

Very low lead exposures and children's neurodevelopment

David C. Bellinger

Children's Hospital Boston, Harvard Medical School,
Harvard School of Public Health, Boston,
Massachusetts, USA

Correspondence to David C. Bellinger, Farley
Basement Box 127, Children's Hospital Boston,
300 Longwood Avenue, Boston, MA 02115, USA
Tel: +1 617 355 6565; fax: +1 617 730 0618;
e-mail: david.bellinger@childrens.harvard.edu

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Purpose of review

We remain far from achieving the goal of eliminating lead-associated neurodevelopmental morbidities in children. New evidence regarding the blood lead levels at which morbidities occur have led to calls for the Centers for Disease Control and Prevention to reduce the current screening guideline of 10 $\mu\text{g}/\text{dl}$. The review evaluates the basis for these calls.

Recent findings

Adverse outcomes, such as reduced intelligence quotient and academic deficits, occur at levels below 10 $\mu\text{g}/\text{dl}$. Some studies suggest that the rate of decline in performance is greater at levels below 10 $\mu\text{g}/\text{dl}$ than above 10 $\mu\text{g}/\text{dl}$, although a plausible mechanism has not been identified. Increased exposure is also associated with neuropsychiatric disorders such as attention deficit hyperactivity disorder and antisocial behavior. Functional imaging studies are beginning to provide insight into the neural substrate of lead's neurodevelopmental effects. Current protocols for chelation therapy appear ineffective in preventing such effects, although environmental enrichment might do so.

Summary

No level of lead exposure appears to be 'safe' and even the current 'low' levels of exposure in children are associated with neurodevelopmental deficits. Primary prevention of exposure provides the best hope of mitigating the impact of this preventable disease.

Keywords

epidemiology, lead toxicity, neurodevelopment, risk assessment, toxicology

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Introduction

The optimism of the 1990s that the 'lead problem' had been solved turned out to be premature and, like the rumor of Mark Twain's death, greatly exaggerated. Despite remarkable successes in recent decades in abating key sources and pathways of exposure, lead remains the most important pediatric environmental health problem, contributing significantly to the burden of childhood disease in both developed [1] and developing countries [2]. The costs associated with lead-associated morbidities are estimated to be in the billions of dollars [3,4]. Deaths from lead intoxication, although rare, still occur [5]. From a public health standpoint, a major concern is a possible 'silent pandemic' [6••] of neurodevelopmental disorders resulting from children's continuing exposure to low levels of lead.

The current review highlights recent developments in the epidemiology of lead exposure, the blood lead levels associated with various neurodevelopmental toxicities, possible mechanisms of neurotoxicity and the role of chelation therapy in preventing adverse sequelae.

Epidemiology

In the late 1970s, the median blood lead level in US preschool children was 15 $\mu\text{g}/\text{dl}$ and 88% of children had a level greater than 10 $\mu\text{g}/\text{dl}$ [7], the current Centers for Disease Control and Prevention (CDC) screening guideline [8]. Regulatory initiatives limiting the lead content of paint and the use of tetraethyl lead as a gasoline additive were remarkably successful in reducing the prevalence of elevated blood lead levels in children. Based on data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, the mean has declined to 1.9 $\mu\text{g}/\text{dl}$ [9]. The percentage of children with a level above 10 $\mu\text{g}/\text{dl}$ is now 1.7%, although this still represents approximately 300 000 children. The magnitude of racial and socioeconomic disparities has also declined, but levels above 10 $\mu\text{g}/\text{dl}$ remain much more common among minority children, children in low-income families and children living in older homes.

Lead has been described as a 'multimedia pollutant' due to the numerous and diverse sources and pathways of potential exposure. Globalization has contributed to the

problem. Sources with international origins include Chinese-made toys with leaded paint, foods imported from Mexico [10,11], ayurvedic medicines from India [12], spices [13] and folk medicines [14,15]. These episodes remind us that it is important to be aware of cultural practices in assessing a child's risk of lead exposure.

Based on new information developed since the CDC last reduced the screening guideline, some have recommended that the screening guideline be reduced to a level as low as 2 $\mu\text{g}/\text{dl}$ [16[•]]. At this time, the CDC does not plan to reconsider the guideline, however, because of the absence of '... effective clinical interventions ... to lower the blood lead levels for children with levels below 10 $\mu\text{g}/\text{dl}$ or to reduce the risk for adverse developmental effects', because 'children cannot be accurately classified as having blood lead levels above or below a value less than 10 $\mu\text{g}/\text{dl}$...' and because of the lack of evidence of a '... threshold below which adverse effects are not experienced...,' meaning that 'any decision to establish a new level of concern would be arbitrary and provide uncertain benefits' (www.cdc.gov/nceh/lead/faq/changebll.htm). To many, these arguments are not persuasive.

How low is 'low enough'? Characteristics of the dose-effect relationship

Meta-analyses of the epidemiological studies available in the 1990s indicated that children's intelligence quotient (IQ) scores decline 2–3 points per 10 $\mu\text{g}/\text{dl}$ increase in blood lead level [17,18]. This estimate of the slope of the dose-effect relationship was derived on the basis of studies in which most children had blood lead levels in the range of 10–30 $\mu\text{g}/\text{dl}$, using regression models in which the relationship was assumed to be linear (i.e. that the IQ decline per microgram per deciliter increase in blood lead level is constant).

Recent studies demonstrate that 10 $\mu\text{g}/\text{dl}$ has no special biological significance with regard to neurodevelopment, suggesting that the current screening guideline is best interpreted as a risk management tool. Significant inverse associations have been reported in study cohorts in which most or all children had a blood lead level below 10 $\mu\text{g}/\text{dl}$ [19–21] and in some cohorts with a mean as low as 1–2 $\mu\text{g}/\text{dl}$ [22,23]. Although one might question how levels so 'low' can pose risk, it is important to recognize that the descriptor 'low' is both an artifact of the units conventionally used to express blood lead level and specific to historical epoch. Different approaches to estimating the natural 'background' level of blood lead in humans converge on the conclusion that it was two orders of magnitude lower than 1–2 $\mu\text{g}/\text{dl}$ [24]. Today's 'average' is not synonymous with 'physiologically normal.'

Not only do many studies support the existence of adverse effects below 10 $\mu\text{g}/\text{dl}$, but the rate of decline in IQ scores might be greater at blood lead levels below 10 $\mu\text{g}/\text{dl}$ than it is at levels above 10 $\mu\text{g}/\text{dl}$ [25–30]. In a pooled analysis of seven major prospective studies involving 1333 children [26], a log-linear model, the functional form that best described the relationship, predicted a 9.2-point decline in IQ over the range of less than 1–30 $\mu\text{g}/\text{dl}$. Two-thirds of this decline (6.2 points) was predicted to occur in the range of less than 1–9.9 $\mu\text{g}/\text{dl}$, with an additional 1.9-point decline between 10 and 19.9 $\mu\text{g}/\text{dl}$, and a 1.1-point decline between 20 and 30 $\mu\text{g}/\text{dl}$. The mechanism that would generate such a supralinear relationship is unknown, but presumably involves a lead-sensitive pathway that is rapidly saturated at blood lead levels below 10 $\mu\text{g}/\text{dl}$ and other, less rapidly saturated pathways at blood lead levels above 10 $\mu\text{g}/\text{dl}$. Additional research is needed to rule out alternative explanations involving methodological artifacts such as residual confounding. Nonlinear relationships are, however, common in toxicology [31] and have been observed in a neurodevelopmental study of methylmercury exposure [32].

No single neurodevelopmental finding unequivocally identifies a child as having an elevated blood lead level, nor does there appear to be a group of findings that, in aggregate, define a 'signature' injury. Lead-associated deficits have been reported in most domains of function, including verbal IQ, performance IQ, academic skills such as reading and mathematics, visual/spatial skills, problem-solving skills, executive functions, fine and gross motor skills, and memory and language skills. If different mechanisms are operative within different blood lead ranges, the neurodevelopmental effects expressed within a study cohort would be expected to depend, in part, on the portion of the blood lead range represented in the cohort. Furthermore, it is likely that the form in which neurodevelopmental toxicity is expressed depends on factors such as age at exposure, coexposures to other neurotoxicants, nutritional status, genotype and the characteristics of the home environment [33,34]. Experimental studies in rodents show that being reared in a stimulating environment can reduce the severity of lead-associated deficits [35]. Enrichment also normalized gene expression of the *N*-methyl-*D*-aspartate receptor in the hippocampus. On the other hand, being reared in a stressful environment can exacerbate lead-associated deficits [36]. Epidemiological studies suggest that the characteristics of the rearing environment might also affect the outcomes of lead-exposed children [37]. The failure to take account of factors that affect the severity and form in which lead toxicity is expressed could explain the large interindividual variability in outcome usually observed at a given lead level [38].

Recent data have challenged the view that children are at greatest risk with respect to lead toxicity in the first few postnatal years. In some studies of school-age IQ, concurrent blood level, not levels measured in early childhood, bore the strongest association with scores [26]. As lead is a bioaccumulative toxicant with complex kinetics, however, concurrent blood lead level at school age is likely to be a reasonable proxy for lifetime exposure, complicating an effort to draw inferences from observational epidemiological studies about age-dependent variation in vulnerability.

Early lead exposure and children's academic success

Recent studies have assessed the import of blood lead levels below 10 $\mu\text{g}/\text{dl}$ on children's success in meeting the challenges they meet in natural settings such as school. In a cross-sectional study of 400 6–10-year-olds, children with blood lead levels of 5–10 $\mu\text{g}/\text{dl}$ scored 5.9–8.7 points lower than children with levels of 1–2 $\mu\text{g}/\text{dl}$ on academic skills such as word reading, reading comprehension, listening comprehension, math reasoning and math calculations [21]. These associations remained significant when adjustment was made for children's IQ scores (which were also inversely associated with blood lead level), suggesting the presence of the aptitude/ability discrepancies often used to identify children with specific learning disabilities. Similarly, in a study of Taiwanese 8–12-year-olds with a mean blood lead level of 5.5 $\mu\text{g}/\text{dl}$, significant inverse associations were found on class ranking in Chinese, history and society, mathematics, and natural science [39]. In Mexican first-graders, a supralinear relationship was observed between blood lead level and math achievement score, with the steepest decline evident among children with levels below 10 $\mu\text{g}/\text{dl}$ [27]. Among 8600 fourth-grade students in North Carolina, inverse associations were found between blood lead levels as low as 2 $\mu\text{g}/\text{dl}$, measured between 0 and 5 years of age, and end-of-grade reading and mathematics achievement scores [40]. Studies using geo-statistical methods have shown that the spatial distribution of learning disabilities coincides with the historical presence of major sources of lead exposure [41].

Early lead exposure and neuropsychiatric outcomes

Although Byers and Lord's [42] early case series identified severe behavior problems as prominent sequelae of lead poisoning, epidemiological studies have only recently begun to focus in detail on psychopathological outcomes. Greater lead burden has consistently been shown to increase the risk of behaviors linked to the inattentive subtype of attention deficit hyperactivity disorder (ADHD), such as distractibility, disorganization

and daydreaming [43]. In NHANES (1999–2002), the risk of parent-reported diagnosis of ADHD increased, in a dose-dependent manner, with blood lead level [44**]. The adjusted odds ratio in the highest quintile of blood lead level (above 2.0 $\mu\text{g}/\text{dl}$) was 4.1. Higher prenatal exposure to lead, inferred on the basis of level of amino levulinic acid dehydratase in second-trimester maternal serum, has been associated with an increased risk of schizophrenia [45]. Experimental studies provide a plausible basis for this. In rhesus monkeys, lead decreases social play and increases self-stimulatory behavior, resulting in abnormal peer relationships [46].

Aggression and explosive temper were among the behavioral problems Byers and Lord [42] identified in lead-poisoned children. Recent studies suggest that early low-level lead exposure produces antisocial behavior. These include ecologic studies of area statistics on lead poisoning prevalence and crime rates [47–49], case-control studies of adjudicated delinquents [50], and prospective cohort studies of community-dwelling children and adolescents [51,52]. Although this issue is controversial [53], the link is supported by an experimental study in which lead exposure reduced the threshold current in the lateral hypothalamus required to elicit predatory attack behavior in cats [54].

Mechanisms of lead neurotoxicity

Progress continues to be made in clarifying the changes in brain development and function that underlie lead's neurodevelopmental effects. Lead has been implicated in diverse processes such as mitochondrial dysfunction, oxidative stress, deregulation of protein turnover, brain inflammation, decreased cellular energy metabolism, lipid peroxidation, altered activity of first and second messenger systems, abnormal neurotrophic factor expression, and altered regulation of gene transcription [55,56].

In rats, early exposure to environmentally relevant lead levels affects hippocampal granule cell neurogenesis and morphology [57], as well as experience-dependent processes by which the barrel field somatosensory cortex is organized into columnar units [58,59]. Childhood lead exposure might be a risk factor for neurologic disorders in adulthood. In rats and primates, developmental exposure induces late overexpression of amyloid precursor protein and aggregated β -amyloid peptides, which increase risk of neurodegeneration [60]. Higher brain lead levels have been found in patients with diffuse neurofibrillary tangles with calcification [61]. In adults, the *ApoE4* allele, which is associated with increased risk of Alzheimer's disease, increases susceptibility to lead neurotoxicity [62], although this does not appear to be the case in children [63].

Some recent studies have employed functional imaging methods. Magnetic resonance spectroscopy (MRS) has revealed reductions in the *N*-acetylaspartate-to-creatine and phosphocreatine ratios in the frontal gray matter of lead-exposed children, consistent with increased neuronal loss [64]. An MRS study in adults showed an association between greater cumulative lead exposure and higher myoinositol-to-creatine ratios in the hippocampus, reflecting glial dysfunction [65]. On a verb generation task, young adults with greater lead exposure in early childhood had less activation in the left frontal cortex and left middle temporal gyrus, and increased activation, perhaps compensatory, in homologous regions of the right hemisphere [66*].

Efficacy of chelation therapy and other interventions in preventing lead neurotoxicity

The results of prospective studies provide little evidence that neurodevelopmental deficits associated with early lead exposure resolve over time [67–70]. In the only randomized trial of chelation therapy, conducted on children with baseline blood lead levels between 20 and 44 $\mu\text{g}/\text{dl}$, succimer was ineffective in preventing or reversing cognitive deficits [71,72], although benefits were observed on neuromotor outcomes such as postural sway and balance [73]. Experimental studies in rodents suggest that certain succimer chelation protocols might improve learning, attention and arousal regulation [74,75]. Overall, however, the human data available on chelation efficacy suggest that primary prevention of exposure is the best strategy for limiting lead-associated neurodevelopmental morbidity. Moreover, several children have died from hypocalcemia following intravenous chelation with Na_2EDTA rather than the recommended CaEDTA [76], illustrating the importance of the CDC's recommendation that a primary care provider should not undertake chelation without consulting with those experienced in this therapy [77].

No data are available regarding nonmedical interventions that prevent or remediate lead-associated neurodevelopmental deficits. If the nature and severity of lead-associated deficits vary with a child's specific characteristics and circumstances, a 'one size fits all' intervention will not be appropriate, suggesting that interventions should be selected to address a child's specific presenting neurodevelopmental problems, as is done for children with idiopathic learning difficulties.

Conclusion

We have not yet reached the point where it is possible to cite a blood lead level that is 'safe.' Even worse, evidence supporting a supralinear dose–effect relationship is

accumulating, suggesting that, despite the remarkable decline in population lead exposures in recent decades, substantial work remains to be done before lead-associated neurodevelopmental morbidity is eliminated. Although cognitive outcomes such as IQ have historically been the focus of most studies, higher lead exposures are being linked to psychosocial disorders such as ADHD and aggression/delinquency. As chelation therapy, at least as presently used, does not appear to prevent or reverse neurodevelopmental deficits, primary prevention of exposure is the best strategy for reducing lead-related morbidity. The efficacy of nonmedical interventions, such as environmental enrichment, has been demonstrated in lead-exposed animals, but the efficacy of such therapies for lead-exposed children is uncertain.

The Advisory Committee on Childhood Lead Poisoning Prevention [78**] recently issued the following recommendations for primary care providers:

- (1) Provide anticipatory guidance to parents of all young children regarding sources of lead and help them identify sources of lead in their child's environment.
- (2) Help parents to understand the uncertainty of a blood lead value and potential reasons for its fluctuation, including error introduced by the sampling methods and laboratory, age and season-related exposures.
- (3) Assess all children for developmental and behavior status, and seek further evaluation and therapy to reduce developmental or behavioral problems, as necessary.
- (4) Discuss with parents the potential impact of lead on child development and promote strategies that foster optimum development, including encouraging parents to influence their child's development positively by providing nurturing and enriching experiences.
- (5) Whenever possible, utilize laboratories that can achieve routine performance of $\pm 2 \mu\text{g}/\text{dl}$ for blood lead analysis.
- (6) Review office procedures and policies to ensure that lead exposure risk assessment or blood lead screening is performed on all children as required by state or local health officials or as recommended by the CDC.
- (7) Perform a diagnostic blood lead test on all children suspected of having lead exposure or an elevated blood lead level and institute the recommended management guidelines if a child's blood lead level increases to above $10 \mu\text{g}/\text{dl}$.
- (8) Become informed about lead exposure prevention strategies of local or state health departments, and partner with public health agencies, community groups and parents to work toward establishing lead-safe environments in homes and schools for all children and the reduction of exposure to lead from all sources.

References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 225–226).

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- This document from the Advisory Committee on Childhood Lead Poisoning Prevention provides clinicians with recommendations.