure was reported to vary from 12 to 54 μg/dl. Lead-related effects on IQ, verbal processing and attention were described, as well as effects on classroom performance. The authors concluded: 'Lead exposure, at doses below those producing symptoms severe enough to be diagnosed clinically, appears to be associated with neuropsychological deficits that may interfere with classroom performance.'

The findings of Needleman and colleagues have been replicated and extended in numerous cross-sectional and longitudinal studies with traditional intelligence testing, i.e. by measuring IQ, the typical endpoint. IQ was chosen because of its strong psychometric properties and because it 'is sufficiently well standardized to be comparable across studies, and exhibits attractive simplicity for the regulator in a public health context' (Winneke and Krämer, 1997). This contentious and, in part, contradictory literature is only briefly summarized; the interested reader is addressed to several recent reviews (e.g. Bellinger and Dietrich, 1994; Winneke and Krämer, 1997) for more detailed information concerning lead and IQ. However, the generally agreed finding from this research is that there is an inverse relationship between IQ and blood lead level. The magnitude of this effect has been the subject of some dispute (e.g. Dietrich *et al*., 1993*a*; Tong *et al*., 1996; Winneke and Krämer, 1997), though a decrement of 1–3 points in full-scale IQ with an increase in blood lead from 10 to 20 μg/dl has been found with some regularity and decrements of 5–10 IQ points with moderate levels of exposure (up to 30 μg/dl) (Wasserman *et al*., 2000*a*, *b*).

While the size of the lead-induced decrement does not appear impressive, the limitations of the studies of lead's effects on IQ must be considered. The children studied have differed in a variety of characteristics, including nationality

and socioeconomic status (Bellinger *et al*., 1992; Tong *et al*., 1996; Winneke and Krämer, 1997; Wasserman *et al*., 2000*b*) and the methods of measuring exposure have also differed, yet the qualitative outcome has been generally consistent. In addition, these studies only report group averages, 'which applies to the individual child only in a probabilistic sense... even small average effects, due to the normal variability of individual susceptibility, will be associated with larger IQ deficits in individual cases of particular susceptibility' (Winneke and Krämer, 1997).

Most impressive, however, is the relative consistency of the findings about lead and IQ despite two important weaknesses in the use of intelligence tests as the yardstick for measuring lead's effects on cognition. First, some components of intelligence tests are influenced by socioeconomic factors. Thus, there is a strong possibility of confounding lead-induced IQ decrements with the adverse influences of socioeconomic status (SES). For this reason, many of the investigators studying lead's effects on children's IQ are careful to control for the ostensibly confounding effect of SES. However, there is accumulating evidence that SES, in addition to its influences as a confounder when IQ tests are used, actually modifies the biological effect of lead on the brain [see below, socioeconomic status (SES)]. Thus, statistical measures taken to eliminate the confounding effects of SES on IQ may well also obscure lead's most potent effects on cognition.

However, the second problem with using IQ as the primary endpoint is by far the more important. Specifically, intelligence tests, under many conditions, are not particularly sensitive to the effects of brain injury. IQ or its equivalent is a single number that is determined on the basis of the child's overall performance on a battery of subtests that assess multiple and often unrelated functions. Brain injury, whether from trauma, hypoxia or toxic exposures, frequently affects functioning in a limited number of neurobehavioural systems. Intelligence test batteries, wherein global outcome measures reflect the aggregate performance of multiple functions, underestimate the effects of such injuries.

A recent case series graphically illustrates the insensitivity of IQ testing to the cognitive effects of brain injury (Dlugos *et al*., 1999). Five children (mean age at surgery was 14 years, 1 month) underwent left temporal lobectomy for temporal lobe epilepsy. Each patient exhibited 'significant language-related cognitive declines after surgery... although VIQ [verbal IQ] dropped significantly in only one patient.' Indeed, VIQ showed non-significant increases in four of five children.

Lezak (1995), in arguing against the use of IQ tests to assess cognitive functioning in brain injury, cites Teuber's (1969) insightful remarks on the subject: 'One must never misconstrue a normal intelligence test result as an indication of normal intellectual status after head trauma, or worse, as indicative of a normal brain: to do so would be to commit the cardinal sin of confusing absence of evidence with evidence of absence.'

In contrast to intelligence test batteries, neuropsychological tests, which are designed to target more limited cognitive domains, are, in general, much more sensitive to the effects of brain damage and, in the case of lead's neurotoxicity, demonstrably so. The European Multicenter Study was a cross-sectional evaluation of the cognitive effects of lead exposure combining the results from individual study groups in Bulgaria, Denmark, Greece, Germany, Hungary, Italy, Romania and Yugoslavia. In addition to IQ testing, neuropsychological tests were administered that assessed visuomotor integration, information processing and reaction time. Although the usual 1- to 3-point decrease in IQ with an increase in blood lead from 10 to 20 μg/dl was found, more robust decreases were reported for the neuropsychological measures (Winneke *et al*., 1990; Winneke and Krämer, 1997).

There have been a number of studies of lead's cognitive effects in which neuropsychological testing was used either in association with an IQ battery or as the primary endpoint. Unfortunately, unlike many of the recent studies of IQ in relation to lead exposure, there is little uniformity in the basic methods of the different groups of investigators. Neuropsychological studies of lead's effects differ in such basics as the characteristics of the study group (e.g. SES, levels of exposure, age at testing), the methods for measuring lead exposure and the choice of tests administered to the study groups. Following is a brief review of the major findings, focusing primarily on studies in which lead exposure was determined from blood samples. Although it is clear that an elevated lead concentration in shed deciduous teeth indicates childhood exposure to lead, the quantitative relation between exposure levels based on tooth concentration and those on blood tests is uncertain (Grobler *et al*., 2000).

Winneke and colleagues (Walkowiak *et al*., 1998) investigated the effects of low-level lead exposure (mean 4.3 μg/dl, upper 95 percentile value 8.9 μg/dl) on cognitive functioning in a cohort of 6- to 7-year-old children in Germany. The primary finding was impaired attention; tests of other aspects of cognition (visual perception, visual memory, finger-tapping and reaction time) were unaffected. Stiles and Bellinger (1993) investigated the effects of similar low levels of exposure (mean <8 μg/dl) in a group high-SES children (mean age 9 years, 9 months) from the Boston area. A neuropsychological test battery was administered and performance correlated with blood lead levels previously assessed at 6, 12, 18, 24 and 57 months as well as the time of neuropsychological testing. In tests of rote verbal learning and also cognitive flexibility, children had a tendency to perseverate (repeat previous incorrect responses), an abnormal behaviour that was significantly correlated with previous blood lead levels. In addition, there was an inverse relation between blood lead level at 24 months and visuospatial constructional ability as well as a measure of fine motor functioning. Unfortunately this study did not include neuropsychological tests of attention.

Dietrich and colleagues (Dietrich *et al*., 1993*b*) studied the effects of low to moderate lead exposure in the neonatal and

postnatal period on motor development. The cohort, 6-year-old children from the inner city in Cincinnati, was divided into quartiles according to exposure level, with the mean of the first quartile 7.28 μg/dl (range 4.7–9 μg/dl), the second 10.59 μg/dl (range 9.13–12.3 μg/dl), the third 14.48 (range 12.39–16.7 μg/dl) and the fourth 22.00 μg/dl (range 16.72–38.15 μg/dl). Fine motor functioning was more affected than gross motor functioning at levels as low as 9 μg/dl. After adjustment for covariates, neonatal blood lead levels were inversely correlated with upper limb speed and dexterity, while postnatal exposure was inversely correlated with bilateral coordination, upper limb speed, dexterity and visuomotor functioning.

Not surprisingly, higher levels of lead exposure are correlated with more severe neuropsychological impairments. Faust and Brown (1987) administered a comprehensive battery of neuropsychological tests to a group of 5- to 12-year-old children with previous blood lead levels in the range of 30–60 μg/dl. In comparison with unexposed matched controls, lead-exposed children performed significantly worse on measures of fine motor functioning, language, verbal memory, higher-order visuospatial functions and concentration.

Long-term follow-up studies of children who had been exposed to lead indicate that neuropsychological deficits, like changes in IQ, persist into adulthood (White *et al*., 1993; Stokes *et al*., 1998). Stokes and colleagues evaluated young adults (mean age 24.3 years) 20 years after their exposure to lead as children (9 months to 9 years of age). The exposed cohort grew up in a town with a lead smelter that was operating without emission-reducing devices. The mean blood lead level for children in this locale was 50 μg/dl in 1974 and 39.6 μg/dl in 1975. Although the blood lead level was only known for about 25% of the exposed cohort, it was 49.3 μg/dl. K X-ray fluorescence of tibia lead content, a recognized measure of cumulative lead exposure, showed that the exposed group had significantly greater body burdens of lead than the matched controls. At the time of the current evaluation, blood lead levels of both groups were low (exposed group 2.9 μg/dl, control group 1.6 μg/dl). The exposed group performed significantly worse on each test of cognitive functioning, including assessments of reaction time, scanning and executive functioning (cognitive flexibility and abstract reasoning), as well as on tests of fine motor functioning and postural stability.

Stokes and colleagues also described abnormalities of the peripheral nervous system that are typically associated with occupational lead exposure of adults (Stokes *et al*., 1998). Vibrotactile thresholds of the fingers, but not the toes, were significantly higher in the lead-exposed group. Clinical neurology texts stress that central nervous system effects are characteristic of childhood lead poisoning while peripheral nervous system effects are more prevalent with adult poisoning (e.g. Adams and Victor, 1993). However, the symptoms of paediatric lead poisoning are typically described when the patient is still a child. It is possible that the somatosensory impairments seen in adults who were poisoned as children reflects an ageing-related emergence of neurological signs and/or the exacerbation of pre-existing signs that were too subtle to be detected by clinical neurological examination.

White and colleagues (White *et al*., 1993) evaluated the neuropsychological functioning of a group of adults 50 years after they had been hospitalized for lead poisoning at the age of 4 years or younger. Since accurate blood lead analysis was not available between 1930 and 1942, when the study group was poisoned, indirect evidence was used to identify exposed individuals. Each person included in the exposure group had a history that provided evidence of exposure to lead (typically pica for leaded paint), a record of symptoms indicative of lead poisoning and also dense metaphyseal bands (lead lines) on X-ray of at least one long bone. Physical symptoms of the type seen during hospitalization for poisoning (e.g. vomiting, anorexia, hyper-irritability) are associated with blood lead levels equal to or exceeding 60 μg/dl. When tested as adults, the lead-exposed group had poorer performance on tasks of abstract reasoning, cognitive flexibility, verbal memory, verbal fluency and fine motor speed.

In addition to the evaluation of effects on cognition, there has been increasing interest in the influences of early lead poisoning on subsequent social/emotional development. Sciarillo and colleagues observed that in 4- to 5-year-old boys and girls there was an increased incidence of a variety of behaviour problems (e.g. depression, somatic complaints) in lead-exposed children and that increases in aggression were observed at a blood lead level of 15 μg/dl (Sciarillo *et al*., 1992). Needleman and colleagues reported that in 7-year-old boys the association between lead and antisocial/delinquent behaviour was borderline but increased to significance in 11-year-olds (Needleman *et al*., 1996). The first prospective longitudinal investigation of prenatal lead exposure and juvenile delinquency (Dietrich *et al*., 2001) showed an increase in antisocial behaviour with low-level lead exposure even after adjusting for a variety of medical (e.g. birth weight, Apgar score, narcotic use during pregnancy) and social (e.g. maternal IQ, highest grade attained by primary caregiver) covariates.

Although lead exposure is associated with increases in problematic behaviour, it is not clear if the observed behaviours are caused directly by lead-induced brain damage or are secondary to the handicaps imposed by cognitive impairments. Brain-injured children frequently experience a loss of confidence in response to the academic difficulties they experience due to cognitive deficiencies. Repeated reminders of one's inadequacies in comparison with peers—nowhere is this more likely than in a classroom where testing allows letter-grade ranking of abilities—ultimately often causes loss of self-esteem and poor social development. However, lead also affects the brain systems that regulate social/emotional functioning. Mendelsohn and colleagues (Mendelsohn *et al*., 1998) studied children who were too young to have experienced

the consequences of academic failure. Children aged 12–36 months with lead levels 25 μg/dl were evaluated using a standardized test battery, the Bayley Scales of Infant Development, to measure factors related to social/emotional functioning. The scores of children who had been exposed to lead were significantly worse than those of non-exposed children in measures of emotional regulation and orientation-engagement.

Selective vulnerability

A general principle of toxicology is that a variety of factors can either increase or decrease an individual's sensitivity to a toxin. As already discussed, several variables associated with normal development increase the vulnerability of young children to the neurotoxic effects of lead. However, there are other factors that affect the response of subgroups of children to lead exposure more selectively.

Socioeconomic status (SES)

One influence on vulnerability that attracted increasing attention is SES. A child's SES clearly affects the likelihood of exposure to lead. The Third National Health and Nutrition Examination Survey (NHANES III) (Brody *et al*., 1994), which studied blood lead levels in the US population between 1988 and 1991, showed that 21% of children in the inner city had blood lead levels equal to or greater than the CDC's maximum allowable level of <10 μg/dl compared with 5.8% of children in other areas. When stratified by income level, 16.3% of children from low-income families had blood lead levels of ⩾10 μg/dl compared with 5.4 and 4.0% of children from middle- and high-income families. However, in addition to the role of lower SES in increasing the probability of lead exposure, there is increasing recognition that the concomitants of poverty also enhance lead's neurotoxicity (e.g. Rutter, 1983).

Since SES has an effect on certain components of standard intelligence tests and IQ was the endpoint in the first investigations of lead's effects on cognitive development, care has been taken to control for confounding influences, typically by the use of multiple regression or covariate analysis. To consider SES simply as a confound might be to underestimate its influence. Rutter hypothesized that economically disadvantaged children, because of a neuropsychological status rendered fragile by environmental influences, might be more vulnerable to the neurotoxic effects of lead. Confirmatory evidence was found by Winneke and Krämer (1984). SES interacted with lead's effects on visual–motor integration and reaction time; performance deficits were greater in poorer lead-exposed children than their more economically fortunate counterparts. The authors concluded that 'the common practice of merely removing the effects of confounding factors, such as socioeconomic status, appears doubtful... In addition, some of the inconsistencies in this area of research might be due to differential sampling of subgroups of lead-exposed children characterized by different levels of psychosocial adversity.'

Similar findings and conclusions were reported by Bellinger (2000) for prenatal lead exposure. Three groups of infants, with umbilical cord blood lead levels of 3 μg/dl (low), 6–7 μg/dl (medium) and ⩾10 μg/dl (high), were studied. Development was assessed at 6, 12, 18 and 24 months of age. Through the first 24 months, the children with high cord lead levels had lower scores on cognitive tests than the children in the medium and low exposure level groups. In addition, however, SES played a modulating role. At 24 months, children with lower SES performed more poorly on cognitive tasks than children with similar high cord lead levels but with higher SES. At younger ages, there was no effect of SES on the cognitive effects of lead exposure. Moreover, at medium levels of cord lead, only those children with lower SES were adversely affected by lead; children with medium cord lead but with higher SES were protected against the adverse effects of lead on cognition.

Although the mechanisms of the effect of SES on lead's neurotoxicity are not known, there are several concomitants of poverty that increase the likelihood not only of a child being exposed to lead but also that, once exposed, more lead will be absorbed. Although the use of lead paint in residential housing was banned by Consumer Product Safety Commission regulations in 1978, no provision was made to remove existing lead-based paint from houses constructed before this edict went into effect. Thus, older houses have increased probability of having been painted with lead paint, and a substantial number (estimated at 42–47 million) of such dwellings still exist (Lin-Fu, 1992). Older houses tend to be concentrated in older urban centres, where many economically disadvantaged families live. Leaded paint is particularly hazardous to children when it is deteriorating and producing lead-containing dust that is absorbed as a result of hand-to-mouth activities. The dangers of lead exposure are also increased by several dietary conditions (i.e. deficiencies in calcium, iron, zinc or protein) that are more frequently encountered in economically disadvantaged children (Chisolm, 1996; Cheng *et al*., 1998).

In addition to increasing lead absorption, dietary factors may also have the potential to increase the effect of lead on the brain. As described (see above), the endothelial cells of brain capillaries form tight junctions that contribute to the BBB. Kerper and Hinkle (1997*a*) showed that lead uptake in primary cultures of bovine brain capillary endothelial cells was activated by depletion of intracellular calcium stores. It has been hypothesized that increased uptake of lead kills capillary endothelial cells and thereby disrupts the BBB (Anderson *et al*., 1996).

The modulating influence of the environment on lead neurotoxicity was underscored in a recent study using laboratory rats. Immediately after weaning, rat pups were put in either impoverished or enriched environments. Half of the animals in each environment were exposed to lead via the drinking water. Although similar levels of lead were observed

in the blood and in the brain, lead-exposed rats reared in impoverished environments showed learning deficits. Conversely, lead-exposed rats raised in enriched environments performed similarly to their unexposed counterparts. Dietary considerations do not explain the differential sensitivity of the groups of rats since, apart from lead exposure, the diet was identical (Schneider *et al*., 2001).

There are a number of environmentally modulated factors that could affect the response of the brain to a neurotoxin such as lead. In the study described previously (Schneider *et al*., 2001), lead-exposed rats in the impoverished environment had significantly decreased neurotrophic factor gene expression in the hippocampus. High-density oligonucleotide microarrays were used to analyse gene expression in young adult mice raised in either enriched environments or in less stimulating conditions (Rampon *et al*., 2000). There were many changes linked to environmental enrichment, those of particular interest being related to the changes in neural structure seen during growth and development, synapse formation, synaptic transmission, neuronal plasticity and cell survival. In addition, environmental enrichment also enhances the survival of new hippocampal neurons, the product of neurogenesis (Kempermann *et al*., 1997).

Genetic factors

In addition to SES, another factor influencing the vulnerability of the brain to lead's neurotoxic effects is genetics. At least three genes have been identified that can influence the accumulation and toxicokinetics of lead in humans (Onalaja and Claudio, 2000).

The *ALAD* gene, which codes for δ-aminolevulinic acid dehydratase (ALAD), has been most heavily studied but, as yet, the consequences of the different alleles for vulnerability to lead poisoning are unclear. ALAD protein is an enzyme that catalyses the condensation of two molecules of 5-aminolevulinic acid (ALA) to form porphobilinogen, the precursor of haem. Lead binds to ALAD, inhibiting its activity and leading to increased levels of non-condensed ALA, which has neurotoxic properties in its own right.

ALAD protein comes in two isoforms, ALAD1 and ALAD2. ALAD2 has higher affinity for lead than does ALAD1 so that individuals with the ALAD1-2 or ALAD2-2 phenotype tend to have higher blood lead levels than those with ALAD1-1. However, whether ALAD2 increases vulnerability, by raising blood lead levels, or decreases it, by keeping lead sequestered in the blood, is not known. Evidence suggestive of the latter was reported by Bellinger and colleagues (Bellinger *et al*., 1994). Attention and executive functioning was assessed in adolescents who had been exposed to lead, as measured by tooth dentin levels. The subjects expressing the ALAD2 phenotype tended to have lower dentin lead levels than those with ALAD1, consistent with the idea that the increased affinity of the ALAD2 phenotype decreases the entry of lead from the blood into other tissues. Moreover, after correction for exposure level, adolescents with the ALAD2 phenotype performed better in virtually all areas than those with ALAD1. Unfortunately, since there were only five individuals with the ALAD2 phenotype, the sample size precluded evaluation of statistical significance.

The second gene, the vitamin D receptor (VDR) gene, is involved in Ca^{2+} absorption through the gut and into calcium-rich tissues such as bone, particularly under conditions when Pb^{2+} levels are high enough to compete with the available Ca^{2+}. The blood-borne variant of vitamin D binds to the VDR in the nuclei of intestinal cells, kidney and bone, thereby activating genes that encode calcium-binding proteins, including calbindin D. These proteins, involved in calcium transport, result in increased absorption of calcium and, if present, lead (Cheng *et al*., 1998). There are at least two alleles (*b* and *B*) and three variants of the VDR genotype, denoted *bb*, *BB* and *Bb*. In occupationally exposed adults, individuals with the *B* allele had higher chelatable lead levels as well as higher lead levels in blood and bone (tibia) (Schwartz *et al*., 2000). There have been no studies that indicate which, if any, of the VDR phenotypes are associated with increased vulnerability to the neurotoxic effects of lead.

The third gene, the haemochromatosis gene, coding for the HFE protein, might also influence lead absorption. Mutated HFE protein causes haemochromatosis in homozygotic individuals, wherein large quantities of iron are deposited in many internal organs; polymorphisms in HFE might influence the absorption of lead, especially since Pb^{2+} can be mistaken for Fe^{2+}, and incorporated into processes requiring Fe^{2+}. In addition, HFE protein may also influence the expression of metal transporters in the gut, including those that can transport lead (Onalaja and Claudio, 2000).

The toxic threshold

Using venous blood lead levels as an index, the upper acceptable limit for children in the early 1960s was 60 μg/dl, the level at which lead poisoning was associated with overt physical symptoms. However, with the recognition that lower blood lead levels that may lack clear physical symptoms also produce brain damage (cf. Lin-Fu, 1972), the threshold was lowered to 40 μg/dl in 1970. As research has demonstrated that lower levels of lead exposure also produce brain injury in children, the upper limit of 'acceptable' blood lead levels has been successively decreased. Thus, in 1975 it was dropped to 30 μg/dl, in 1985 to 25 μg/dl and finally, in 1991, to 10 μg/dl (Pueschel *et al*., 1996). Because there has been considerable new research into the neurotoxicity of lead in the past 10 years, is the threshold of 10 μg/dl established in 1991 still reasonable?

The concentration of 10 μg/dl corresponds to a molar concentration of 0.48 μM. Several of the effects of lead occur at concentrations several orders of magnitude lower than the clinical threshold. For example, lead affects calmodulin (Ferguson *et al*., 2000) and synaptotagmin I (Bouton *et al*., 2001) at nanomolar concentrations and PKC at picomolar

concentrations (Bressler *et al*., 1999). Thus, in terms of adverse effects on neuronal function, it can be argued that there is no 'safe' level. In addition, effects taking place at higher concentrations, in the micromolar range, are not ruled out with blood lead levels <10 μg/dl, since active transport mechanisms regularly increase central concentrations of various ions, including Ca^{2+} and presumably Pb^{2+}, to levels that far exceed that in the systemic circulation.

Electrophysiological studies in children have described effects of lead, at exposure levels below 10 μg/dl, on sensory functioning. Otto and Fox (1993) reported changes in cortical visual evoked potentials in children from 3 to 12 years of age with blood lead levels from 6 to 59 μg/dl. Rothenberg and colleagues recorded the brainstem auditory evoked response (BAER) in children 5–7 years of age who had been exposed to lead prenatally (Rothenberg *et al*., 2000). The mean maternal blood lead level at 20 weeks of pregnancy was 7.7 μg/dl and was significantly associated with changes in the BAER. Although the functional significance of these changes is not clear, it may be relevant that increases in auditory threshold have been reported with blood lead levels ranging from 6 to 18 μg/dl (Holdstein *et al*., 1986).

Blood lead levels below 10 μg/dl have also been shown to be associated with changes in neurochemistry and behaviour. Tang and colleagues investigated the effects of prenatal lead exposure on the behaviour of 9-month-old infants (Tang *et al*., 1999). In addition to measuring cord blood lead levels at delivery, the authors used plasma from the samples to evaluate the concentrations of the dopamine metabolite homovanillic acid and the serotonergic metabolite 5-hydroxy-indoleacetic acid. The mean cord blood lead level was 3.9 μg/dl, with the 5th and 95th percentiles of the range 2.5 and 7.0 μg/dl, respectively. Correlation analysis showed that both 5-hydroxyindoleacetic acid levels and measures of sociability were negatively associated with cord blood lead levels. The authors interpreted their results as suggesting that low-level prenatal lead exposure 'could produce a neurotoxic effect on the developing serotonergic system' and 'may affect the sociability of infants.'

With regard to the threshold for cognitive effects of lead exposure, Schwartz (1994) performed a meta-analysis of studies of IQ in children with varying blood lead levels. The principal findings were that there was an inverse relation between IQ and blood lead level and that the slope increased with blood lead levels ⩽15 μg/dl, 'suggesting that a threshold of 10 μg/dl is implausible.'

Schwartz's results are particularly important since IQ tests, in contrast to neuropsychological tests, are not especially sensitive to the effects of brain injury. Moreover, the results of neuropsychological testing support Schwartz's conclusion. Walkowiak and colleagues (Walkowiak *et al*., 1998) found attentional deficits with low-level lead exposure (mean 4.3 μg/dl, upper 95 percentile value 8.9 μg/dl). Stiles and Bellinger (1993), investigating the effects of similar low levels of exposure (mean <8 μg/dl), reported impaired performance in tests of rote verbal learning and of cognitive flexibility. Dietrich and colleagues (Dietrich *et al*., 1993*a*, *b*) found that fine motor functioning was negatively affected at blood lead levels as low as 9 μg/dl. In children with low SES, prenatal blood lead levels <10 μg/dl were associated with cognitive impairments when assessed at 24 months of age (Bellinger, 2000).

Recent findings also show the negative consequences of low-level lead exposure for academic skills. Lanphear and colleagues studied 4853 children and adolescents who had participated in the NHANES III (Third National Health and Nutrition Examination Survey) (Lanphear *et al*., 2000). 'An inverse relationship between blood lead concentration and arithmetic and reading scores was observed for children with blood lead concentrations lower than 5.0 μg/dl.'

Conclusions

The information reviewed in the present paper has several implications for public health policy.

In the USA, the present threshold at which blood lead levels are considered to be unacceptable, 10 μg/dl, is too high. The existing literature indicates that the safe level of lead in the blood has not yet been identified; there is solid evidence for detrimental effects on behavioural and cognitive development with blood lead levels below 10 μg/dl.

In some localities, the strategy for dealing with childhood lead poisoning is to screen, by blood lead testing, to identify children who have been exposed to poisonous levels of lead. In other areas only those children considered to be at risk of lead poisoning, by virtue of living in pre-1978 housing, are tested. In many regions there is no formalized procedure for detecting lead poisoning. However, due to the short half life of lead in the blood (several weeks), the period during which lead can be detected in the blood can be far shorter than the duration of its toxic actions in the brain. Once deposited, lead is eliminated very slowly because of its half-life of ~2 years in the brain. Moreover, once in the brain, lead cannot be removed by chemical chelating agents (Rogan *et al*., 2001). Accordingly, even after lead levels in the blood have decreased to seemingly insignificant concentrations, the lead that has been deposited in the brain continues to exert its neurotoxic influence. Thus, once an elevated blood lead concentration has been detected, it is too late to prevent lead's deleterious effects on the developing brain. This fact, plus the very low blood lead levels established to negatively impact development, indicate that the only way to prevent childhood lead poisoning is to prevent lead from ever getting into children's bodies.

Both genetic factors and some as-yet unidentified variables associated with SES affect the vulnerability of a particular individual to lead's neurotoxic effects. Additional research is needed to further characterize the genetic influences and the concomitants of SES that affect a child's biological response to lead.

Acknowledgements

The authors were supported in part by funds from the Office of Mental Retardation and Developmental Disabilities of the New York State Department of Mental Hygiene and the F.M.Kirby Foundation. The authors gratefully acknowledge Dr John Rosen and Dr Ausma Rabe for helpful discussions of and comments on earlier drafts of this paper.

References

Adams RD, Victor M. Principles of neurology, 5th ed. New York: McGraw-Hill; 1993.

Anderson AC, Pueschel SM, Linakis JG. Pathophysiology of lead poisoning. In: Pueschel SM, Linakis JG, Anderson AC, editors. Lead poisoning in children. Baltimore (MD): P.H. Brookes; 1996. p. 75–96.

Antonio MT, Corpas I, Leret ML. Neurochemical changes in newborn rat's brain after gestational cadmium and lead exposure. Toxicol Lett 1999; 104: 1–9.

Audesirk G. Electrophysiology of lead intoxication: effects on voltage sensitive ion channels. [Review]. Neurotoxicology 1993; 14: 137–47.

Audesirk G, Audesirk T. The effects of inorganic lead on voltage sensitive calcium channels differ among cell types and among channel subtypes. Neurotoxicology 1993; 14: 259–65.

Beal MF, Brouillet E, Jenkins BG, Ferrante RJ, Kowall NW, Miller JM, et al. Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. J Neurosci 1993; 13: 4181–92.

Bellinger DC. Effect modification in epidemiological studies of low-level neurotoxicant exposures and health outcomes. [Review]. Neurotoxicol Teratol 2000; 22: 133–40.

Bellinger D, Dietrich KN. Low-level lead exposure and cognitive function in children. [Review]. Pediatr Ann 1994; 23: 600–5.

Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 1992; 90: 855–61.

Bellinger D, Hu H, Titlebaum L, Needleman HL. Attentional correlates of dentin and bone lead levels in adolescents. Arch Environ Health 1994; 49: 98–105.

Bettaiya R, Yallapragada PR, Hall E, Rajanna S. In vitro effect of lead on Ca^{2+}-ATPase in synaptic plasma membranes and microsomes of rat cerebral cortex and cerebellum. Ecotoxicol Environ Saf 1996; 33: 157–62.

Bouton CM, Frelin LP, Forde CE, Godwin HA, Pevsner J. Synaptotagmin I is a molecular target for lead. J Neurochem 2001; 76: 1724–35.

Bradbury MW, Deane R. Permeability of the blood–brain barrier to lead. [Review]. Neurotoxicology 1993; 14: 131–6.

Bressler JP, Goldstein GW. Mechanisms of lead neurotoxicity. [Review]. Biochem Pharmacol 1991; 41: 479–84.

Bressler J, Kim KA, Chakraborti T, Goldstein G. Molecular mechanisms of lead neurotoxicity. [Review]. Neurochem Res 1999; 24: 595–600.

Brody DJ, Pirkle JL, Kramer RA, Flegal KM, Matte TD, Gunter EW, et al. Blood levels in the U.S. population. Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). JAMA 1994; 272: 277–83.

Brown LL, Schneider JS, Lidsky TI. Sensory and cognitive functions of the basal ganglia. [Review]. Curr Opin Neurobiol 1997; 7: 157–63.

Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. Lancet 1996; 348: 992–6.

Cheng Y, Willett WC, Schwartz J, Sparrow D, Weiss S, Hu H. Relation of nutrition to bone lead and blood lead levels in middle-aged to elderly men. The Normative Aging Study. Am J Epidemiol 1998; 147: 1162–74.

Chisolm JJ Jr. Medical management. In: Pueschel SM, Linakis JG, Anderson AC, editors. Lead poisoning in childhood. Baltimore (MD): P.H. Brookes; 1996. p. 141–62.

Chuang HY, Schwartz J, Gonzales-Cossio T, Lugo MC, Palazuelos E, Aro A, et al. Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. Environ Health Perspect 2001; 109: 527–32.

Coria F, Berciano MT, Berciano J, LaFarga M. Axon membrane remodeling in the lead-induced demyelinating neuropathy of the rat. Brain Res 1984; 291: 369–72.

Cory-Schlecta DA, Schaumburg HH. Lead, inorganic. In: Spencer PS, Schaumburg HH, Ludolph AC, editors. Experimental and clinical neurotoxicology. 2nd ed. New York: Oxford University Press; 2000. p. 708–20.

Crumpton T, Atkins DS, Zawia NH, Barone S Jr. Lead exposure in pheochromocytoma (PC12) cells alters neural differentiation and Sp1 DNA binding. Neurotoxicology 2001; 22: 49–62.

Dabrowska-Bouta B, Sulkowski G, Bartosz G, Walski M, Rafalowska U. Chronic lead intoxication affects the myelin membrane status in the central nervous system of adult rats. J Mol Neurosci 1999; 13: 127–39.

Dabrowska-Bouta B, Sulkowski G, Walski M, Struzynska L, Lenkiewicz A, Rafalowska U. Acute lead intoxication in vivo affects myelin membrane morphology and CNPase activity. Exp Toxicol Pathol 2000; 52: 257–63.

Deng W, McKinnon RD, Poretz RD. Lead exposure delays the differentiation of oligodendroglial progenitors in vitro. Toxicol Appl Pharmacol 2001; 174: 235–44.

Devoto P, Flore G, Ibba A, Fratta W, Pani L. Lead intoxication during intrauterine life and lactation but not during adulthood reduces nucleus accumbens dopamine release as studied by brain microdialysis. Toxicol Lett 2001; 121: 199–206.

Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL. The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol Teratol 1993a; 15: 37–44.

Dietrich KN, Berger OG, Succop PA. Lead exposure and the motor developmental status of urban six-year-old children in the Cincinnati Prospective Study. Pediatrics 1993b; 91: 301–7.

Dietrich KN, Ris MD, Succop PA, Berger OG, Bornschein RL. Early exposure to lead and juvenile delinquency. Neurotoxicol Teratol 2001; 23: 511–8.

Dlugos DJ, Moss EM, Duhaime A-C, Brooks-Kayal AR. Language-related cognitive declines after left temporal lobectomy in children. Pediatr Neurol 1999; 21: 444–9.

Dyatlov VA, Platoshin AV, Lawrence DA, Carpenter DO. Lead potentiates cytokine- and glutamate-mediated increases in permeability of the blood–brain barrier. Neurotoxicology 1998; 19: 283–91.

Dyck PJ, O'Brien PC, Ohnishi A. Lead neuropathy: 2. Random distribution of segmental demyelination among 'old internodes' of myelinated fibers. J Neuropathol Exp Neurol 1977; 36: 570–5.

Faust D, Brown J. Moderately elevated blood lead levels: effects on neuropsychologic functioning in children. Pediatrics 1987; 80: 623–9.

Ferguson C, Kern M, Audesirk G. Nanomolar concentrations of inorganic lead increase Ca^{2+} efflux and decrease intracellular free Ca^{2+} ion concentrations in cultured rat hippocampal neurons by a calmodulin-dependent mechanism. Neurotoxicology 2000; 21: 365–78.

Fox DA, Campbell ML, Blocker YS. Functional alterations and apoptotic cell death in the retina following developmental or adult lead exposure. Neurotoxicology 1997; 18: 645–64.

Gardella C. Lead exposure in pregnancy: a review of the literature and argument for routine prenatal screening. [Review]. Obstet Gynecol Survey 2001; 56: 231–8.

Gilbert ME, Mack CM, Lasley SM. Chronic developmental lead exposure increases the threshold for long-term potentiation in rat dentate gyrus in vivo. Brain Res 1996; 736: 118–24.

Gillis KD, Mossner R, Neher E. Protein kinase C enhances exocytosis from chromaffin cells by increasing the size of the readily releasable pool of secretory granules. Neuron 1996; 16: 1209–20.

Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. [Review]. J Nutr 2001; 131: 649S–666S.

Grobler SR, Theunissen FS, Kotze TJ. The relation between lead concentrations in human dental tissues and in blood. Arch Oral Biol 2000; 45: 607–9.

Gulson BL, Pounds JG, Mushak P, Thomas BJ, Gray B, Korsch MJ. Estimation of cumulative lead release (lead flux) from the maternal skeleton during pregnancy and lactation. J Lab Clin Med 1999; 134: 631–40.

Hanas JS, Rodgers JS, Bantle JA, Cheng Y-G. Lead inhibition of DNA-binding mechanism of Cys_2His_2 zinc finger proteins. Mol Pharmacol 1999; 56: 982–8.

He L, Poblenz AT, Medrano CJ, Fox DA. Lead and calcium produce rod photoreceptor cell apoptosis by opening the mitochondrial permeability transition pore. J Biol Chem 2000; 275: 12175–84.

Hitzfeld B, Taylor DM. Characteristics of lead adaptation in a rat kidney cell line. I. Uptake and subcellular and subnuclear distribution of lead. Mol Toxicol 1989; 2: 151–62.

Holdstein Y, Pratt H, Goldsher M, Rosen G, Shenhav R, Linn S, et al. Auditory brainstem evoked potentials in asymptomatic lead-exposed subjects. Laryngol Otol 1986; 100: 1031–46.

Holtzman D, Olson JE, DeVries C. Bensch K. Lead toxicity in primary cultured cerebral astrocytes and cerebellar granular neurons. Toxicol Appl Pharmacol 1987; 89: 211–25.

Jablonska L, Walski M, Rafalowska U. Lead as an inductor of some morphological and functional changes in synaptosomes from rat brain. Cell Mol Neurobiol 1994; 14: 701–9.

Johnson MA. High calcium intake blunts pregnancy-induced increases in maternal blood lead. [Review]. Nutr Rev 2001; 59: 152–6.

Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature 1997; 386: 493–5.

Kern M, Audesirk G. Inorganic lead may inhibit neurite development in cultured rat hippocampal neurons through hyperphosphorylation. Toxicol Appl Pharmacol 1995; 134: 111–23.

Kern M, Audesirk G. Stimulatory and inhibitory effects of inorganic lead on calcineurin. Toxicology 2000; 150: 171–8.

Kerper LE, Hinkle PM. Lead uptake in brain capillary endothelial cells: activation by calcium store depletion. Toxicol Appl Pharmacol 1997a; 146: 127–33.

Kerper LE, Hinkle PM. Cell ular uptake of lead is activated by depletion of intracellular calcium stores. J Biol Chem 1997b; 272: 8346–52.

Lanphear BP, Dietrich K, Auinger P, Cox C. Cognitive deficits associated with blood lead concentrations <10μg/dl in US children and adolescents. Public Health Rep 2000; 115: 521–9.

Lasley SM, Green MC, Gilbert ME. Influence of exposure period on in vivo hippocampal glutamate and GABA release in rats chronically exposed to lead. Neurotoxicology 1999; 20: 619–29.

Lasley SM, Green MC, Gilbert ME. Rat hippocampal NMDA receptor binding as a function of chronic lead exposure level. Neurotoxicol Teratol 2001; 23: 185–9.

Lawrence DA. In vivo and in vitro effects of lead on humoral and cell-mediated immunity. Infect Immun 1981; 31: 136–9.

Legare ME, Barhoumi R, Hebert E, Bratton GR, Burghardt RC, Tiffany-Castiglioni E. Analysis of Pb^{2+} entry into cultured astroglia. Toxicol Sci 1998; 46: 90–100.

Leggett RW. An age-specific kinetic model of lead metabolism in humans. [Review]. Environ Health Perspect 1993; 101: 598–616.

Lezak MD. Neuropsychological assessment. 3rd ed. New York: Oxford University Press; 1995.

Li PJ, Sheng YZ, Wang QY, Gu LY, Wang YL. Transfer of lead via placenta and breast milk in human. Biomed Environ Sci 2000; 13: 85–9.

Lin-Fu JS. Undue absorption of lead among children—a new look at an old problem. [Review]. New Engl J Med 1972; 286: 702–10.

Lin-Fu J. Modern history of lead poisoning: a century of discovery and rediscovery. In: Needleman HL, editor. Human lead exposure. Boca Raton (FL): CRC Press; 1992. p. 23–43.

Lindahl LS, Bird L, Legare ME, Mikeska G, Bratton GR, Tiffany-Castiglioni E. Differential ability of astroglia and neuronal cells to accumulate lead: dependence on cell type and on degree of differentiation. Toxicol Sci 1999; 50: 236–43.

Lorton D, Anderson WJ. The effects of postnatal lead toxicity on the development of cerebellum in rats. Neurobehav Toxicol Teratol 1986; 8: 51–9.

McCoy L, Richfield EK, Cory-Schlecta DA. Regional decreases in alpha-[^{3}H]amino-3-hydroxy-5-methylisoxazole-4-propionic acid ([^{3}H]AMPA) and 6-[^{3}H]cyano-7-nitroquinoxaline-2,3-dione ([^{3}H]CNQX) binding in response to chronic low-level lead exposure: reversal versus potentiation by chronic dopamine agonist treatment. J Neurochem 1997; 69: 2466–76.

Mendelsohn AL, Dreyer BP, Fierman AH, Rosen CM, Legano LA, Kruger HA, et al. Low-level lead exposure and behavior in early childhood. Pediatrics 1998; 101: E10.

Moorhouse SR, Carden S, Drewitt PN, Eley BP, Hargreaves RJ, Pelling D. The effect of chronic low level lead exposure on blood–brain barrier function in the developing rat. Biochem Pharmacol 1988; 37: 4539–47.

Nachshen DA. Selectivity of the Ca binding site in the synaptosome Ca channels. Inhibition of Ca influx by multivalent metal cations. J Gen Physiol 1984; 83: 941–67.

Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, et al. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. New Engl J Med 1979; 300: 689–95.

Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. JAMA 1996; 275: 363–9.

Nihei MK, McGlothan JL, Toscano CD, Guilarte TR. Low level Pb^{2+} exposure affects hippocampal protein kinase Cã gene and protein expression in rats. Neurosci Lett 2001; 298: 212–6.

Norenberg MD, Martinez-Hernandez A. Fine structural localization of glutamine synthetase in astrocytes in rat brain. Brain Res 1979; 161: 303–10.

Onalaja AO, Claudio L. Genetic susceptibility to lead poisoning. [Review]. Environ Health Perspect 2000; 108 Suppl 1: 23–8.

Otto DA, Fox DA. Auditory and visual dysfunction following lead exposure. [Review]. Neurotoxicology 1993; 14: 191–208.

Patrick GW, Anderson WJ. Dendritic alterations of cerebellar Purkinje neurons in postnatally lead-exposed kittens. Dev Neurosci 2000; 22: 320–8.

Pueschel SM, Linakis JG, Anderson AC. Lead poisoning: a historical perspective. In: Pueschel SM, Linakis JG, Anderson AC, editors. Lead poisoning in childhood. Baltimore (MD): P.H. Brookes; 1996. p. 1–13.

Rafalowska U, Struzynska L, Dabrowska-Bouta B, Lenkiewicz A. Is lead toxicosis a reflection of altered energy metabolism in brain synaptosomes? [Review]. Acta Neurobiol Exp (Warsz) 1996; 56: 611–7.

Rampon C, Jiang CH, Dong H, Tang Y-P, Lockhart DJ, Schultz PG, et al. Effects of environmental enrichment on gene expression in the brain. Proc Natl Acad Sci USA 2000; 97: 12880–4.

Reddy GR, Zawia NH. Lead exposure alters Egr-1 DNA-binding in the neonatal rat brain. Int J Dev Neurosci 2000; 18: 791–5.

Regunathan S, Sundaresan R. Effects of organic and inorganic lead on synaptosomal uptake, release, and receptor binding of glutamate in young rats. J Neurochem 1985; 44: 1642–6.

Roberts JR, Reigart JR, Ebeling M, Hulsey TC. Time required for blood lead levels to decline in nonchelated children. J Toxicol Clin Toxicol 2001; 39: 153–60.

Rogan WJ, Dietrich KN, Ware JH, Dockery DW, Salganik M, Radcliffe J, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. New Engl J Med 2001; 344: 1421–6.

Rothenberg SJ, Poblano A, Schnaas L. Brainstem auditory evoked response at five years and prenatal and postnatal blood lead. Neurotoxicol Teratol 2000; 22: 503–10.

Rutter M. Low level lead exposure: sources effects and implications. In: Rutter M, Russell-Jones R, editors. Lead versus health. Chichester (UK): John Wiley; 1983. p. 333–70.

Schneider JS, Lee MH, Anderson DW, Zuck L, Lidsky TI. Enriched environment during development is protective against lead-induced neurotoxicity. Brain Res 2001; 896: 48–55.

Schwartz J. Low-level lead exposure and children's IQ: a meta analysis and search for a threshold. Environ Res 1994; 65: 42–55.

Schwartz BS, Lee B-K, Lee G-S, Stewart WF, Simon D, Kelsey K, Todd AC. Associations of blood lead, dimercaptosuccinic acid-chelatable lead and tibia lead with polymorphisms in the vitamin D receptor and [delta]-aminolevulinic acid dehydratase genes. Environ Health Perspect 2000a; 108: 949–54.

Sciarillo WG, Alexander G, Farrell KP. Lead exposure and child behavior. Am J Public Health 1992; 82: 1356–60.

Scortegagna M, Hanbauer I. The effect of lead exposure and serum deprivation on mesencephalic primary cultures. Neurotoxicology 1997; 18: 331–9.

Shukla GS, Hussain T, Chandra SV. Possible role of regional superoxide dismutase activity and lipid peroxide levels in cadmium neurotoxicity: in vivo and in vitro studies in growing rats. Life Sci 1987; 41: 2215–21.

Sierra EM, Tiffany-Castiglioni E. Reduction of glutamine synthetase activity in astroglia exposed in culture to low levels of inorganic lead. Toxicology 1991; 65: 295–304.

Silbergeld EK. Mechanisms of lead neurotoxicity, or looking beyond the lamppost. [Review]. FASEB J 1992; 6: 3201–6.

Silbergeld EK, Wolinsky JS, Goldstein GW. Electron probe microanalysis of isolated brain capillaries poisoned with lead. Brain Res 1980; 189: 369–76.

Slomianka L, Rungby J, West MJ, Danscher G, Andersen AH. Dose-dependent bimodal effect of low-level lead exposure on the

developing hippocampal region of the rat: a volumetric study. Neurotoxicology 1989; 10: 177–90.

Stiles KM, Bellinger DC. Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. Neurotoxicol Teratol 1993; 15: 27–35.

Stokes L, Letz R, Gerr F, Kolczak M, McNeil FE, Chettle DR, et al. Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. Occup Environ Med 1998; 55: 507–16.

Struzynska L, Dabrowska-Bouta B, Rafalowska U. Acute lead toxicity and energy metabolism in rat brain synaptosomes. Acta Neurobiol Exp (Warsz) 1997; 57: 275–81.

Sundström R, Müntzing K, Kalimo H, Sourander P. Changes in the integrity of the blood–brain barrier in suckling rats with low dose lead encephalopathy. Acta Neuropathol (Berl) 1985; 68: 1–9.

Tang HW, Yan HL, Hu XH, Liang YX, Shen XY. Lead cytotoxicity in primary cultured rat astrocytes and Schwann cells. J Appl Toxicol 1996; 16: 187–96.

Tang H-W, Huel G, Campagna D, Hellier G, Boissinot C, Blot P. Neurodevelopmental evaluation of 9-month-old infants exposed to low levels of lead in utero: involvement of monoamine neurotransmitters. J Appl Toxicol 1999; 19: 167–72.

Teuber H-L. Neglected aspects of the post-traumatic syndrome. In: Walker AE, Caveness WF, Critchley M, editors. The late effects of head injury. Springfield (IL): C.C. Thomas; 1969. p.

Tiffany-Castiglioni E, Sierra EM, Wu J-N, Rowles TK. Lead toxicity in neuroglia. [Review]. Neurotoxicology 1989; 10: 417–43.

Tong S, Baghurst P, McMichael A, Sawyer M, Mudge J. Lifetime exposure to environmental lead and children's intelligence at 11–13 years: the Port Pirie cohort study. BMJ 1996; 312: 1569–75.

Tong S, von Schirnding YE, Prapamontol T. Environmental lead exposure: a public health problem of global dimensions. [Review]. Bull World Health Organ 2000; 78: 1068–77.

Villeda-Hernandez J, Barroso-Moguel R, Méndez-Armenta M, Nava-Ruíz C, Huerta-Romero R, Ríos C. Enhanced brain regional lipid peroxidation in developing rats exposed to low level lead acetate. Brain Res Bull 2001; 55: 247–51.

Walkowiak J, Altmann L, Krämer U, Sveinsson K, Turfeld M, Weishoff-Houben M, et al. Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. Neurotoxicol Teratol 1998; 20: 511–21.

Wasserman GA, Musabegovic A, Liu X, Kline J, Factor-Litvak P, Graziano JH. Lead exposure and motor functioning in $4\frac{1}{2}$ year-old children: the Yugoslavia prospective study. J Pediatr 2000a; 137: 555–61.

Wasserman GA, Liu X, Popovac D, Factor-Litvak P, Kline J, Waternaux C, et al. The Yugoslavia Prospective Lead Study: contributions of prenatal and postnatal lead exposure to early intelligence. Neurotoxicol Teratol 2000b; 22: 811–8.

Webb SJ, Monk CS, Nelson CA. Mechanisms of postnatal neurobiological development: implications for human development. Dev Neuropsychol 2001; 19: 147–71.

White RF, Diamond R, Proctor S, Morey C, Hu H. Residual cognitive deficits 50 years after lead poisoning during childhood. Br J Ind Med 1993; 50: 613–22.

Widzowski DV, Finkelstein JN, Pokora MJ, Cory-Schlecta DA. Time course of postnatal lead-induced changes in dopamine receptors and their relationship to changes in dopamine sensitivity. Neurotoxicology 1994; 15: 853–65.

Wilson MA, Johnston MV, Goldstein GW, Blue ME. Neonatal lead exposure impairs development of rodent barrel field cortex. Proc Natl Acad Sci USA 2000; 97: 5540–5.

Winneke G, Krämer U. Neuropsychological effects of lead in children: interactions with social background variables. Neuropsychobiology 1984; 11: 195–202.

Winneke G, Krämer U. Neurobehavioral aspects of lead neurotoxicity in children. [Review]. Cent Eur J Public Health 1997; 5: 65–9.

Winneke G, Brockhaus A, Ewers U, Krämer U, Neuf M. Results from the European Multicenter Study on lead neurotoxicity in children: implications for risk assessment. Neurotoxicol Teratol 1990; 12: 553–9.

Zawia NH, Harry GJ. Developmental exposure to lead interferes with glial and neuronal differential gene expression in the rat cerebellum. Toxicol Appl Pharmacol 1996; 138: 43–7.

Zawia NH, Sharan R, Brydie M, Oyama T, Crumpton T. Sp1 as a target site for metal-induced perturbations of transcriptional regulation of developmental brain gene expression. Brain Res Dev Brain Res 1998; 107: 291–8.

Zheng W, Lu Y-M, Lu G-Y, Zhao Q, Cheung O, Blaner WS. Transthyretin, thyroxine, and retinol-binding protein in human cerebrospinal fluid: effect of lead exposure. Toxicol Sci 2001; 61: 107–14.

Received June 25, 2002.
Accepted July 4, 2002