Iron deficiency increases blood concentrations of neurotoxic metals in children

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Iron deficiency affects approximately one-third of the world’s population, occurring most frequently in children aged 6 months to 3 years. Mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese, lead, and cadmium, and a diet deficient in iron can lead to excess absorption of manganese, lead, and cadmium. Iron deficiency may lead to cognitive impairments resulting from the deficiency itself or from increased metal concentrations caused by the deficiency. Iron deficiency combined with increased manganese or lead concentrations may further affect neurodevelopment. We recently showed that blood manganese and lead concentrations are elevated among iron-deficient infants. Increased blood manganese and lead levels are likely associated with prolonged breast-feeding, which is also a risk factor for iron deficiency. Thus, babies who are breast-fed for prolonged periods should be given plain, iron-fortified cereals or other good sources of dietary iron.

Key words: Iron, Deficiency, Manganese, Lead, Breast-feeding

Introduction

Iron deficiency, which is the most frequent and widespread nutritional deficiency in the world, affects approximately one-third of the world’s population¹, and occurs most frequently in rapidly growing children aged 6 months to 3 years who have an inadequate dietary iron intake². Iron deficiency is the only micronutrient deficiency that is also prevalent in virtually all developed countries³. The United States (US) National Health and Nutrition Examination Surveys (NHANES) 2003–2006 found that 14.4% of children aged 1–2 years were iron deficient⁴. To this end, one of the US national health objectives for 2010 was to reduce iron deficiency by 5%–9% in vulnerable populations, such as toddlers aged 1–2 years and pregnant women⁵.

Many cross-sectional studies have found that iron-deficiency anemia (or other indications of chronic severe iron deficiency) in infancy is associated with poor cognitive development, poor motor development, and behavioral problems⁶,⁷. Longitudinal studies find persisting differences in cognitive development among children with iron deficiency⁸,⁹. Most studies report lower scores despite iron treatment and correction of anemia⁷,¹⁰,¹¹.

Prolonged breast-feeding, which is a risk factor for iron deficiency in infants, is associated with increased blood manganese and lead levels¹²,¹³. Infants breast-fed over a prolonged period tend to be iron deficient, and thus have higher blood levels of other metals. However, not all infants who are breast-fed for an extended period are iron deficient. This may be due to variations in the iron status of infants depending on whether they are provided with iron-rich food during the prolonged breast-feeding.
Inhalation of metals, such as manganese, lead, and cadmium, is the most common cause of adult toxic metal exposure in environmental and occupational settings, whereas food intake is the major source of absorbed metals in neonates and infants, who are more vulnerable than adults to metals absorbed through the intestine. Mechanisms of iron absorption are similar to those of other divalent metals, particularly manganese, lead, and cadmium, and a diet deficient in iron can lead to excess absorption of manganese, lead, and cadmium. The gastrointestinal absorption of such divalent metals appears to involve intestinal iron transporters, such as apical divalent metal transporter 1 (DMT1), which also mediates the uptake of the divalent metals. Expression of DMT1 is upregulated in the presence of low iron stores, explaining the increased metal uptake and higher blood concentrations of metals in iron-deficient individuals. Among divalent metals, both manganese and lead may adversely affect neurodevelopment in children. Iron deficiency in children may affect cognitive impairment, resulting from the deficiency itself or from the increased metal concentrations caused by the iron deficiency. Therefore, iron deficiency combined with increased manganese or lead concentrations may further affect neurodevelopment.

**Manganese**

Manganese is a naturally occurring element abundant in the environment and is an essential dietary nutrient for humans. Because manganese is an essential element, its absorption, disposition, and biliary excretion are actively controlled by homeostatic mechanisms to maintain specific concentrations. These processes also play an important role in manganese toxicokinetics, which differ from those of nonessential, toxic metals such as lead and cadmium. Over-exposure to manganese can cause a neurologic impairment clinically known as “manganism,” a motor syndrome similar to, but differentiated from, idiopathic Parkinson disease. Recent epidemiological evidence suggests that low-level environmental exposure to manganese may adversely affect neurodevelopment in children. Claus Henn et al. found an inverted U-shaped relationship between blood manganese concentrations and neurodevelopment in 12-month-old infants, with both manganese deficiency and manganese excess associated with lower scores. In a study conducted in Quebec, children aged 6 to 13 years who had been exposed to drinking water containing elevated levels of manganese had significantly lower intelligence quotient (IQ) scores, with a 6.2-point difference observed between children in the highest vs. lowest manganese quintiles. Manganese exposure has also been associated with an increased risk of hyperactive behavior problems.

Inhalation of manganese is the most common environmental cause of manganism. Another source is the presence of a portal systemic shunt due to liver cirrhosis or portal vein thrombosis, which prevents the clearance of manganese via biliary excretion. Animal and human studies have also demonstrated that iron deficiency markedly enhances intestinal absorption of manganese. Iron shares similar absorption mechanisms with essential divalent metals, particularly manganese. Thus, a diet deficient in iron can lead to excess absorption of manganese; therefore, iron deficiency can be a risk factor for the subsequent accumulation of manganese in the central nervous system.

Previous studies have shown that iron deficiency increases blood manganese concentrations in adults as well. However, only a small number of case studies have examined the effect of iron deficiency on blood manganese levels in infants and children. We, too, recently showed that blood manganese levels are elevated among iron-deficient infants. Iron–manganese interactions underlie gender differences in blood manganese concentrations at different life stages. There are no gender differences in blood manganese concentrations before menarche, but blood manganese concentrations become higher in postpubertal women who have lower ferritin concentrations due to menstruation. Moreover, blood manganese levels become lower after menopause due to correspondingly higher ferritin concentrations.

**Lead**

Lead is a widespread environmental pollutant that can damage the central nervous, renal, cardiovascular, reproductive, and hematological systems. Recently, new evidence of adverse central nervous effects at increasingly low levels of exposure is rapidly published. Blood lead concentrations significantly below 10 μg/dL are associated with negative outcomes such as reduced IQ, executive function deficits, and attention deficit hyperactivity disorder. One of the more notable recent findings is that the slope of the dose-effect relationship between blood lead concentration and neurodevelopment is not linear, but rather supralinear, such that the rate of decline in children’s IQ scores is greater at blood lead levels below 10 μg/dL than at levels greater than 10 μg/dL. In early 2012, the US Centers for Disease Control (US CDC) concluded that a blood lead concentration of 5 μg/dL places a woman’s fetus at increased risk of adverse effects and warrants follow-up testing, patient education, and nutritional, environmental, and behavioral interventions to reduce lead exposure. Also in 2012, the US CDC abandoned use of the term “level of concern” regarding childhood lead poisoning, citing a lack of evidence that any blood lead level can be considered “safe.”
Several previous studies have assessed the temporal relationship between iron deficiency and increased blood lead concentrations\(^{11,21,51,52}\). A longitudinal study showed an association between iron deficiency and high blood lead levels in young children, with blood lead levels ranging from <5 μg/dL to 40 μg/dL\(^{53}\). In another study of children aged 10–15 years, the mean blood lead concentration was found to be 6.9 μg/dL in iron-deficient children and 4.3 μg/dL in normal children, and that iron supplementation significantly decreased blood lead concentrations in the former group\(^{21}\). A clinical trial assessing the impact of iron supplementation on blood lead concentrations in infants with iron deficiency found that changes in blood lead concentrations corresponded closely with changes in iron status\(^{13,51}\). In contrast to the studies described above, others have found no association between iron deficiency and increased blood lead concentrations\(^{53-59}\). This discrepancy may be due in part to differences in the age distribution of the study subjects, the assumptions used, or the degrees of lead exposure. For example, no association was observed in studies where the subjects were older female children or adolescents\(^{51,55,60}\). In postmenarche women, estrogen promotes bone mineralization and redistributes blood lead into bone; thus, women have lower blood lead concentrations than men and there is no association between high blood lead levels and iron deficiency in postmenarche adolescents owing to the overshadowing effects of estrogen on lead levels\(^{59}\). Some studies of children with lower blood lead concentrations (11.0 μg/dL and 11.4 μg/dL) have reported no association\(^{54,58}\). However, longitudinal studies of children with blood lead levels in a similar range have shown an association between iron status and blood lead concentration in children following iron supplementation\(^{21,51,52}\). Furthermore, we recently observed an association between iron supplementation and blood lead levels in infants with very low blood lead concentrations (1.416–1.846 μg/dL)\(^{13}\). Such minor increases in blood lead concentrations due to iron deficiency may have toxicological implications in children, considering the lack of evidence that any level of lead in the blood can be considered “safe.”

Cadmium

Cadmium is a ubiquitous environmental pollutant with a biological half-life in the body exceeding 10 years. Cadmium levels in the body accumulate with age, since only a minute part of the body burden (0.01%–0.02%) is excreted per day\(^{20}\). Cadmium has been reported to have cumulative effects on mortality and cardiovascular, renal, and developmental diseases\(^{61}\), and blood cadmium concentration is a valid biomarker of recent cadmium exposure\(^{49}\). Cadmium levels have been reported to increase as iron stores decrease in premenopausal women\(^{48,53,64-70}\). However, no association between iron deficiency and elevated cadmium levels has been observed in postmenopausal women\(^{71-73}\) or in men\(^{70,74}\), and few studies to date have analyzed the association between iron deficiency and elevated cadmium levels in children\(^{53}\). Furthermore, the studies performed in children have yielded conflicting results. Some studies reported an association between iron deficiency and cadmium\(^{75,76}\), whereas others found no such association\(^{77,78}\), and one study reported only an association between ferritin and cadmium concentrations in female adolescents\(^{53}\). Our recent study showed no association between iron deficiency and cadmium concentration in infants\(^{79}\). In contrast, assessment of the same study subjects showed that iron deficiency was associated with increased blood lead and manganese concentrations\(^{12,13}\). Our finding that iron deficiency and blood cadmium levels in infants are not related\(^{79}\) is compatible with some previous studies in children\(^{77,78}\) but not with others\(^{75,76}\). These discrepancies may be partly owing to differences in cadmium exposure levels or to the age distribution of study participants. For example, the two studies that found an association between iron deficiency and cadmium levels documented children living in an heavily air-polluted area of Turkey\(^{76}\) and children with blood cadmium concentrations more than 7 folds higher than those in our previous study\(^{79}\). The study subjects in our previous study were infants living in a nonpolluted area who had very low blood cadmium concentrations. Furthermore, most previous studies included children and/or adolescents as study subjects, but not infants\(^{53,75-78}\).

The placenta may act as a partial barrier to fetal exposure to cadmium\(^{69}\), and only 5%–10% of maternal blood cadmium is transferred to human milk owing to metallothionein binding of cadmium in blood cells\(^{81}\). Cadmium concentrations tend to increase with age\(^{62,74,82,83}\). Thus, the likelihood of exposure to cadmium may be reduced in infants and they may not show elevated blood cadmium levels associated with iron deficiency. In contrast, lead is more abundant than cadmium in sources to which infants may be exposed, thus lead is more often absorbed by infants with iron deficiency\(^{18}\). Manganese is abundant in foods as an essential element, and is also easily absorbed in subjects with iron deficiency\(^{20,29,32,33}\).

Conclusions

First, the data summarized here emphasize the importance of assessing iron and hematologic status in children when addressing environmental exposure to neurotoxic metals, such as manganese and lead, and related neurobehavioral effects. Given the high prevalence of iron deficiency in children, the
epidemiology of iron deficiency should be studied to assess its role as an important susceptibility factor, especially when carrying out environmental health risk assessments concerning low exposure to neurotoxic metals in children. Second, these findings indicate the possible role of exposure to neurotoxic metals in aggravating iron-related developmental and behavioral problems in children. Third, increased blood manganese and lead concentrations are probably associated with prolonged breastfeeding, which is also a risk factor for iron deficiency. Thus, babies who are breast-fed for prolonged periods should be given plain, iron-fortified cereals, or other good sources of dietary iron.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

**References**

1. de Benoist B, McLean E, Egli I, Cogswell M. Worldwide prevalence of anaemia 1993–2005: WHO Global Database of Anaemia. Technical Report. Geneva: World Health Organization, 2008.

2. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-3):1-29.

3. Iron deficiency anaemia: assessment, prevention and control: a guide for programme managers. Geneva: World Health Organization, 2001.

4. Cogswell ME, Looker AC, Pfeiffer CM, Cook JD, Lacher DA, Beard JL, et al. Assessment of iron deficiency in US preschool children and nonpregnant females of childbearing age: National Health and Nutrition Examination Survey 2003-2006. Am J Clin Nutr 2009;89:1334-42.

5. Healthy people 2010. Washington, DC: Department of Health and Human Services, 2000.

6. Lozoff B. Iron deficiency and child development. Food Nutr Bull 2000;22(4 Suppl):S560-71.

7. Georgieff MK. Long-term brain and behavioral consequences of early iron deficiency. Nutr Rev 2011;69 Suppl 1:S43-8.

8. Logan S, Martins S, Gilbert R. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. Cochrane Database Syst Rev 2001;(2):CD001444.

9. Szajewska H, Ruszczynski M, Chmielewska A. Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: a systematic review of randomized controlled trials. Am J Clin Nutr 2010;91:1684-90.

10. Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64(5 Pt 2):S34-43.

11. Peirano PD, Algarín CR, Chamorro R, Reyes S, Garrido MI, Duran S, et al. Sleep and neurofunctions throughout child development: lasting effects of early iron deficiency. J Pediatr Gastroenterol Nutr 2009;48 Suppl 1:S8-15.

12. Park S, Sim CS, Lee H, Kim Y. Blood manganese concentration is elevated in infants with iron deficiency. Biol Trace Elem Res 2013;155:184-9.

13. Park S, Sim CS, Lee H, Kim Y. Effects of iron therapy on blood lead concentrations in infants. J Trace Elem Med Biol 2014;28:56-9.

14. Lucchini RG, Kim Y. Health effects of manganese. In: Vojtisek M, Prakash R, editors. Metals and neurotoxicity. India: Society for Science and Environment, 2009:119-47.

15. Lonnerdal B. Manganese nutrition of infants. In: Klimis-Tavaezis DJ, editor. Manganese in health and disease. Boca Ratonpp: CRC Press, 1994:175-91.

16. Hurley LS, Kren CL. Manganese. In: Underwood E, Mertz W, editors. Trace elements in human health and animal nutrition. New York: Academic Press, 1987:185-223.

17. Mackenzie B, Gartt MD. Iron imports. II. Iron uptake at the apical membrane in the intestine. Am J Physiol Gastrointest Liver Physiol 2005;289:G981-6.

18. Davis CD, Wolf TL, Greger JL. Varying levels of manganese and iron affect absorption and gut endogenous losses of manganese by rats. J Nutr 1992;122:1300-8.

19. Kim Y, Park JK, Choi Y, Yoo CI, Lee CR, Lee H, et al. Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected. Neurotoxicology 2005;26:107-11.

20. Kim Y, Lee BK. Iron deficiency increases blood manganese level in the Korean general population according to KNHANES 2008. Neurotoxicology 2011;32:247-54.

21. Choi JW, Kim SK. Association between blood lead concentrations and body iron status in children. Arch Dis Child 2003;88:791-2.

22. Watson WS, Hume R, Moore MR. Iron and lead absorption in humans. Am J Clin Nutr 1982;36:823-9.

23. Piasek M, Blanusa M, Kostial K, Laskey JW. Low iron diet and parenteral cadmium exposure in pregnant rats: the effects on trace elements and fetal viability. Biometals 2004;17:1-14.

24. Tallkvist J, Bowlus CL, Lonnerdal B. DMT1 gene expression and cadmium absorption in human absorptive enterocytes. Toxicol Lett 2001;122:171-7.

25. Ryu DY, Lee SJ, Park DW, Choi BS, Klaassen CD, Park JD. Dietary iron regulates intestinal cadmium absorption through iron transporters in rats. Toxicol Lett 2004;152:19-25.

26. Gavric MD, Dolan KG. An expression system for a transporter of iron and other metals. Methods Mol Biol 2002;196:147-54.

27. Zoller H, Koch R0, Theurl I, Obrist P, Pietrangelo A, Montosi G, et al. Expression of the duodenal iron transporters divalent-metal transporter 1 and ferroportin 1 in iron deficiency and iron overload. Gastroenterology 2001;120:1412-9.

28. Finley JW. Manganese absorption and retention by young women is associated with serum ferritin concentration. Am J Clin Nutr 1999;70:37-43.

29. Bellinger DC. Prenatal exposures to environmental chemicals and children’s neurodevelopment: an update. Saf Health Work 2013;4:1-11.

30. Calne DB, Chu NS, Huang CC, Lu CS, Olanow W. Manganeseism and idiopathic parkinsonism: similarities and differences. Neurology 1994;44:1583-6.

31. Olanow CW. Manganese-induced parkinsonism and Parkinson’s disease. Ann N Y Acad Sci 2004;1012:209-23.

32. Kim Y, Kim JW. Toxic encephalopathy. Saf Health Work 2012;3:243-56.

33. Karki P, Lee E, Aschner M. Manganese neurotoxicity: a focus on glutamate transporters. Ann Occup Environ Med 2013;25:4.
Figueroa H, Hernandez-Avila M, et al. Early postnatal blood manganese levels and children’s neurodevelopment. Epidemiology 2010;21:433-9.
35. Bouchard MF, Sauve S, Barbeau B, Legrand M, Brodeur ME, Bouffard T, et al. Intellectual impairment in school-age children exposed to manganese from drinking water. Environ Health Perspect 2011;119:138-43.
36. Bouchard M, Laforest F, Vandelac L, Bellinger D, Mergler D. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ Health Perspect 2007;115:122-7.
37. Khan K, Factor-Litvak P, Wasserman GA, Liu X, Ahmed E, Parvez F, et al. Manganese exposure from drinking water and children’s classroom behavior in Bangladesh. Environ Health Perspect 2011;119:1501-6.
38. Hauser RA, Zesiewicz TA, Rosemurgy AS, Martinez C, Olanow CW. Manganese intoxication and chronic liver failure. Ann Neurol 1994;36:871-5.
39. Butterworth RF, Spahr L, Fontaine S, Layrargues GP. Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. Metab Brain Dis 1996;10:259-67.
40. Park NH, Park JK, Choi Y, Yoo CI, Lee CR, Lee H, et al. Whole blood manganese correlates with high signal intensities on T1-weighted MRI in patients with liver cirrhosis. Neurotoxicology 2003;24:909-15.
41. Finley JW, Johnson PE, Johnson IK. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. Am J Clin Nutr 1994;60:949-55.
42. Chua AC, Morgan EH. Effects of iron deficiency and iron overload on manganese uptake and deposition in the brain and other organs of the rat. Biol Trace Elem Res 1996;55:39-54.
43. Kwik-Uribe CL, Gietzen D, German JB, Golub MS, Keen CL. Chronic marginal iron intakes in mice result in persistent changes in dopamine metabolism and myelin composition. J Nutr 2000;130:2821-30.
44. Erikson KM, Shihabi ZK, Aschner JL, Aschner M. Manganese accumulates in iron-deficient rat brain regions in a heterogeneous fashion and is associated with neurochemical alterations. Biol Trace Elem Res 2002;87:143-56.
45. Bjoorj MM, Goodarzi F, Baserdaghat MA. Long-term follow-up of workplace and well water manganese effects on iron status indexes in manganese miners. Arch Environ Health 2002;57:919-28.
46. Brna P, Gordon K, Dooley JM, Price V. Manganese toxicity in a child with iron deficiency and polycythemia. J Child Neurol 2011;26:891-4.
47. Sahni V, Leger Y, Panaro L, Allen M, Giffin S, Fury D, et al. Case report: a metabolic disorder presenting as pediatric managanism. Environ Health Perspect 2007;115:1776-9.
48. Meltzer HM, Bartsch AJ, Borch-Johnsen B, Ellingsen DG, Alexander J, Thomassen Y, et al. Low iron stores are related to higher blood concentrations of manganese, cobalt and cadmium in non-smoking, Norwegian women in the HUNT 2 study. Environ Res 2010;110:497-504.
49. Lee BK, Kim Y. Effects of menopause on blood manganese levels in women: analysis of 2008-2009 Korean National Health and Nutrition Examination Survey data. Neurotoxicology 2012;33:401-5.
50. US Centers for Disease Control and Prevention. Low level lead exposure harms children: a renewed call for primary prevention [Internet]. Atlanta (GA): US Centers for Disease Control and Prevention; [c2014] [cited 2012 Dec 1]. Available from: http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf.
51. Wright RO, Tsaih SW, Schwartz J, Wright RJ, Hu H. Association between iron deficiency and blood lead level in a longitudinal analysis of children followed in an urban primary care clinic. J Pediatr 2003;142:9-14.
52. Wolf AW, Jimenez E, Lozoff B. Effects of iron therapy on infant blood lead levels. J Pediatr 2003;143:789-95.
53. Barany E, Bergdahl IA, Bratteby LE, Lundh T, Samuelson G, Skerfving S, et al. Iron status influences trace element levels in human blood and serum. Environ Res 2005;98:215-23.
54. Hammad TA, Sexton M, Langenberg P. Relationship between blood lead and dietary iron intake in preschool children. A cross-sectional study. Ann Epidemiol 1996;6:30-3.
55. Hershko C, Konijn AM, Moreb J, Link G, Grauer F, Weissenberg E. Iron depletion and blood lead levels in a population with endemic lead poisoning. Isr J Med Sci 1984;20:1039-43.
56. Rosado JL, Lopez P, Kordas K, Garcia-Vargas G, Ronquillo D, Alatorre J, et al. Iron and/or zinc supplementation did not reduce blood lead concentrations in children in a randomized, placebo-controlled trial. J Nutr 2006;136:2378-83.
57. Serwint JR, Damokosh AI, Berger OG, Chisolm JJ Jr, Gunter EW, Jones RL, et al. No difference in iron status between children with low and moderate lead exposure. J Pediatr 1999;135:108-10.
58. Wolf AW, Jimenez E, Lozoff B. No evidence of developmental III effects of low-level lead exposure in a developing country. J Dev Behav Pediatr 1994;15:224-31.
59. Clark M, Royal J, Seeler R. Interaction of iron deficiency and lead and the hematologic findings in children with severe lead poisoning. Pediatrics 1988;81:247-54.
60. Yip R, Dallman PR. Developmental changes in erythrocyte protoporphyrin: roles of iron deficiency and lead toxicity. J Pediatr 1984;104:710-3.
61. Sim CS, Kim Y, Lee H, Park CY, Ham JO, Lee BK. Iron deficiency increases blood lead levels in boys and pre-menarche girls surveyed in KNHANES 2010-2011. Environ Res 2014;130:1-6.
62. ATSDR. Toxicological profile for cadmium. Atlanta, GA: Agency for Toxic Substances and Disease Registry, 2008.
63. Jarup L, Akesson A. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 2009;238:201-8.
64. Vahter M, Berglund M, Akesson A, Liden C. Metals and women’s health. Environ Res 2002;88:145-55.
65. Akesson A, Berglund M, Schutz A, Bjellerup P, Bremme K, Vahter M. Cadmium exposure in pregnancy and lactation in relation to iron status. Am J Public Health 2002;92:284-7.
66. Berglund M, Akesson A, Nermell B, Vahter M. Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. Environ Health Perspect 1994;102:1058-66.
67. Gallagher CM, Chen JJ, Kovach JS. The relationship between body iron stores and blood and urine cadmium concentrations in US never-smoking, non-pregnant women aged 20-49 years. Environ Res 2011;111:702-7.
68. Kippler M, Ekstrom EC, Lonnerdal B, Goessler W, Akesson A, El Arifeen S, et al. Influence of iron and zinc status on cadmium accumulation in Bangladeshi women. Toxicol Appl Pharmacol 2007;222:221-6.
69. Mijal RS, Holzman CB. Blood cadmium levels in women of child bearing age vary by race/ethnicity. Environ Res 2010;110:505-12.
70. Satarug S, Ujjin P, Vanavanikutk Y, Baker JR, Moore MR. Influence of body iron store status and cigarette smoking on cadmium body burden of healthy Thai women and men. Toxicol Lett 2004;148:177-85.
71. Kim SH, Kim Y, Kim NS, Lee BK. Gender difference in blood cadmium concentration in the general population: Can it be explained
by iron deficiency? J Trace Elem Med Biol 2014;28:322-7.

72. Horiguchi H, Oguma E, Sasaki S, Miyamoto K, Ikeda Y, Machida M, et al. Comprehensive study of the effects of age, iron deficiency, diabetes mellitus, and cadmium burden on dietary cadmium absorption in cadmium-exposed female Japanese farmers. Toxicol Appl Pharmacol 2004;196:114-23.

73. Tsukahara T, Ezaki T, Moriguchi J, Furuki K, Fukui Y, Ukai H, et al. No significant effect of iron deficiency on cadmium body burden or kidney dysfunction among women in the general population in Japan. Int Arch Occup Environ Health 2003;76:275-81.

74. Olsson IM, Bensryd I, Lundh T, Ottosson H, Skerfving S, Oskarsson A. Cadmium in blood and urine: impact of sex, age, dietary intake, iron status, and former smoking: association of renal effects. Environ Health Perspect 2002;110:1185-90.

75. Turgut S, Polat A, Inan M, Turgut G, Emmungil G, Bican M, et al. Interaction between anemia and blood levels of iron, zinc, copper, cadmium and lead in children. Indian J Pediatr 2007;74:827-30.

76. Shah F, Kazi TG, Afridi HI, Kazi N, Baig JA, Shah AQ, et al. Evaluation of status of trace and toxic metals in biological samples (scalp hair, blood, and urine) of normal and anemic children of two age groups. Biol Trace Elem Res 2011;141:131-49.

77. Zhao TT, Chen B, Wang HP, Wang R, Zhang H. Evaluation of toxic and essential elements in whole blood from 0- to 6-year-old children from Jinan, China. Clin Biochem 2013;46:612-6.

78. Choi JW, Kim SK. Relationships of lead, copper, zinc, and cadmium levels versus hematopoiesis and iron parameters in healthy adolescents. Ann Clin Lab Sci 2005;35:428-34.

79. Park JH, Park S, Kim Y. Iron deficiency is not associated with increased blood cadmium in infants. Ann Occup Environ Med 2014;26:3.

80. Truska P, Rosival L, Balazova G, Hinst J, Rippel A, Palusova O, et al. Blood and placental concentrations of cadmium, lead, and mercury in mothers and their newborns. J Hyg Epidemiol Microbiol Immunol 1989;33:141-7.

81. Radisch B, Luck W, Nau H. Cadmium concentrations in milk and blood of smoking mothers. Toxicol Lett 1987;36:147-52.

82. Lee BK, Kim Y. Iron deficiency is associated with increased levels of blood cadmium in the Korean general population: analysis of 2008-2009 Korean National Health and Nutrition Examination Survey data. Environ Res 2012;112:155-63.

83. US Centers for Disease Control and Prevention. NHANES, Key statistics from NHANES (data are for 2003-2006) [Internet]. Atlanta, GA: US Centers for Disease Control and Prevention; [2014] [cited 2012 Dec 1]. Available from: http://wwwn.cdc.gov/nchs/nhanes/bibliography/key_statistics.aspx.