

REVIEW

Lead pollution – A risk factor for cardiovascular disease in Asian developing countries

Mohammad Perwaiz Iqbal

Department of Biological & Biomedical Sciences, Aga Khan University, Stadium Road, P.O. Box-3500, Karachi, Pakistan

Abstract: Lead (Pb) pollution is a serious problem in the developing countries, especially in South Asia. No levels of blood Pb can be considered safe for human health. While hypertensive effects of Pb have been well studied, there are only a few studies on the relationship of Pb exposure to the development of cardiovascular disease (CVD) in the Asian developing countries. The underlying mechanism is still unclear; however, oxidative stress and hyperhomocysteinemia appear to be most plausible hypotheses for the development of atherosclerosis leading to CVD. Enforcement of regulations for control of Pb pollution, increased public awareness about the harmful effects of Pb, cessation of smoking, frequent use of fruit juices and avoidance from iron and folate deficiencies would be required to protect masses from the deleterious effects of Pb.

Keywords: Blood lead levels, cardiovascular diseases, developing countries, lead poisoning, Pakistan.

INTRODUCTION

Lead (Pb) pollution is a problem world-wide; however in developing countries such as Pakistan it is much more prevalent due to non-functional regulatory measures. Pb is not known to be needed for any of the physiological functions in the body, therefore, its concentration in blood should ideally be negligible, however, due to environmental pollution, Pb gets inhaled or ingested and gets deposited in the body, especially in bones and can stay over there for many years.

Major sources contributing to greater exposure to Pb include polluted air, Pb-contaminated water, drinks and foods, Pb-based paints, batteries, toys and cosmetics. Leaded petrol, however, has remained a major source of Pb pollution for a number of years, especially in the developing countries (Kadir *et al.*, 2008).

Effects of Pb pollution on human health can be assessed by determining the concentration of blood Pb. For a number of years, international bodies such as Centers for Disease Control and Prevention (CDC) considered levels of blood Pb > 10 µg/dl as elevated blood levels (American Academy of Paediatrics, 1998). However, research over the past 15 years has shown that no blood Pb levels can be considered safe for human health (Menke *et al.*, 2006).

Blood Pb levels in some of the developed and developing countries in Asia

Figure 1 shows the mean blood Pb levels below 10 µg/dl

in some of the Asian countries. It is apparent that developed Asian countries with strong economies and better human development index, such as Japan, Korea, Singapore and Taiwan have mean blood Pb levels well below the 10 µg/dl level – a threshold previously considered by CDC and WHO as elevated levels (Kutbi *et al.*, 1989; Liou *et al.*, 1996; Kaji *et al.*, 1997; Hashim *et al.*, 2000; Neo *et al.*, 2000; Ozden *et al.*, 2004; Senanayake *et al.*, 2004; Billharz 2005; Chomchai *et al.*, 2005; Riddell *et al.*, 2007; Min *et al.*, 2007).

On the other hand, the developing Asian countries in Middle East (Egypt, Saudi Arabia, United Arab Emirates) and South Asia (Iran, India, Pakistan and Bangladesh) and China, as shown in Figure 2, have mean blood Pb levels well above 10 µg/dl despite introducing unleaded gasoline for use in automobiles (Kaiser *et al.*, 2001; Bener *et al.*, 2001; Rahbar *et al.*, 2002; Boseila *et al.*, 2004; Jain and Hu, 2006; Iranpour *et al.*, 2007; Huo *et al.*, 2007).

The blood levels of Pb in some of the developing countries in South East Asia may not appear to be too high above this threshold of 10 µg/dl, but the levels in these countries were alarmingly high some 15-20 years ago. Phasing out Pb from petrol has had the major impact. For example, in Pakistan mean blood Pb levels have come down from 38 µg/dl in 1989 to 15.6 µg/dl in 2002 (Kadir *et al.*, 2008). Even the petrol pump workers in Karachi in 2008 were not found to have significantly different mean levels of blood Pb from normal healthy subjects (12.9±3.7 µg/dl vs 14.5±6.1 µg/dl, respectively; Yakub *et al.*, 2009).

*Corresponding author: perwaiz.iqbal@aku.edu

Similarly, in India in 1999, 51% of 22,000 children and adults were found to have blood Pb levels above 10 µg/dl (The George Foundation, 2002), however, after the introduction of unleaded gasoline mean levels have come down to about 11 µg/dl (Jain and Hu, 2006; Niranjana and Madhusudana, 2006).

Some of the other developing countries in this region such as Indonesia, Thailand, Sri Lanka, Philippines and Malaysia have been successful in reducing the mean blood concentrations in their populations in the range 2.4 µg/dl - 6.9 µg/dl. Nepal at the edge of the Himalayas is quite unique with low mean levels of blood Pb (3.4 µg/dl) even before the introduction of unleaded petrol (Piomelli *et al.*, 1980; Iqbal MP, 2010).

Reasons for high mean blood Pb levels in Asian developing countries in spite of introducing unleaded petrol

While systems are in place in developed countries, for example USA, to enforce regulations that new paints should not have concentrations of Pb more than 90 ppm, Asian developing countries - India, Thailand and Sri Lanka have 31% - 45% of paint samples with Pb levels far in excess of 90 ppm (Toxic Link, 2009). Lead-based traditional cosmetics and folk remedies are still very popular in South Asian countries (Rahbar *et al.*, 2002). Moreover, folate and iron deficiencies are highly prevalent in India, Pakistan and Bangladesh. Recent studies have indicated that these deficiencies greatly increase the risk of lead poisoning (Zimmermann *et al.*, 2006; Solon *et al.*, 2008).

While the number of smokers in the developed countries is declining, they are on the rise in Asian developing countries. Increased public awareness about the risks associated with smoking and ban on advertisement in the media are the main reasons for decline in number of smokers in the developed countries. On the other hand, the number in the developing countries, especially in South East Asia, appears to be increasing because of the aggressive campaigning by the tobacco industry.

LEAD POLLUTION AND HUMAN HEALTH

As mentioned above, no concentration of blood Pb can be considered safe for human health. Even blood Pb levels as low as 2 µg/dl have been found to be associated with myocardial infarction and stroke mortality (Menke *et al.*, 2006). Another study in Korea revealed that mean blood Pb concentration of 2.4 µg/dl in children (5-13 years of age) was affecting their height (Min *et al.*, 2008). "Joint FAO/WHO Expert Committee on Food Additives re-evaluated Pb in June 2010 and withdrew the provisional tolerable weekly intake guideline value on the grounds that it was inadequate to protect against the IQ loss" (Childhood Lead Poisoning, 2010). Major health risks

associated with Pb exposure include cardiovascular disease (CVD), cognitive impairment and anemia (Jain *et al.*, 2005; Vaziri 2008; Solon *et al.*, 2008).

Pb exposure and CVD

Since CVD is the leading cause of death all around the world (Lopez *et al.*, 2006), recent studies in the developed countries have been on investigating the relationship between Pb exposure and development of this disease. In this regard, hypertensive effects of Pb have been studied most extensively. Reviews and meta-analyses of at least 30 original studies have revealed positive association between blood Pb levels and hypertension (Navas-Acien *et al.*, 2006). However, a causal relationship of Pb exposure with clinical CVD outcomes has not been established as yet. Most of the studies examining the relationship between Pb exposure and development of CVD (coronary heart disease, stroke and peripheral artery disease) have been carried out in the developed world, and there are only a few studies on this subject from South Asian countries (Childhood Lead Poisoning, 2010).

Two studies carried out in Pakistan show significantly elevated blood Pb levels in hypertensive patients compared to normotensive subjects. For example, Rahman *et al.*, (2006) showed mean levels of blood Pb in hypertensive patients in a population from Islamabad to be 25.5 µg/dl compared to 13.9 µg/dl in normal healthy subjects. Bukhari *et al.*, (2005) have reported highest mean concentration of Pb in serum of hypertensive patients with ischemic heart disease compared to hypertensive patients with nonexistent ischemic heart disease. Both of these studies, however, did not touch upon the mechanistic aspects of the disease.

A recent study carried out on a rural population in China showed a clear relationship between air pollution exposure from indoor biomass combustion and blood pressure in adult women, thereby increasing the risk for cardiovascular events (Baumgartner *et al.*, 2011). It is conceivable that if biomass fuel is polluted with Pb, the risk of CVD would even further increase in individuals getting such air pollution exposure.

A couple of studies over the past 6 years have indicated an association between blood Pb and homocysteine – an established risk factor for atherosclerosis (Schafer *et al.*, 2005; Chia *et al.*, 2007). Similar association between blood Pb and plasma homocysteine has been found in a Karachi population suggesting that relationship of Pb exposure to development of CVD could be through increased levels of plasma homocysteine (Yakub and Iqbal, 2010). There have also been a few reports from this region showing elevated blood Pb levels compromising the total antioxidant status indicating a clear relationship between Pb exposure and oxidative stress (Bijoor *et al.*, 2007; Iqbal and Yakub, 2011).

How Pb could be contributing to the development of CVD?

Despite a number studies on relationship of Pb exposure to the development of CVD, the underlying mechanism remains unclear (Chia *et al.*, 2007). A couple of plausible mechanisms have been put forward. The first one is “oxidative stress hypothesis”, which states that Pb disrupts the balance between antioxidants and prooxidants. Pb is known to increase generation of free radicals, most notably reactive oxygen species (ROS),

which may compromise the antioxidant protection in the body leading to increased oxidative damage to cell membrane, proteins and nucleic acids (Jomova and Valko, 2011). Moreover, Pb has been known to replace essential divalent ions such as calcium and zinc and also inhibit enzymes containing sulfhydryl groups thereby adversely affecting some of the essential metabolic processes in the cell (Farooq *et al.*, 2008). Another suggested mechanism is based on relationship between Pb exposure and development of atherosclerosis (Nemsadze

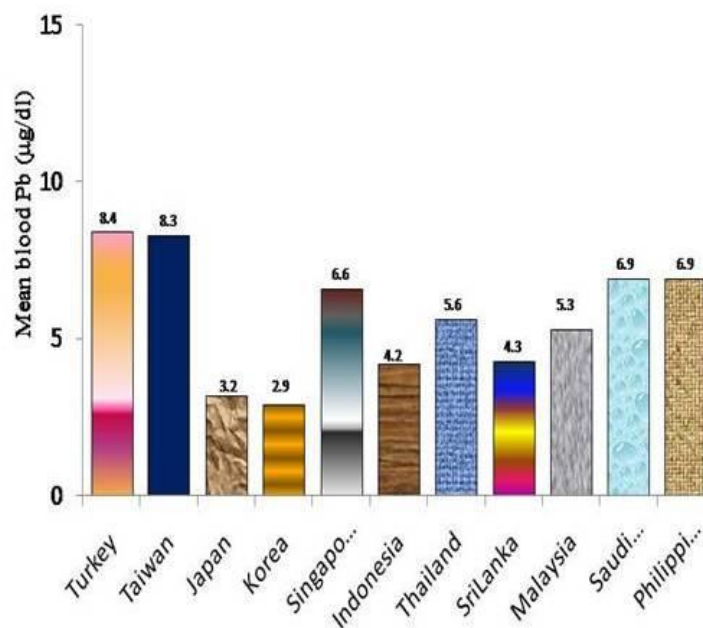


Fig. 1: Asian countries with mean blood Pb levels below 10 µg/dl. Values are based on published reports and do not represent the national data. References have been provided in the text.

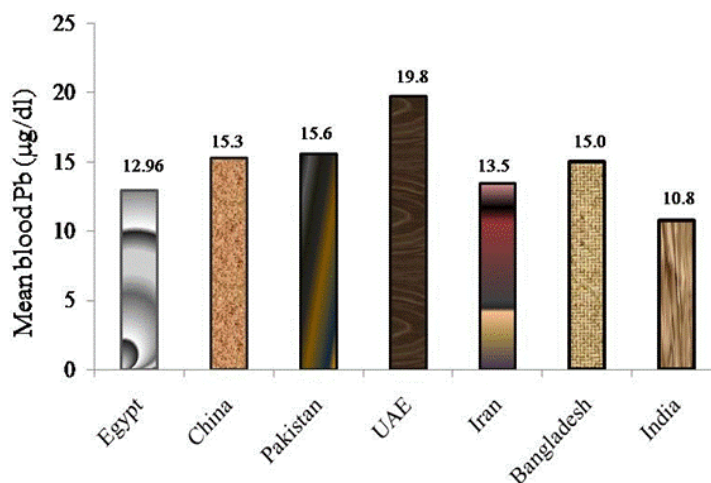


Fig. 2: Developing Asian countries with mean blood Pb levels above 10 µg/dl. Values are based on published reports and do not represent the national data. References have been provided in the text.

et al., 2009). Pb appears to be affecting the vasoactive function of vascular endothelium through increased production of ROS and decreased availability of nitric oxide leading to pathogenesis of atherosclerosis. In another report, Pb along with other heavy metals has been found to be part of carotid plaque of CVD patients. The levels of metal in plaque depended upon the working environment of the patient (Mamaralis *et al.*, 2010). In another study, Pb was found to be contributing to initiation of atherosclerosis by causing intimal hyperplasia (Zellar *et al.*, 2010).

Role of homocysteine in initiation of atherosclerosis is well established. Therefore, hyperhomocysteinemia associated with Pb exposure could be another mechanism towards development of CVD. In addition, there are other factors related to increased blood Pb levels and CVD such as folate deficiency for which no convincing explanation is available other than its relationship with hyperhomocysteinemia.

Recommendations to protect masses against Pb toxicity

1. Public advocacy for creating more awareness among masses through print and electronic media that even low level exposure to Pb is not without a risk to human health.
2. Adoption of healthy food habits such as high consumption of fruit juices. Recently, it has been shown that increased juice consumption is associated with decreased levels of blood Pb in a Pakistani population (Yakub and Iqbal, 2010). Moreover, Pb contaminated foods, drinks, cosmetics should be avoided. Smoking has been one of the major factors contributing to Pb pollution. Even passive smoking has been shown to be contributing to high blood Pb levels (Kaji *et al.*, 1997). There should be relentless campaigning against smoking.
3. Consumption of iron-fortified foods by children. It has been reported that iron and Pb share an intestinal transporter. Therefore, Pb absorption is enhanced in iron deficiency (Zimmermann *et al.*, 2006). Iron sufficiency protects against Pb accumulation in the body.
4. Impressing upon the policy makers to enforce rules and regulations towards control of Pb pollution. Those at greater risk such as children must be allowed to grow in a smoke-free and Pb-free environment because the future of developing countries, especially Pakistan depends on healthy population.

CONCLUSION

Exposure of masses to Pb pollution is a serious problem in Asian developing countries. Even small quantities of Pb in blood could be associated with increased risk for development of CVD. Oxidative stress and

hyperhomocysteinemia appear to be the most plausible mechanisms for the development of atherosclerosis due to Pb exposure. Control of Pb pollution and increased public awareness are the steps needed to reduce the risk of CVD and other disorders related to Pb exposure.

REFERENCES

- American Academy of Pediatrics (1998). Screening for elevated blood lead levels. *Pediatrics*, **101**(6):1072-1078.
- Baumgartner J, Schauer JJ, Ezzati M, Lu L, Cheng C, Patz JA and Bautista LE (2011). Indoor air pollution and blood pressure in adult women living in rural China. *Environ. Health Perspect.*, **119**: 1390-1395.
- Bener A, Almehdi AM, Alwash R and Al-Neamy FRM (2001). A pilot survey of blood lead levels in various types of workers in the United Arab Emirates. *Environ. Int.* **27**(4): 311-314.
- Bijoor AR, Sinha R and Venkatesh T (2007). Low-levels of blood lead and antioxidant status. *J. Indian Soc. Toxicol.*, **3**(2): 1-4.
- Billharz S (2005). Blood lead level tests in Bandung, Indonesia show encouraging results. *Jakarta Post*. <http://cleanairnet.org/caiasia/1412/article-60001.html>
- Bukhari IH, Hassan MN, Haleem A and Bhatti MM (2005). Role of metals (cadmium and lead) in patients of hypertension and their relationship with ischemic heart disease. *Res. J. Agric. & Biol. Sci.*, **1**(2): 190-191.
- Boseila SA, Gabr AA and Hakim IA (2004). Blood lead levels in Egyptian children: Influence of social and environmental factors. *Am. J. Publ. Health*, **94**(1): 47-49.
- Chia SE, Ali SM, Lee BL, Lim GH, Jin S, Dong N, TU NTH, Ong CN and Chia KS (2010). Association of blood lead and homocysteine levels among lead exposed subjects in Vietnam and Singapore. *Occup. Environ. Med.*, **64**: 668-93.
- Chomchai C, Padungtod C and Chomchai S (2005). Predictors of elevated blood lead level in Thai children: a pilot study using risk assessment questionnaire. *J. Med. Assoc. Thai.*, **88**(8): S53-S59.
- Childhood Lead Poisoning, World Health Organization (2010). WHO Document Production Services, Geneva, Switzerland, pp.1-74.
- Farooq Y, Hussain MM, Aleem SB and Farooq MA (2008). Lead intoxication: The extent of problem and its management. *Pak. J. Physiol.*, **4**(2): 36-41.
- Hashim JH, Hashim Z, Omar A and Shamsudin SB (2000). Blood lead levels of urban and rural Malaysian primary school children. *Asia Pac. J. Publ. Health*, **12**(2): 65-70.
- Huo X, Peng L, Xu X, Zheng L, Qiu B, Qi Z, Zhang B, Han D and Piao Z (2007). Elevated blood lead levels of children in Guiyu, an electronic waste recycling town in China. *Environ. Health Perspect.*, **115**(7): 1113-1117.

- Iranpour R, Besharati AA, Nasser F, Hashemipour M, Balali-Mood M and Kelishadi R (2007). Comparison of blood lead levels of mothers and cord blood in intrauterine growth retarded neonates and normal term neonates. *Saudi Med. J.*, **28**(6): 877-880.
- Jain NB, Laden F, Guller U, Shankar A, Kazani S and Garshick E (2005). Relation between blood lead levels and childhood anemia in India. *Am. J. Epidemiol.*, **161**(10): 968-973.
- Jain NB and Hu H (2006). Childhood correlates of blood lead levels in Mumbai and Delhi. *Environ. Health Perspect.*, **114**(3): 466-470.
- Jomova K and Valko M (2011). Advances in metal – induced oxidative stress and human disease. *Toxicology*, **283**(23): 65-87.
- Iqbal MP and Yakub M (2011). High blood lead levels compromise the total antioxidant status of normal healthy adults in a population in Karachi. *Pak. J. Med. Sci.*, **27**(2): 371-374.
- Iqbal MP (2010). Lead pollution – a risk to human health: An Asian Perspective. Proceedings of Association of Academies of Sciences in Asia (AASA) International symposium on “One Green Asia”, Korean Academy of Science and Technology, Seoul, Korea, pp.117-122.
- Kadir MM, Janjua NZ, Kristensen S, Fatmi Z and Sathiakumar N (2008). Status of children’s blood lead levels in Pakistan: implications for research and policy. *Public Health*, **122**(7): 708-715.
- Kaiser R, Henderson AK, Daley WR, Naughton M, Khan MH, Rahman M, Kieszak S and Rubin CH (2001). Blood lead levels of primary school children in Dhaka, Bangladesh. *Environ. Health Perspect.*, **109**(6): 563-566.
- Kaji M, Gotoh M, Takagi Y and Masuda H (1997). Blood lead levels in Japanese children: Effects of passive smoking. *Environmental Health and Preventive Medicine*, **2**: 79-81.
- Lopez AD, Mather CD, Ezzati M, Jamison DT and Murray CT (2006). Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. *Lancet*, **367**: 1747-1757.
- Kutbi II, Saber A and Guinena AH (1989). Measurement of blood-lead levels in school children of Jeddah Saudi Arabia and assessment of sub-toxic levels of lead on some sensitive hematological parameters. *J. Environ. Sci. Health*, **24**: 943-955.
- Liou SH, Wu TN, Chiang HC, Yang GY, Wu YQ, Lai JS, Ho ST, Guo YL, Ko YC and Chang PY (1996). Blood lead levels in the general population of Taiwan, Republic of China. *Int. Arch. Occup. Environ. Health*, **66**(4): 255-260.
- Mamarelis I, Pissaridi K, Dritsa V, Kotileas P, Tsiligiris V, Tzilalis V and Anastassopoulou J (2010). Oxidative stress and atherogenesis. An FT-IR Spectroscopic study. *In vivo*. **24**: 883-888.
- Menke A, Muntner P, Batuman V, Silbergeld E K and Guallar E (2006). Blood lead below 0.48 micromol/L (10 microg/dL) and mortality among US adults. *Circulation*, **114**: 1388-1394.
- Min JY, Min KB, Cho SII, Kim R, Sakong J and Paek D (2007). Neurobehavioral function in children with low blood lead concentration. *Neurotoxicology*, **28**: 421-425.
- Min KB, Min JY, Cho SI, Kim R, Kim H and Paek D (2008). Relationship between low blood lead levels and growth in children of white-collar civil servants in Korea. *Int. J. Hyg. Environ. Health*, **211**: 82-87.
- Navas-Acien A, Guallar E, Silbergeld EK and Rothenberg SJ (2007). Lead exposure and cardiovascular disease – a systematic review. *Environ. Health Perspect.*, **115**(3): 472-482.
- Nemsadze K, Sanikidze T, Ratiani L, Gabunia L and Sharashenidze T (2009). Mechanism of lead induced poisoning. *Georgian Med. News*, (172-173): 92-96.
- Neo KS, Goh KT and Sam CT (2000). Blood lead levels of a population group not occupationally exposed to lead in Singapore. *Southeast Asian J. Trop. Med. Public Health*, **31**(2): 295-300.
- Niranjan S and Madhusudana B (2006). Spatial variation in elevated blood lead levels among young children in Mumbai, India. *Popul. Space and Place*, **12**: 243-255.
- Özden TA, Kilic A, Toparlak D, Gökçay G and Saner G (2004). Blood level in school children. *Indoor and Built Environment*, **13**(2): 149-154.
- Piomelli S, Corash L, Corash MB, Seaman C, Mushak P, Glover B and Padgett R (1980). Blood lead concentrations in a remote Himalayan population. *Science*, **210**(4474): 1135-1137.
- Rahbar MH, White F, Agboatwalla M, Hozhabri S and Luby S (2002). Factors associated with elevated blood lead concentrations in children in Karachi, Pakistan. *Bull. World Health Organ.*, **80**(10): 769-775.
- Rahman S, Khalid N, Zaidi JH, Ahmad S and Iqbal MZ (2006). Non-occupational lead exposure and hypertension in Pakistani adults. *J. Zhejiang. Univ. Sci. B.*, **7**(9): 732-737.
- Riddell TJ, Solon O, Quimbo S A, Tan CMC, Butrick E and Peabody JW (2007). Elevated blood-levels among children living in the rural Philippines. *Bull. World Health Organ.*, **85**: 674-680.
- Schafer JH, Glas TA, Bressler J, Todd AC and Shwartz (2005). Blood lead is a predictor of homocysteine levels in a population-based study of older adults. *Environ. Health Perspect.*, **113**: 31-35.
- Senanayake MP, Rodrigo MDA and Malkanthi R (2004). Blood lead levels of children before and after introduction of unleaded petrol. *Ceylon Medical Journal*, <http://www.cababstractsplus.org/abstracts/Abstract.aspx?AcNo=20043136577>
- Solon O, Riddell TJ, Quimbo SA, Butrick E, Aylward GP, Bacate ML and Peabody JW (2008). Associations

- between cognitive function, blood lead concentration, and nutrition among children in the central Philippines. *J. Pediatr.*, **152**(2): 155-157.
- The George Foundation (2002). Lead Poisoning. <http://tgfworld.org/lead.html>
- Toxic Link, Executive Summary (2009). Global study to determine lead in new decorative paints in 10 countries. http://www.ipen.org/ipenweb/documents/work%20documents/paint_executivesummary.pdf
- Vaziri ND (2008). Mechanisms of lead-induced hypertension and cardiovascular disease. *Am. J. Physiol. Heart Circ. Physiol.*, **295**(2): H454-H465.
- Yakub M, Iqbal MP, Mahboobali N, Haider G and Azam I (2009). Blood lead and plasma homocysteine in petrol pump workers in Karachi: Role of vitamins B6, B12, folate and C. *J. Chem. Soc. Pak.*, **31**(2): 319-323.
- Yakub M and Iqbal MP (2010). Association of blood lead (Pb) and plasma homocysteine: A cross sectional survey in Karachi, Pakistan. *PLoS ONE.*, **5**(7): e11706.doi:10.1371/journal.pone.0011706.
- Zeller I, Knoflach M, Seubert A, Kreutmayer SB, Steizmüller ME and Wallnoefer E, Blunder S, Frotschnig S, Messner B, Willeit J, Debbage P, Wick G, Kiechl S, Laufer G and Bernhard G (2010). Lead contributes to arterial intimal hyperplasia through nuclear factor erythroid 2-related factor-mediated endothelial interleukin 8 synthesis and subsequent invasion of smooth muscle cell. *Arterioscler Thromb. Vasc. Biol.*, **30**(9): 1733-1740.
- Zimmermann MB, Muthayya S, Moretti D, Kurpad A and Hurrell RF (2006). Iron fortification reduces blood lead levels in children in Bangalore, India. *Pediatrics*, **117**(6): 2014-2021.