

Lead

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ABSTRACT. Children differ from adults in the relative importance of lead sources and pathways, lead metabolism, and the toxicities expressed. The central nervous system effects of lead on children seem not to be reversible. Periods of enhanced vulnerability within childhood have not consistently been identified. The period of greatest vulnerability might be endpoint specific, perhaps accounting for the failure to identify a coherent "behavioral signature" for lead toxicity. The bases for the substantial individual variability in vulnerability to lead are uncertain, although they might include genetic polymorphisms and contextual factors. The current Centers for Disease Control and Prevention screening guideline of 10 $\mu\text{g}/\text{dL}$ is a risk management tool and should not be interpreted as a threshold for toxicity. No threshold has been identified, and some data are consistent with effects well below 10. Historically, most studies have concentrated on neurocognitive effects of lead, but higher exposures have recently been associated with morbidities such as antisocial behavior and delinquency. Studies of lead toxicity in experimental animal models are critical to the interpretation of nonexperimental human studies, particularly in addressing the likelihood that associations observed in the latter studies can be attributed to residual confounding. Animal models are also helpful in investigating the behavioral and neurobiological mechanisms of the functional deficits observed in lead-exposed humans. Studies of adults who have been exposed to lead are of limited use in understanding childhood lead toxicity because developmental and acquired lead exposure differ in terms of the maturity of the organs affected, the presumed mechanisms of toxicity, and the forms in which toxicities are expressed. *Pediatrics* 2004;113:1016–1022; *lead toxicity, children, toxicology, epidemiology.*

ABBREVIATION. CDC, Centers for Disease Control and Prevention.

Although children are viewed as the most vulnerable segment of the population with regard to lead poisoning, recognition of lead as an adult toxicant preceded by thousands of years the first description of childhood lead poisoning.¹ For millennia, exposure to lead was primarily via occupation, but the introduction of leaded paint for residential use in the 19th century brought large amounts of this metal within easy reach of children.²

The later use of lead as a gasoline additive, begun in the 1920s and lasting into the 1990s in the United States,³ contributed further to the contamination of environmental media with which children have intimate daily commerce, including air, dusts, and soils.

DIFFERENCES BETWEEN CHILDREN AND ADULTS IN LEAD SOURCES, METABOLISM, AND TOXICITIES

Children and adults differ somewhat in the relative importance of different lead exposure sources and pathways, in aspects of lead metabolism, and in the specific ways in which toxicities are expressed. To a greater extent than adults, young children normally explore their environment via hand-to-mouth activity, behaviors that are likely to increase the lead intake of a child who lives in an environment with hazards such as leaded paint in poor repair or elevated levels of lead in house dust or yard soils.^{4,5} The average fractional gastrointestinal absorption of lead is much greater in infants and young children than in adults,⁶ and absorption is increased in the presence of nutritional deficiencies that are more common in children than in adults (eg, iron, calcium).^{7,8}

In both children and adults, lead toxicity can be expressed as derangements of function in many organ systems. Although lead causes central nervous system abnormalities in adults,^{9–11} peripheral neuropathies tend to be more prominent. In the developing nervous system, in contrast, central effects are more prominent than peripheral effects.¹² Moreover, peripheral nervous system effects in adults tend to reverse after cessation of exposure,^{13,14} whereas the central effects in children seem not to do so,^{15–18} perhaps because lead perturbs the complex processes by which synaptic connections are selected and modified.¹⁹ Even pharmacotherapy, at least succimer administered to young children who present with blood lead levels of 20 to 44 $\mu\text{g}/\text{dL}$, does not seem to reduce or reverse cognitive injury.²⁰ An important exception to these generalizations is that neurobehavioral deficits associated with modest elevations of prenatal lead levels, if ever present, seem largely to attenuate by the time children reach school age.²¹

CRITICAL WINDOWS OF VULNERABILITY AND INTERINDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY

It is difficult to identify discrete windows of enhanced developmental vulnerability to lead exposure. The intraindividual stability of blood lead level over time is substantial, particularly in lead-rich environments such as the inner city or areas around

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lead smelters, where many of the major epidemiologic studies have been conducted.^{22,23} In addition, under many exposure scenarios, the half-life of lead in blood is greater in children than in adults.^{5,24} When blood lead levels do vary over time, age at exposure and magnitude of exposure are often highly confounded, with blood lead level peaking in the age range of 1 to 3 years.²⁵ This is probably because this period encompasses both the onset of independent ambulation and the time when a child's oral exploration of the environment is greatest. As a result, if a study were to find that blood lead level measured at age 2 is most predictive of some critical neurocognitive outcome at school age, then it would be difficult to ascertain whether this reflects a special vulnerability of the central nervous system at age 2 or that blood lead levels tend to be highest during this period. Some studies support the former hypothesis,²⁶ whereas others have found that school-age neurocognitive outcomes are most strongly related to recent or concurrent blood lead levels.^{22,27} The findings of yet other studies fail to provide evidence for the existence of any critical periods of vulnerability.²⁸

Another reason that it is difficult to identify a single critical period of heightened vulnerability to lead toxicity is that there might be many such periods, depending on the particular endpoint of interest. Using primate models, Rice^{29,30} demonstrated that the timing of developmental lead exposure affected the nature and the severity of deficit on a variety of tasks (spatial discrimination reversal, non-spatial discrimination reversal, and a fixed-interval response operant task). In contrast, performance on a spatial delayed alternation task was not affected by age at exposure.³¹ Morgan et al³² observed different expressions of attentional dysfunction in rats depending on the timing of lead exposure. It seems eminently plausible that this fundamental principle of toxicology applies to children as well, although the evidence is meager. This is likely to be attributable, in no small measure, to the absence in most human epidemiologic studies of sufficiently detailed exposure data that capture, at least, features such as timing, duration, and dose. If the specific effects of lead do differ according to exposure scenario, then this lacunae in exposure data would account, at least in part, for the general lack of success in discerning a coherent "behavioral signature" of lead exposure in children.³³ This suggests, however, that we should not necessarily expect strict consistency across studies in the patterns of neurocognitive impairment associated with lead.^{33,34}

An individual's vulnerability to neurodevelopmental injury is also likely to vary according to host characteristics that are, at present, largely unknown. Individuals differ widely in the blood lead level at which signs of clinical intoxication appear, with some individuals seeming well at a blood lead level that in others results in encephalopathy or even death. Plots of "subclinical" blood lead level and endpoints such as covariate-adjusted IQ reveal tremendous scatter of observations around the regression lines (eg,³⁵), with low R^2 values associated with the regressions, suggesting that children are variable

in their responses to lower levels of exposure, as well. An important implication is that children with the same blood lead level should not be considered to be at equivalent developmental risk.

The potential sources of individual variability in lead-associated neurodevelopmental risk are legion, although none has been confirmed with even a moderate degree of certainty. One type of explanation focuses on toxicokinetic and toxicodynamic factors. It is assumed that blood lead level, the biomarker of internal dose that is most often used, is a valid index of the biologically effective dose at the brain, the critical target organ for neurotoxicity. The many intervening steps that link the internal dose and the response in the brain, however, provide many opportunities for interindividual differences in sensitivity to arise.³⁶ Certain genetic polymorphisms involved in lead metabolism are thought to affect individual vulnerability, including those for the vitamin D receptor¹¹ and for lead-binding red blood cell proteins such as amino levulinic acid dehydratase.^{37,38} Supportive evidence is sparse, however.³⁹ Gender differences have been reported in the immunotoxicity of gestational lead exposure in rats.⁴⁰ In humans, gender differences in neurotoxicity have been reported,⁴¹⁻⁴⁵ although in some studies, it is male individuals who seem to be more vulnerable, whereas in others it is female individuals. Co-exposure to other toxicants is another candidate explanation for individual differences in susceptibility, although greater attention has been paid to the potential of co-exposures to be confounders than to be effect modifiers. In a rodent model, the effect of lead on mortality, spatial learning, and the N-methyl-D-aspartate receptors differed depending on whether pups were exposed to lead alone or in combination with magnesium and zinc.⁴⁶ Finally, characteristics of a child's rearing environment might influence the toxicity of a given lead dose.⁴⁷ Lead seems to be similar to other biological risks, such as low birth weight, in that children from environments that offer fewer developmental resources and supports express deficits at a lower blood lead level than do children from more optimal environments^{45,48} and show less recovery after exposure.⁴³

FUNCTIONAL FORM OF THE DOSE-EFFECT RELATIONSHIP: A THRESHOLD?

A threshold value below which lead has no apparent adverse developmental effect has not been identified. The 1991 Centers for Disease Control and Prevention (CDC) statement on childhood lead poisoning⁴⁹ set 10 $\mu\text{g}/\text{dL}$ as the screening action guideline. Although this blood lead level was intended to serve as a risk guidance and management tool at the community level, it has been widely—and incorrectly—imbued with biological significance for the individual child. Indeed, it often seems to be interpreted as a threshold, such that a level $<10 \mu\text{g}/\text{dL}$ is viewed as "safe" and a higher level as "toxic." The truth is unlikely to be so simple, however. No single number can be cited as a threshold, divorced from a context that specifies factors such as the endpoint of interest, the age at exposure and at assessment, the duration

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of blood lead elevation, and characteristics of the child's rearing environment. Although few data were available at the time on putative effects below 10 $\mu\text{g}/\text{dL}$, the 1991 CDC statement stated that adverse effects are likely to occur in this range (p. 9). This should not be surprising given that even after 2 decades of steady decline in population blood lead levels,⁵⁰ the mean still lies between 1⁵¹ and 2⁵² orders of magnitude greater than estimates of natural background levels in humans. It strains credulity to conclude that the threshold for neurotoxicity lies within the narrow and, in an evolutionary sense, still quite elevated range of present-day blood lead levels. Data reported since the 1991 CDC statement support this position. Among children in the Boston prospective study, for whom the mean blood lead level at age 2 years was 7 $\mu\text{g}/\text{dL}$ (90th percentile, 13 $\mu\text{g}/\text{dL}$), a significant inverse association was found between blood lead level and both IQ and academic achievement at 10 years of age.²⁶ No point of inflection in this relationship was identified when nonparametric regression models were fitted, and the data were most consistent with a linear (ie, nonthreshold) model extending to the lowest blood lead levels represented in the cohort (<1 $\mu\text{g}/\text{dL}$).⁵³ In the Third National Health and Nutrition Examination Survey sample, among 4853 6- to 16-year-old children, current blood lead was inversely associated with 4 measures of cognitive function, even when the sample was restricted to children with blood lead levels <5 $\mu\text{g}/\text{dL}$.⁵⁴ Blood lead histories of the children were not available, however, so it is possible that their levels had been much higher at younger ages and that it was those levels that were responsible for the later performance deficits of the children with higher concurrent blood lead levels. Moreover, measures of key potential confounders such as parent IQ and home environment were not available, although strong confounding by these factors within such a narrow range of blood lead levels is unlikely. These limitations were addressed in the study of Canfield et al.⁵⁵ In the subgroup of 101 children whose blood lead levels were <10 $\mu\text{g}/\text{dL}$ at 6, 12, 18, 24, 36, 48, and 60 months of age, significant covariate-adjusted associations were observed between blood lead level and IQ at ages 3 and 5. Chiodo et al.⁵⁶ also reported significant inverse associations between neuropsychological function and blood lead levels <10 $\mu\text{g}/\text{dL}$. In the Canfield et al.⁵⁵ study, moreover, the slope of the association was greater in the subgroup of children whose peak blood lead was <10 $\mu\text{g}/\text{dL}$ than it was in the complete study sample that included children whose peak blood lead levels exceeded 10 $\mu\text{g}/\text{dL}$. Reanalyses of the Boston prospective study⁵⁷ suggested the same pattern. Collectively, these new studies provide compelling evidence that 10 $\mu\text{g}/\text{dL}$ should not be viewed as a threshold. The precise shape of the dose-effect relationship in the lower portion of the exposure range remains uncertain, however. Although the data are consistent with the slope being steeper below 10 $\mu\text{g}/\text{dL}$ than above 10 $\mu\text{g}/\text{dL}$, a convincing mechanism has not been proposed.

The neurocognitive effects of pediatric lead toxicity have garnered the greatest attention from both researchers and regulators, perhaps for reasons of ease of measurement by the former and ease of interpretation by the latter. Indeed, enough studies provide data on endpoints such as IQ to make meta-analyses feasible,^{21,58-60} with all such efforts reaching similar conclusions, viz, that an IQ decline of 1 to 5 points is associated with a 10- $\mu\text{g}/\text{dL}$ increase in blood lead (eg, from 10 to 20 $\mu\text{g}/\text{dL}$). Many studies have identified distractibility, poor organizational skills, and hyperactivity as possible reasons for the reduced global cognitive function of more highly exposed children.⁶¹⁻⁶⁶

Recently, the range of outcomes examined in relation to childhood lead exposure has been expanded, building on older reports of serious behavioral pathologies in case series of children with subencephalopathic lead poisoning. In 1 of these early reports, Byers and Lord⁶⁷ noted that poor school progress among children who were previously treated for lead poisoning was attributable not only to their cognitive deficits but also to their aggression and explosive tempers. Within the past decade, several studies have suggested that even "subclinical" lead exposure is a risk factor for antisocial, delinquent behaviors. For example, a history of childhood lead poisoning was the strongest predictor of adult criminality among male individuals in the Philadelphia subsample of the Collaborative Perinatal Project.⁶⁸ Needleman et al.⁶⁹ found that male adolescents with increased bone lead levels self-reported more delinquent acts and were rated by both their parents and teachers as having scores that exceeded clinical cut-offs on the Attention, Aggression, and Delinquent Behavior scales of the Child Behavior Checklist. Furthermore, between ages 7 and 12, the behaviors of boys with higher bone lead levels deteriorated more than did the behaviors of boys with lower bone lead levels. Among adolescents in the Cincinnati Lead Study, the frequencies of self-reported delinquent and antisocial behaviors were significantly associated with both prenatal and early postnatal blood lead levels.⁷⁰ In a case-control study, adjudicated delinquents had significantly higher bone lead levels than did community control youths and were 4 times more likely to have a bone lead level at the 80th percentile of the distribution (approximately the detection limit).⁷¹ Finally, in a set of historical analyses, Nevin⁷² reported striking, provocative concordances between temporal trends in the amount of lead used commercially and in violent crime and unwed pregnancies. Although such ecologic analyses provide a weak basis for causal inference, they do suggest hypotheses that should be evaluated in settings in which information is available on exposure, outcome, and potential confounders at the individual rather than the community level. Much work remains to be done to clarify the potential contribu-

tions of lead, as well as other environmental pollutants, to child psychiatric morbidity.^{73,74}

UTILITY OF ANIMAL STUDIES

Because studies of children's environmental lead exposure must necessarily be observational rather than experimental (apart from randomized clinical trials comparing alternative treatment modalities), much of the controversy surrounding their interpretation has focused on the possibility that residual confounding, rather than lead toxicity itself, explains the associations between higher body burdens and reduced function. Such discussions are difficult to conclude to everyone's satisfaction because there is no logical conclusion to the line of argument that posits a succession of unmeasured factors that might be responsible for creating such spurious associations. Moreover, errors in model specification can result in bias toward the null hypothesis in the estimate of lead's neurotoxicity, if statistical adjustments are made for factors that are in the causal pathway between lead and poor outcome. For this reason, animal behavioral models of lead toxicity, in which the possibility of confounding (in either direction) is reduced by random assignment to exposure groups and by active control of relevant (known) genetic and environmental factors, are crucial elements of the total database to which regulators can and should appeal in setting exposure standards. The inference that low-level lead exposure causes human behavioral morbidity becomes more plausible when behavioral changes are also observed after lead is administered to animals under experimental conditions. Indeed, the striking similarities between the general pattern of behavioral abnormalities in lead-exposed animals and in "free range" lead-exposed children provides support, albeit indirect, for the inference that the relationships observed in humans are causal.^{33,75}

The converse is true, as well, in that sometimes the results of animal studies suggest that an association observed in humans might not reflect a causal influence. For instance, analyses of the Second National Health and Nutrition Examination Survey data set suggested that very modest elevations in current blood lead level, well within the range of community exposures, were associated with increased hearing threshold in children.^{76,77} Although some studies of animal models provide limited evidence of a modest effect at high blood lead levels,⁷⁸ the results of a recent study in 31 rhesus monkeys with blood lead levels of 35 to 40 $\mu\text{g}/\text{dL}$ for the first 2 postnatal years cast doubt on the validity of the conclusion that low-level lead exposure causes hearing deficits in children. In this study, no lead-associated effects were detected on any level of auditory processing using tympanometry (middle ear function), otoacoustic emissions (cochlear function), or auditory brainstem-evoked potentials (auditory nerve, brainstem pathways).⁷⁹ This might explain why recent studies of 2 cohorts of Ecuadorian children with substantially elevated blood lead levels (means of 40 and 52 $\mu\text{g}/\text{dL}$) failed to find a significant association between blood lead level and hearing threshold.^{80,81}

One reason that animal models of lead toxicity are so useful in understanding childhood lead toxicity is the deep level of analysis that they allow in the effort to identify the behavioral mechanism(s) of functional deficit. The assessments included in most human epidemiologic studies tend to be global or apical tests of cognition and achievement rather than experimental, laboratory tests. One reason for this is that exposure-associated decrements on such tests are more highly valued by risk analysts and regulators as bases for exposure standards. Although poor performance on global tests is often strongly predictive of adaptive difficulties in school or the workplace,⁸² the mere fact of poor performance provides relatively little insight into the reasons for it, ie, about the underlying "behavioral lesion." For example, in many studies, higher lead levels are associated with reduced scores on a design-copying task. A child might perform poorly on such a task for many reasons, however, including poor visual-perceptual skills, poor fine motor control, metacognitive or organizational deficits, poor impulse control, anxiety, or a depressed mood. In a diagnostic clinical evaluation, the relative merits of these various hypotheses can be explored using a test battery tailored to the child's presentation and modified on the basis of the tester's observations as the evaluation proceeds. In a field epidemiologic study, an investigator might have 1-time access to a child for perhaps 3 hours, needing to administer a fixed battery to all children to ensure comparability of the data and the circumstances of its collection. Under such constraints, dissection of a behavioral deficit by means of a detailed process analysis is not feasible, and an exposure-associated decrement in performance on apical tests tends to be "explained," inappropriately, in terms of a deficit in a complex construct such as "attention" or "memory." Limited efforts to deconstruct such global constructs have been conducted in lead-exposed children. Application of an assessment battery based on a neuropsychological model of attention⁸³ revealed that elevated dentine lead levels were associated with deficits in 2 of the 4 elements of attention in this model: the ability to select a focus and carry out operations on it, and the ability to shift focus in a flexible and adaptive manner.³⁹ The continuous accessibility of experimental animals makes them an ideal resource for explicating the bases for the global deficits observed in human subjects. They are literally a captive audience from whom cooperation and consent for repeated testing is not required and who do not need to miss work or school to participate. Fine-grained process analyses of the behaviors of lead-exposed primates, for instance, are consistent across laboratories and with the limited human data available,³⁹ in identifying several specific aspects of the global construct "attention" that are sensitive to lead: a tendency to be distracted by irrelevant stimuli, to respond in a perseverative manner, an inability to inhibit inappropriate responses, difficulty changing response strategies when reinforcement contingencies shift, and difficulty abstracting general rules (ie, "learning how to learn").³³ No substantial obstacles stand in the way of efforts to administer to

children batteries that would allow similarly fine-grained dissection of behavior, and investigators are currently working toward this goal.^{84,85}

Animal models are also better suited than human studies to the task of testing limits to evaluate the effects of lead on the ability to weather "periods of behavioral transition,"⁸⁶ as well as to identify factors that exacerbate or reduce lead toxicity (ie, effect modification). In the laboratory, one can "program" life histories to explore the impact of different factors on the severity and nature of lead-associated deficits and to see whether the point at which and the way in which an animal's behavior breaks down over time or under stress are affected by previous lead exposure. Animal models can also be helpful in probing the nature and bases of individual differences in sensitivity to lead toxicity.²⁹

Animal models are of relatively little help, however, in evaluating lead's effects on the ability to manipulate symbolic or abstract systems, such as reading or mathematics, that have no compelling nonhuman analogues. In addition, studies of lead's effects on behavioral systems that tend to be species specific (eg, communication, affect, reproduction, social behaviors) are less relevant to understanding childhood lead toxicity than are nonhuman models of systems with strong cross-species parallels in the morphology of behavior, such as problem solving and learning.⁸⁷

UTILITY OF ADULT STUDIES

Studies conducted on adults are likely to be of limited relevance in understanding lead toxicity in children, particularly with regard to nervous system effects. This organ continues to undergo substantial changes well into the second decade of postnatal life, involving the establishment of hemispheric dominance, the completion of myelination (particularly in the frontal lobes), synaptic pruning, and synaptic reorganization. As a result, the impact of an acquired brain lesion in an adult can differ dramatically from the impact of a similar lesion incurred during development.⁸⁸ Even in the absence of an insult, the brain-behavior relationships underlying complex cognitive processes can differ substantially between adults and children. For example, lesions that spare language in proficient speakers can impair language acquisition, suggesting that the neural substrate for language processing is not as highly localized in children as in adults.⁸⁹ A functional magnetic resonance imaging study of performance on a verbal fluency task identified the expected regions of activation in both children and adults (left inferior frontal cortex, left middle frontal gyrus) but more widespread cortical activation among children than in adults, particularly in the right hemisphere (right inferior frontal gyrus).⁹⁰ This seems not to be attributable simply to age-related differences in competence but to age-related differences in functional neuroanatomy. In another functional magnetic resonance imaging study, comparing visual lexical processing in adults and 7- to 10-year-olds, different patterns of activation were found in children and adults, even when the 2 age groups were matched in terms of accuracy on the

task.⁹¹ This suggests that, to some extent, the specific regions of the brain enlisted to solve a particular problem change with age. Thus, it seems that the adult and the developing child differ in so many critical respects that few lessons about pediatric lead neurotoxicity can be gleaned from studying adult lead neurotoxicity.

CONCLUSION

Conceptually, excessive lead exposure in children poses a relatively simple problem. We know where the most important hazards are in the environments of young children, the major pathways of exposure, the range of effects (to a level of detail far greater than for any other environmental pollutant), and at least the general features of the dose-effect relationships for the most intensively studied endpoints. Studies continue to describe apparent effects that were previously unknown, as well as show that known effects can be detected at lower and lower levels of exposure. Fortunately, even as these advances in knowledge were being achieved, children's exposures to lead were in dramatic decline, with the mean blood lead level now barely $>2 \mu\text{g}/\text{dL}$.⁹² Although much is known about the effects of lead on brain chemistry and physiology, we nevertheless lack a unifying model of the mechanisms of lead neurotoxicity. It is not obvious, however, that additional evidence on the health effects of lead or the mechanisms of its protean toxicities is needed to motivate public health interventions to reduce children's lead exposure. In terms of housing and community interventions, apart from the obvious immediate and long-term benefits of complete residential lead abatement, if conducted properly, as a way to reduce childhood exposures, we know relatively little about other environmental, nutritional, or social interventions that are effective (including cost-effective). Given the apparent absence of commitment at a societal level to eradicate this entirely preventable childhood disease even in the face of economic analysis that demonstrates it to be cost-effective,⁹³ it seems that the answer to the question posed 10 years ago, "Lead toxicity in the 21st century: will we still be treating it?"⁹⁴ is, sadly, "Yes."

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