ARTYKUŁ REDAKCYJNY

EDITORIAL

RECENT STUDIES OF LEAD NEUROTOXICITY IN CHILDREN: OLD METAL, NEW QUESTIONS

OSTATNIE BADANIA NAD NEUROTOKSYCZNOŚCIĄ OŁOWIU. DAWNO ZNANY METAL – NOWE ZAGADNIENIA

David C. Bellinger

Children's Hospital Boston
Harvard Medical School
Harvard School of Public Health

Abstract

Many times in the history of lead toxicology the view has prevailed that „the problem" has been solved, and that exposure to lead is no longer a major public health concern. Each time, additional research has demonstrated the prematurity of this judgment. In the last decade, an extraordinary number of new studies have illustrated that „the problem" remains, and that it has dimensions never before considered. Children's intelligence has traditionally been considered to be the most sensitive endpoint and used as the basis for risk assessment and standard setting. For IQ, the dose-effect relationship appears to be supra-linear, with greater deficits per μg/L increment below than above 100 μg/L. Recent studies have found that greater lead exposure in early childhood is also associated with a wide variety of other outcomes, with some associations evident at biomarker levels comparable to those at which IQ deficits are observed. Among these endpoints are poorer academic achievement, ADHD, conduct disorder, and antisocial behavior. In animals, early life lead exposure has been implicated in neurodegenerative disorders later in life, perhaps via epigenetic mechanisms. Studies employing neuroimaging modalities such as volumetric, diffusion tensor, and functional MRI are providing insights into the neural bases of the cognitive impairments associated with greater lead exposure. Several recent risk assessments (e.g., EFSA, JECFA) have concluded that research has yet to identify a threshold level below which lead can be considered „safe".

Keywords: lead, neurotoxicity, children, epidemiology

Streszczenie

Wiele razy w historii toksykologii ołowiu przeważał pogląd, że problem ten został rozwiązany a ekspozycja na ołów nie jest już poważnym zagadnieniem zdrowia publicznego. Za każdym razem dalsze dodatkowe badania wykazywały, że taki pogląd jest przedwczesny. W ostatniej dekadzie nadzwyczajnie duża liczba nowych badań ukazała, że „problem" pozostaje i że jego rozmiary są tak szerokie jak nigdy przedtem tego nie spodziewano się. Inteligencja dzieci tradycjonalnie była uważana za najbardziej czuły końcowy wskaźnik i była używana jako podstawa dla oceny ryzyka i ustalania standardów. Dla IQ związek dawka–skutek okazał się być supra-linearnym z większymi deficytami przez zwiększenie μg/L ołowiu poniżej aniżeli powyżej stężenia 100 μg/L w krwi. Ostatnie badania wykazały, że większa ekspozycja na ołów we wczesnym okresie dzieciństwa jest również związana z szeroką różnorodnością występowania innych następstw, które są skojarzone ewidentnie na poziomie biomarkerów porównywalnie do tych, przy których obserwuje się deficyty IQ.

Nadesłano: 17.06.2011
Zatwierdzono do druku: 20.07.2011

Wśród tych końcowych następstw wymienia się gorszą zdolność do uczenia się na poziomie akademickim, ADHD, zaburzenia zachowania i zachowania antyspołeczne U zwierząt wczesna ekspozycja w wieku rozwojowym ma związek z występowaniem chorób neurodegeneracyjnych w późniejszym okresie życia, być może na drodze mechanizmów epigenetycznych. Badania z użyciem metod obrazowania układu nerwowego jak wolumetryczny tensor dyfuzyjny i czynnościowe MRI dostarczają wglądu w neurologiczne podstawy uszkodzenia poznawczego związanego z większą ekspozycją na ołów. Liczne ostatnie oceny ryzyka (np. EFSA, JECFA) świadczą, że badania naukowe jeszcze nie zdołały zidentyfikować takiego progowego poziomu ołowiu w krwi, poniżej którego można by uważać, że jest on bezpieczny dla zdrowia.

Słowa kluczowe: ołów, neurotoksyczność, dzieci, epidemiologia

---

Knowledge that lead is neurotoxic, especially to children, is more than a century old, yet remarkable advances in our understanding of the scope of its adverse effects continue to be made. Although great success has been achieved in reducing population exposures, recent research has identified surprising new dimensions of lead's toxicities. This commentary focuses specifically on lead neurotoxicity in children, broadly surveying epidemiologic literature from the past decade. Recent studies on lead's renal, cardiovascular, adult central nervous system, and reproductive effects are reviewed elsewhere [1].

The list of the aspects of brain function and development that are impaired as a result of lead exposure, and the mechanisms by which these impairments occur, is impressive. The latter include apoptosis and excitotoxicity, reduced energy production in the mitochondria, reduced oxygen transport due to interference with heme synthesis, increased oxidative stress, alteration of first, second, and third messenger systems, and alteration of patterns of gene expression and transcription [2]. In rodents exposed to environmentally-relevant levels of lead exposure, neurogenesis is reduced in the hippocampus, neurons that are born are less likely to survive, and those that do survive tend to have aberrant morphology [3]. In imaging studies of young adults for whom detailed histories of early life blood lead levels are available, greater early lead exposure is associated with reduced volumes in several brain regions [4, 5]. Reduced fractional anisotrophy and other changes in the white matter suggest altered myelination and reduced axonal integrity [6]. Lead-associated changes in brain metabolism are suggested by studies that found reduced levels of N-acetyl aspartate, creatine and phosphocreatine, glycerolphosphocholine and phosphocholines in several regions of grey and white matter [7]. Yuan et al. [8] reported significant lead-associated changes in activation patterns in the left frontal cortex and left middle temporal gyrus on a verb generation task.

These changes in neuronal structure and function are accompanied by persistent impairments at the level of behavior. In a pooled analysis of 7 international prospective studies, involving 1,333 children, concurrent blood lead level was inversely related to covariate-adjusted IQ in childhood, with a supralinear form providing the best fit to the data [9]. Specifically, the reduction in IQ per μg/dL in blood lead level was greater at blood lead levels below 100 μg/L than it was at levels greater than 100. Although an explanation for this somewhat surprising finding has not been identified, it has since been found in several other studies [10, 11]. The IQ deficits appear to be long-lasting. A follow-up study of a cohort enrolled at birth showed that childhood blood lead level is a significant predictor of IQ at age 30 years [12].

While the lead-related deficits in IQ might be considered to be modest in magnitude, deficits are also apparent in outcomes that have clear implications for children's well-being. For example, Surkan et al. [13] found that children with a blood lead level of 50–100 μg/L scored significantly worse than children with a blood lead level of 10–20 μg/L on tests of reading and mathematics, even when the comparisons were adjusted for the children's Full-Scale IQ scores. This finding suggests that even among children with similar Full-Scale IQ scores, those with a higher blood lead level find academic tasks more challenging. Such a discrepancy between aptitude (i.e., IQ) and ability (i.e., academic achievement) is a hallmark sign of a specific learning disability. Furthermore, children with greater lead exposure achieve reduced levels of success in meeting the goals set for learning in school. Miranda et al. [14] found, in a study involving 8,600 4th graders in the U.S., that the percentage of children who failed an end-of-grade reading test was monotonically related to blood lead level, with the association apparent down to a blood lead level of 10 μg/L. This finding was replicated in an even larger study of more than 56,000 children [15], and, furthermore, showed that the impact of lead was stronger among children who had other risk factors for neurodevelopmental impairment.

It has been known for decades that greater lead exposure is associated with behaviors that suggest attentional deficits, including increased distractibility, poorer persistence, greater disorganization, and inability to follow directions. This observation has been explored in several recent studies that examined the association between blood lead level and Attention Deficit Hyperactivity Disorder (ADHD). Using the data of NHANES 1999–2002, Braun et al. [16] found that the odds ratio for parent-reported ADHD among children with a blood lead level greater than 20 μg/L was 4, using children with a blood lead level below 8 μg/L as the reference group. The odds ratios for children with a blood lead level of 11–13 or 14–20 were approximately 2 and 3, respectively, suggesting a roughly linear dose-response relationship. The finding of an increased risk of ADHD among children with greater lead exposure has also been reported in other studies from the U.S. [17, 18], and in studies from Korea [19], Romania [20], and China [21].

A recent line of investigation involves the possible relationship between increased early lead exposure and aggression, including criminality. This is not a new hypothesis as an early case series [22] raised this possibility that one effect of lead poisoning is „loss of the normal inhibitory function" and the promotion of socially disruptive behaviors. Needleman et al. [23] reported that 11 year olds children with higher bone lead levels were rated by both their parents and teachers as more impaired on the Aggression and Delinquency scales of the Child Behavior Checklist. Needleman et al. [24] followed-up this observation, comparing the bone lead levels of adolescents who were adjudicated delinquents to the levels of controls. Among both boys and girls, the delinquents were significantly more likely than the controls to have a detectable bone lead level. Other studies reporting a link between delinquency and lead exposure include Dietrich et al. [25], Stretesky and Lynch [26, 27], Nevin [28, 29], Fergusson et al. [30], Marcus et al. [31], and Olympio et al., [32]. Using data from NHANES 1999–2002, Braun et al. [33] reported significantly increased adjusted odds of meeting DSM-IV criteria for conduct disorder among 8–15 year old children with a concurrent blood lead level greater than 8 μg/L. The strongest epidemiological evidence for an association between early life lead exposure and criminality, however, comes from a prospective study conducted by Wright et al. [34] on a group of 250 socio-economically-disadvantaged children, 19–24 years old, for whom blood lead level was measured several times between gestation and age 6 years. The median blood lead level through age 5 was 123 μg/dL (range 60–263). The investigators obtained records, from the county criminal justice system, of the number of times the participants had been arrested since age 18 years. A variety of blood lead indices were developed, including prenatal, average childhood, and 6-year blood lead level. Using the number of arrests for violent offenses as the outcome, the covariate-adjusted rate ratios associated with each 50 μg/L increase in blood lead level were 1.34 (95% CI: 0.88–2.03), 1.30 (95% CI: 1.03–1.64), and 1.48 (95% CI: 1.1.5–1.89), respectively, for the three blood lead indices. The reason that this study is persuasive is that the data on exposure and covariates were collected decades before the data on outcome were collected, eliminating the likelihood of selection bias and other biases that threaten the validity of cross-sectional or retrospective analyses.

The plausibility of a role for childhood lead exposure as a risk factor for aggression is supported by experimental studies of rats, hamsters, cats, and monkeys. In rhesus monkeys, Laughlin et al. [35] showed that exposure to 1 mg of lead per kg per day in the first year of life resulted in persistent alterations in play behavior even after cessation of lead exposure. These alterations included reductions in rough-and-tumble play, and increases in self-stimulation and fear grimacing. The authors noted that these suggested, „…a pattern of inappropriate social interactions which are unlikely to promote social integration and reproductive success." Moore et al. [36] reported that lead-exposed monkeys demonstrated an increased propensity for impulsive responding, namely tactile defensiveness, expressed as increased fear and withdrawal in response to innocuous stimulation (i.e., stimulation of the face and neck with a feather). Finally, Li et al. [37] found that lead exposure reduced the amount of electrical stimulation of the lateral hypothalamus required to elicit predatory attack of an anesthetized rat in cats. In this study, the amount of stimulation required subsequently increased when lead exposure was stopped, but fell when exposure was resumed.

In aggregate, the recent evidence on lead-associated neurological morbidity in children suggests that early life exposure results in a cascade of effects, involving deficits in IQ, executive function, impulse control, and ability to delay gratification and downstream effects such as reduced academic achievement, increased likelihood of incomplete schooling, disorders such as ADHD, conduct disorder, antisocial behavior, and, perhaps, substance abuse.

The focus tends to be on developmental processes that are directly impacted by lead exposure, but it is important to consider a more complex model in which lead exposure is viewed as a predictor rather than an outcome. In animal models, early lead exposure limits the capacity to respond successfully

to a later insult. For example, rats exposed to lead in early life show a reduced capacity to recover beam walking and proprioceptive limb placing skills following the administration, in adulthood, of a photochemically-induced ischemic stroke in the hind limb parietal sensorimotor cortex [38].

Recent studies in rodents and non-human primates suggest that developmental exposure to lead might be a risk factor for neurodegenerative disease in adulthood. Animals exposed to lead only in early life show elevations, in adulthood, of beta-amyloid protein precursor (APP) mRNA, APP, and its amyloidogenic product, Abeta, in old age [39]. In monkeys, Abeta staining and amyloid plaques accumulate most striking in the frontal cortex [40]. In addition, DNA methylation is decreased and oxidative damage to DNA is increased in lead-exposed animals, suggesting that an epigenetic process might underlie these delayed effects.

An active but relatively undeveloped area of investigation concerns individual variation in susceptibility to lead neurotoxicity. In several studies, effect modification by socio-economic status (SES) has been noted, with poorer children suffering disproportionately from lead exposure [41]. Because SES is a complex construct that encompasses a variety of more proximal factors that can influence child neurodevelopment, considerable effort has been invested in identifying which component of SES, or more likely, components, influence response to lead exposure. Among the classes of components likely to be important are health co-morbidities (including exposure to other toxicants), genotype, the rearing environment, stress, access to health care, quality of schools, neighborhood characteristics, and nutrition. Some of these components, or aspects of them, have been investigated. For example, two studies suggest that the adverse effects of lead are greater if a child is co-exposed to higher levels of manganese [42, 43]. The learning deficits of lead-exposed rats are attenuated if they are raised in an „enriched" environment that includes exposure to other rats, larger spaces, and more toys [44]. An enriched environment also normalizes aspects of NMDA and BDNF gene expression in the hippocampus. Animals raised by dams subjected both to lead exposure and to stressful procedures show greater learning deficits as well as altered patterns of stress responsivity [45].

The evolution over the past forty years in the level of lead exposure at which important adverse effects appear continues unabated, and two recent risk assessments concluded that a level of lead exposure that is „safe" has yet to be identified [46, 47]. Although impressive reductions in population exposures have occurred in many developed countries as a result of interventions, lead exposure in developing countries remains an important public health problem. The World Health Organization estimated that in 2000, less than 10% of the world's children had a blood lead level of 200 μg/L or greater, but that 99% of them lived in developing countries and that nearly 1% of the global burden of disease could be attributed to lead exposure [48].

References

1. Bellinger, D.C. The protean toxicities of lead: New chapters in a familiar story. International Journal of Environmental Research and Public Health, 2011;8:2593–2628.
2. Lidsky, T.I., Schneider, J.S. Lead neurotoxicity in children: Basic mechanisms and clinical correlates. Brain 2003; 126:5–19.
3. Verina T, Rohde CA, Guilarte TR. Environmental lead exposure during early life alters granule cell neurogenesis and morphology in the hippocampus of young adult rats. Neuroscience 2007;145:1037–1047.
4. Cecil, K.M.; Brubaker, C.J.; Adler, C.M.; Dietrich, K.N.; Altaye, M.; Egelhoff, J.C.; Wessel, S.; Elangovan, I.; Hornung, R.; Jarvis, K.; Lanphear, B.P. Decreased brain volume in adults with childhood lead exposure. PLoS Medicine 2008, 5, e112.
5. Brubaker, C.J.; Dietrich, K.N.; Lanphear, B.P.; Cecil, K.M.. The influence of age of lead exposure on adult gray matter volume. Neurotoxicology 2010, 31, 259–266.
6. Brubaker, C.J.; Schmithorst, V.J.; Haynes, E.N.; Dietrich, K.N.; Egelhoff, J.C.; Lindquist, D.M.; Lanphear, B.P.; Cecil, K.M. Altered myelination and axonal integrity in adults with childhood lead exposure: a diffusion tensor imaging study. Neurotoxicology 2009, 30, 867–875.
7. Cecil, K.M.; Dietrich, K.N.; Altaye, M.; Egelhoff, J.C.; Lindquist, D.M.; Brubaker, C.J.; Lanphear, B.P. Proton magnetic resonance spectroscopy in adults with childhood lead exposure. Environmental Health Perspectives 2011, 119, 403–408.
8. Yuan, W.; Holland, S.K.; Cecil, K.M.; Dietrich, K.N.; Wessel, S.D.; Altaye, M; Hornung, R.W.; Ris, M.D.; Egelhoff, J.C.; Lanphear, B.P. The impact of early childhood lead exposure on brain organization: A functional magnetic resonance imaging study of language function. Pediatrics 2006, 118, 971–977.
9. Lanphear, B.P.; Hornung, R.; Khoury, J.; Yolton, K.; Baghurst, P.; Bellinger, D.C.; Canfield, R.L.; Dietrich, K.N.; Bornschein, R.; Greene, T.; Rothenberg, S.J.; Needleman, H.L.; Schnaas, L.; Wasserman, G.; Graziano, J.; Roberts, R. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environmental Health Perspectives 2005, 113, 894–899.
10. Tellez-Rojo, M.M.; Bellinger, D.C.; Arroyo-Quiroz, C.; Lamadrid-Figueroa, H.; Mercado-García, A.; Schnaas-Arrieta, L.; Wright, R.O.; Hernández-Avila, M.; Hu, H. Longitudinal associations between blood lead concentrations lower than 10?g/dL and neurobehavioral development in environmentally exposed children in Mexico City. Pediatrics 2006, 118, e323–e330.
11. Kordas, K.; Canfield, R.L.; López, P.; Rosado, J.L.; Vargas, G.G.; Cebrián, M.E.; Rico, J.A.; Ronquillo, D.; Stoltzfus, R.J. Deficits in cognitive function and achievement in Mexican first-graders with low blood lead concentrations. Environmental Research 2006, 100, 371–386.

12. Mazumdar, M.; Bellinger, D.C.; Abanilla, K.; Bacic, J.; Needleman, H.L. Low-level environmental lead exposure in childhood and adult intellectual function: a follow-up study. Environmental Health 2011, 10, 24.
13. Surkan, P.J.; Zhang, A.; Trachtenberg, F.; Daniel, D.B.; McKinlay, S.; Bellinger, D.C. Neuropsychological function in children with blood lead levels <10 μg/dL. Neurotoxicology 2007, 28, 1170–1177.
14. Miranda, M.L.; Kim, D.; Galeano, M.A.; Paul, C.J.; Hull, A.P.; Morgan, S.P. The relationship between early childhood blood lead levels and performance on end of grade tests. Environmental Health Perspectives 2007, 115, 1242–1247.
15. Miranda, M.L.; Kim, D.; Reiter, J.; Overstreet Galeano, M.A.; Maxson, P. Environmental contributors to the achievement gap. Neurotoxicology 2009, 30, 1019–1024.
16. Braun, J.M.; Kahn, R.S.; Froehlich, T.; Auinger, P.; Lanphear, B.P. Exposures to environmental toxicants and attention deficit hyperactivity disorder in US children. Environmental Health Perspectives 2006, 114, 1904–1909.
17. Nigg, J.T.; Knottnerus, G.M.; Martel, M.M.; Nikolas, M.; Cavanagh, K.; Karmaus, W.; Rappley, M.D. Low blood lead levels associated with clinically diagnosed attention deficit/hyperactivity disorder and mediated by weak cognitive control. Biological Psychiatry 2008, 63, 325–331.
18. Nigg, J.T.; Nikolas, M.; Knottnerus, G.M.; Cavanagh, K.; Friderici, K. Confirmation and extension of association of blood lead with attention-deficit/hyperactivity disorder (ADHD) and ADHD symptom domains at population-typical exposure levels. Journal of Child Psychology and Psychiatry 2010, 51, 58–65.
19. Ha, M.; Kwon, H.J.; Lim, M.H.; Jee, Y.K.; Hong, Y.C; Leem, J.H.; Sakong, J.; Bae, J.M.; Hong, S.J.; Roh, Y.M.; Jo, S.J. Low blood levels of lead and mercury and symptoms of attention deficit hyperactivity in children: a report of the Chil-dren's Health and Environment Research (CHEER). Neurotoxicology 2009, 30, 31–36.
20. Nicolescu, R.; Petcu, C.; Cordeanu, A.; Fabritius, K.; Schlumpf, M.; Krebs, R.; Kramer, U.; Winneke, G. Environmental exposure to lead, but not other neurotoxic metals, relates to core elements of ADHD in Romanian children: Performance and questionnaire data. Environmental Research 2010, 110, 476–483.
21. Wang, H.L.; Chen, X.T.; Yang, B.; Ma, F.L.; Wang, S.; Tang, M.L.; Hao, M.G.; Ruan, D.Y. Case–control study of blood lead levels and attention deficit hyperactivity disorder in Chinese children. Environmental Health Perspectives 2008, 116, 1401–1406.
22. Byers, R.K.; Lord, E.E. Late effects of lead poisoning on mental development. American Journal of Diseases of Children 1943, 66, 471–494.
23. Needleman, H.L.; Riess, J.A.; Tobin, M.J.; Biesecker, G.E.; Greenhouse, J.B. Bone lead levels and delinquent behavior. Journal of the American Medical Association 1996, 275, 363–369.
24. Needleman, H.L.; McFarland, C.; Ness, R.B.; Fienberg, S.E.; Tobin, M.J. Bone lead levels in adjudicated delinquents: a case–control study. Neurotoxicology and Teratology 2002, 24, 711–717.
25. Dietrich, K.N.; Ris, M.D.; Succop, P.A.; Berger, O.G.; Bornschein, R.L. Early exposure to lead and juvenile delinquency. Neurotoxicology and Teratology 2001, 23, 511–518.
26. Stretesky, P.B.; Lynch, M.J. The relationship between lead exposure and homicide. Archives of Pediatrics and Adolescent Medicine 2001, 155, 579–582.
27. Stretesky, P.B; Lynch, M.J. The relationship between lead and crime. Journal of Health and Social Behavior 2004, 45, 214–219.
28. Nevin, R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environmental Research 2000, 83, 1–22.
29. Nevin, R. Understanding international crime trends: the legacy of preschool lead exposure. Environmental Research 2007, 104, 315–336.
30. Fergusson, D.M.; Boden, J.M.; Horwood, L.J. Dentine lead levels in childhood and criminal behaviour in late adolescence and early adulthood. Journal of Epidemiology and Community Health 2008, 62, 1045–1050.
31. Marcus, D.K.; Fulton, J.J.; Clarke, E.J. Lead and conduct problems: A meta-analysis. Journal of Clinical Child & Adolescent Psychology 2010, 39, 234–241.
32. Olympio, K.P.K.; Oliveira, P.V.; Naozuka, J.; Cardoso, M.R.A.; Marques, A.F.; Gunther, W.M.R.; Bechara, E.J.H. Surface dental enamel lead levels and antisocial behavior in Brazilian adolescents. Neurotoxicology and Teratology 2010, 32, 273–279.
33. Braun, J.M.; Froehlich, T.E.; Daniels, J.L.; Dietrich, K.N.; Hornung, R.; Auinger, P.; Lanphear, B.P. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001–2004. Environmental Health Perspectives 2008, 116, 956–962.
34. Wright, J.P.; Dietrich, K.N.; Ris, M.D.; Hornung, P.W.; Wessel, S.D.; Lanphear, B.P. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. PLoS Medicine 2008, 5, e101.
35. Laughlin, N.K., Bushnell, P.J., Bowman, R.E. Lead exposure and diet: differential effects on social development in the rhesus monkey. Neurotoxicology and Teratology 1991;13:429–40.
36. Moore, C.F.; Gajewski, L.L.; Laughlin, N.K.; Luck, M.L.; Larson, J.A.; Schneider, M.L. Developmental lead exposure induces tactile defensiveness in Rhesus monkeys (Macaca mulatta). Environmental Health Perspectives 2008, 116, 1322–1326.
37. Li, W.; Han, S.; Gregg, T.R.; Kemp, F.W.; Davidow, A.L.; Louria, D.B.; Siegel, A.; Bogden, J.D. Lead exposure potentiates predatory attack behavior in the cat. Environmental Research 2003, 92, 197–206.
38. Schneider, J.S., Decamp, E. Postnatal lead poisoning impairs behavioral recovery following brain damage. Neurotoxico-logy 2007;28:1153-7.
39. Basha, M.R., Murali, M., Siddiqi, H.K., Ghosal, K., Siddiqi, O.K., Lashuel, H.A., Ge, Y.W., Lahiri, D.K., Zawia, N.H. Lead (Pb) exposure and its effect on APP proteolysis and Abeta aggregation. FASEB Journal 2005;19:2083–4.
40. Wu, J., Basha, M.R., Zawia, N.H. The environment, epigenetics and amyloidogenesis. Journal of Molecular Neuroscience 2008;34:1–7.
41. Bellinger, D.C. Lead neurotoxicity and socioeconomic status: conceptual and analytical issues. Neurotoxicology 2008;29:828–832
42. Kim, Y.; Kim, B.N.; Hong, Y.C; Shin, M.S.; Yoo, H.J.; Kim, J.W.; Bhang, S.Y.; Cho, S.C. Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. Neurotoxicology 2009, 30, 564–571.
43. Claus Henn, B., Ettinger, A.S., Schwartz, J., Téllez-Rojo, M.M., Lamadrid-Figueroa, H., Hernández-Avila, M., Schnaas, L., Amarasiriwardena, C., Bellinger, D.C., Hu, H., Wright, R.O. Early postnatal blood manganese levels and children's neurodevelopment. Epidemiology 2010, 21, 433–439.
44. Guilarte, T.R., Toscano, C.D., McGlothan, J.L., Weaver, S.A Environmental enrichment reverses cognitive and molecular deficits induced by developmental lead exposure. Annals of Neurology 2003;53:50–6.

45. Rossi-George, A., Virgolini, M.B., Weston, D., Thiruchelvam, M., Cory-Slechta, D.A.Interactions of lifetime lead exposure and stress: behavioral, neurochemical and HPA axis effects. Neurotoxicology 2011;32(1):83–99.
46. European Food Safety Authority. Scientific Opinion on lead in food. EFSA Panel on Contaminants in the Food Chain. EFSA Journal 2010; 8:1570.
47. Joint FAO/WHO Expert Committee on Food Additives. Summary and Conclusions, Seventy-third meeting, June 2010. (http://www.who.int/foodsafety/publications/chem/summary73.pdf).
48. Fewtrell, L.; Kaufmann, R.; Pruss-Ustun, A. Lead: Assessing the environmental burden of disease. Environmental burden of disease series No. 2, Geneva: World Health Organization, 2003.

Address for correspondence:
David C. Bellinger
Children's Hospital Boston
Harvard Medical School
Harvard School of Public Health
david.bellinger@childrens.harvard.edu