Available online at www.medicinescience.org

ORIGINAL RESEARCH

Medicine Science 2017;6(3):531-6

Medicine Science International Medical Journal

Effects of age, gender, BMI, settlement and smoking on lead and cadmium accumulation in heart tissue

Aybike Dip[1], Servet Birgin. Iritas[1], Gorkem Mergen[2], Ahmet Hakan Dinc[3], Tulin Soylemezoglu[2]

[1]Turkey Ministry of Justice, Council of Forensic Medicine, Adana, Turkey
[2]Ankara University, Institute of Forensic Medicine, Ankara, Turkey
[3]TBMM (The Grand National Assembly of Turkey) Hospital, Ankara, Turkey

Received 08 February 2017; Accepted 05 April 2017
Available online 11.04.2017 with doi: 10.5455/medscience.2017.06.8615

Abstract
Cadmium (Cd) and lead (Pb) are well-known risk factors for peripheral arterial and some other cardiovascular diseases. The aim of the study was to determine the level of both toxic metals, in the human heart tissue and compare the accumulation to their age, gender, body mass index, living environment and smoking habit. Heart tissues of the 112 autopsy cases, representing a sample set of population living in capital city of Turkey: Ankara Province (both in city center and suburban), were collected from Turkey Ministry of Justice, Council of Forensic Medicine in Ankara Branch. Lead and cadmium analysis was carried out by Graphite Furnace Atomic Spectrometry technique. Cd/Pb results and individuals' information were assessed by SPSS statistically. Average value of Pb was found as 1374.99±237.01ppb and Cd was found as 287.54±66.43ppb in all heart tissue samples. Consideration of metal levels in autopsy heart tissues by age, statistically significant positive correlation in Cd was observed ($p<0.05$). There was no correlation found between metal levels with gender and BMI values. Both Pb and Cd levels of the samples who lived in urban was significantly greater than in suburban areas ($p<0.05$). Significant increase Cd level were observed in smokers' heart tissues ($p<0.05$), however, contrary to expectations, Pb has no statistically significant result.

Keywords: Lead, cadmium, heart tissue, accumulation, smoking, AAS

Introduction

Cadmium (Cd) and lead (Pb) are most abundant heavy metals playing role on many illness or cancer types of human. Most of the metals enter body via various routes and accumulate in different tissues. Environmental metal exposure and individual factors changes metal accumulation level or target tissue in human body. While metal accumulation assessed mostly in blood and urine samples, follow up researches of target tissues have been useful in explaining more dynamic findings than blood or urine specimen.

It is estimated that about 25000 to 30000 tons of Cd are released to environment each year, about half from the weathering of rocks into the river water and then to oceans, by discharge from industrial facilities or sewage treatment plants, atmospheric deposition, by leaching from landfills or soil, or phosphate fertilizers. Cadmium in drinking water contributes only to less than a few percent of the total cadmium intake [1]. Cigarette smoke and diet are the main sources of Cd in daily life and smoking the more serious one in health concern [2,3]. Each cigarette contains 1-2 μg Cd and more than a half may pass through the lungs by smoking and enters the systemic circulation. Aside from smoking, living near hazardous waste sides or factories releasing Cd into air has also another risk of exposure. In heavily contaminated areas, vicinity of cadmium emitting plants or in mining districts, water and rivers also substantially contaminated by cadmium [2,4-5]. It has been reported that cadmium exerts its adverse cardiovascular effects by promoting atherosclerosis as well as disadvantageous functional and metabolic changes in the heart [6]. In particular, high susceptibility of the heart to cadmium was reported in a human 15 year follow-up study in line with the fact that the heart is a relatively sensitive organ due to its low anti-oxidant capacity [7]. Similarly, animal studies also shows cadmium cause some changes in cardiovascular functions [8-10]. Environmental exposure to cadmium has been found to be associated with an increased prevalence of heart failure, although the precise toxic effects of cadmium exposure on myocardial function remain unknown [11]. Recent data from the National Health and Nutrition Examination Survey suggests that cadmium exposure remains a rather important determinant of all-cause cardiovascular mortality in certain populations of US adults [12].

***Coresponding Author:** Aybike Dip, Turkey Ministry of Justice, Council of Forensic Medicine, Adana, Turkey
Phone: +90 533 7748531
E-mail: dip.aybike@gmail.com

Lead exposure has widely seen in urban environments especially near emission sources although leaded gasoline had been banned in 1986 in USA and 1996 in Turkey. It is a toxic element and its physiological role in the human body is unexplained. The toxic effects of Pb have been known for centuries and all exposures result from human activities. Lead is easily absorbed through gastrointestinal and respiratory tract, and distributed to soft tissues and finally bones where it is stored over decade [13-14]. When Pb is ingested by food or water, 10-15 % of taken quantity is absorbed by gastrointestinal system of adults and this ratio increases up to 50 % for children [15]. About 99% of absorbed Pb remains in erythrocytes for 30-35 days (only 1% of lead is found in plasma and serum) and distributed to soft tissues of liver, renal cortex, aorta, brain, lungs within 4-6 weeks [16]. Accumulated Pb is stored in bones with 20-30 years half-life period. As divalent cation, it inhibits enzymes and proteins due to high capacity of binding to sulfhydryl groups [17]. Lead exposure in human is generally assessed by blood Pb level. A lot of clinical researches show that Pb exposure correlates increasing incidence of hypertension, cerebrovascular and cardiovascular diseases [18-21]. Population research on the cardiovascular effects of Pb has focused largely on the association with blood pressure and hypertension. Meta-analyses of more than 60 researches show strong relationship between systolic and diastolic blood pressure and elevated blood Pb level [22-24]. High blood Pb level also correlates cardiovascular mortality and prevalence of peripheral arterial diseases [25-26].

Both metals more or less seem doubtful about cardiovascular illness previously proven by a lot of researches. Although they are effective on heart tissue, their toxic effect studied mostly on indirect mechanisms by liver and kidney. In the view of previous researches about cardiovascular effect of both metals, instead of routine biological samples like hair, blood or urine, Cd and Pb accumulation were assessed by measuring their levels in human heart tissue. After Cd and Pb concentrations measured, results were compared to gender, body mass index, living environment and smoking habit to reveal their effect on accumulation.

Materials and Methods

Sample Collection

Heart tissue samples were collected from autopsy cases of 112 adults (88 male and 24 female aged 18 - 86) in cooperation with Turkey Ministry of Justice, The Council of Forensic Medicine. Carcinoma or tumor metastasis tissue samples was elucidated. The subjects were excluded from the analysis if they had been reported as occupational exposure to heavy metals, any kind of specific heart diseases or metal intoxication. A small questionnaire was conducted to the relatives of each autopsy cases to get the demographic information includes gender, height and weight, smoking habit and living area. Samples without smoking habit and settlement information were withdrawn from the statistical evaluation.

Left ventricles of heart tissues were taken from 112 autopsy cases not later than 24h after death due to tissue autolysis. Each heart tissue sample was taken with stainless lancet and weighed approximately 1 g. Tissue samples were washed with %5 nitric acid solution and deionized water and then placed into 2ml-polypropylene tubes. They were stored at -20 ^{0}C until microwave oven digestion process.

Sample preparation

Frozen tissue samples were kept at room temperature until thawed. Wet tissues were weighed and transferred to glass tables and left in oven at 75 ^{0}C over night to dry.

Dry tissues were weighed to determine their dry weight and transferred into high temperature resistant teflon tubes. Ten ml %65 nitric acid solution were added to dry tissues and ingested in microwave.

Microwave digestion was operated at 210 ^{0}C for 10 min with 600 watts. Ingested tissue samples were taken into 50ml-revolved caps propylene tubes and reconstituted to 25ml by deionized water. Samples were stored +4 ^{0}C until analysis time.

Instrumentation and Chemicals

Measurements were performed by a Varian AA240Z Atomic Absorption Spectrometer equipped with a Varian GTA120 graphite furnace and Zeeman background correction system (Varian, Victoria, Australia). Varian SpectrAA version 5.1 PRO software programme coupled with Graphite Furnace Atomic Absorption Spectrometer (GFAAS) system was utilized for determination of Pb and Cd. Boosted-discharge hollow cathode lamp was used as the excitation source for Pb. Continuous flow of argon (Ar) gas was maintained in the graphite tube for inertness until atomization. Digestion procedure for heart tissues was carried out by Mars Xpress microwave system (CEM, Matthews, USA) with PTFE microwave digestion vessels.

1000µg/mL Pb and 1000µg/mL Cd stock solution was obtained from SCP Science (Courtaboeuf, France). Triton-X-100 was obtained from Scharlau (Barcelona, Spain). HNO_3 (65%v/v) and ammoniumdihydrogen phosphate were purchased from Merck (Darmstadt, Germany). All chemicals were analytical reagent grade unless otherwise specified. Ultra pure water (Human UP 900 Scholar-UV, Korea), with resistivity of 18MΩ cm, was used to prepare the solutions throughout all experimental process. Argon gas with purity of 99.999% was purchased from a local supplier company Oksan, (Ankara, Turkey).

Analysis for Lead and Cadmium

Lead and cadmium levels were measured by GFAAS technique. Varian AA240Z Zeeman Atomic Absorption

Spectrometer was used to determine the level of Pb and Cd. Calibration studies were executed for each metals. All calibrations were repeated between every 30-sample measurements. Wavelength was set to 283.3 nm and 228.8 nm for Pb and Cd, respectively. Peak height used for calibration and integrations were done by calibration calculation. Every sample including calibration standards were analyzed 3 times (n=3) and Ar was used as medium gas. Absorbance data was collected during optimized atomization stage at 2100ºC for Pb and 1769ºC for Cd, respectively. Data was computed by Varian SpectrAA® software and converted to metal concentrations ng/g (dry heart tissue) which is expressed as ppb in this article.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 15.0 software for Windows was used for the statistical analysis. Independent variables were age, gender, body mass index, living environment and smoking habits and differences among groups were assessed with the Independent-Samples T Test and One Way Anova after the set of variables tested for homogeneity. The value for $p<0.05$ was accepted as significant.

Results

When samples were considered totally without any classifications, wide rages of levels were observed for both toxic metals. Table 1 summarizes minimum and maximum levels of Pb and Cd measured in total autopsy cases. Mean value of Pb found as 1374.99 ± 237.01ppb and of Cd found as 287.54 ± 66.43ppb.

Table 1. General assessment of metal levels in autopsy heart tissues.

Metals	n	Min value	Max value	Mean ± SD
Pb (ppb)	112	16.32	11318.40	1374.99 ± 237.01
Cd (ppb)	112	27.11	6452.09	287.54 ± 66.43

Gender: No statistically significant Cd or Pb tissue accumulation was observed for both gender. However, average Pb in men's heart tissues was higher than in women and average Cd was higher in women than in men (Table 2).

Table 2. Relationship between lead and cadmium levels in heart tissue with gender.

	Gender	n	Mean ± SD	Min value	Max value	p
Pb	Female	24	1429.84 ± 245.28	56.24	7825.70	
(ppb)	Male	88	1096.55 ± 183.58	23.16	7536.83	0,473
	Total	112	1165.61 ± 197.16	23.16	7825.70	
Cd	Female	24	178.86 ± 13.82	27.11	606.14	
(ppb)	Male	88	207.78 ± 18.29	30.20	943.36	0,498
	Total	112	202.35 ± 17.52	27.11	943.36	

(* $p<0.05$)

Age: Aging is related to major changes in body by physiological functions that affect the kinetics of most toxic metals. In order to compare the metal accumulation distribution, cases were divided into three age group as 18-35 (young adults), 35-60 (middle aged adults) and over 60 (older adults) (Table 3). There was no statistical difference in Pb for all age group. Moreover, high Pb was measured for 18-35 age group and the low Pb level, nearly half of 18-35 age group, was measured for 35-60 age group. For Cd statistically significant correlation was observed with aging; as age increases, the Cd in the heart tissues also increases ($p<0.05$).

Table 3. Relationship between lead and cadmium levels in heart with age.

	Age	n	Mean ± SD	Min value	Max value	*p*
	18-35	36	1463.66 ±231.90	50.52	7825.70	
Pb	35-60	52	971.68 ±173.18	23.16	6582.28	0,520
(ppb)	60-	24	1130.66 ±191.44	51.48	7536.83	
	Total	112	1165.61 ±197.17	23.16	7825.70	
	18-35	36	137.71 ±9.19	27.11	386.60	
Cd	35-60	52	225.88 ±18.52	30.20	796.17	**0,022***
(ppb)	60-	24	249.32 ±22.34	47.30	943.36	
	Total	112	202.35 ±17.52	27.11	943.36	

(* $p<0.05$)

BMI: Metal levels and body mass index (BMI) also assessed (Table 4). Body mass index was calculated by dividing weight in kilograms by height in meters squared. The 0-24.9 kg/m^2 BMI accepted as normal weight and above 24.9 kg/m^2 BMI accepted as overweight. Average values of both Cd and Pb were found higher for overweight group but no statistically significant correlation was observed ($p>0.05$).

Table 4. Relationship between lead and cadmium levels with BMI.

	BMI kg/m^2	n	Mean ± SD	Min value	Max value	*p*
Pb	0-24.9	43	1018.47 ± 182.93	39.75	7825.70	
(ppb)	24.9-	69	1255.17 ± 206.14	23.16	7807.44	0,542
	Total	112	1165.61 ± 197.17	23.16	7825.70	
Cd	0-24.9	43	188.56 ± 15.21	27.11	796.17	
(ppb)	24.9-	69	210.95 ± 18.89	30.20	943.36	0,513
	Total	112	202.35 ± 17.53	27.11	943.36	

(* p<0.05)

Settlement: Autopsy cases were grouped according to their living environment effected by environmental pollutants (urban/high exposure risk and sub-urban/low exposure risk) (Table 5). Both Cd and Pb were found statistically higher for who lived in urban than sub-urban (p<0.05).

Table 5. Relationship between lead and cadmium levels with settlement

	Settlement	n	Mean ± SD	Min value	Max value	p
Pb	Sub-urban	42	625.15 ± 98.91	25.79	4733.97	
(ppb)	Urban	67	1364.60 ± 222.80	23.16	7825.70	**0.045***
	Total	109	1079.68 ± 188.04	23.16	7825.70	
Cd	Sub-urban	42	152.33 ± 13.58	27.11	606.14	
(ppb)	Urban	67	224.92 ± 17.75	33.83	943.36	**0.024***
	Total	109	196.80 ± 16.58	27.11	943.36	

(* p<0.05)

Smoking: Accumulation of Pb and Cd in heart tissues for smokers and non-smokers was evaluated lastly (Table 6). Average Pb was higher for smokers' than non-smokers but results were statistically insignificant (p>0.05). However, Cd was found in smokers' heart tissues significantly greater than non-smokers' (p<0.05).

Table 6. Relationship between lead and cadmium levels with smoking.

	Smoking	n	Mean ± SD	Min value	Max value	p
Pb	Non-Smokers	39	1162.95 ± 191.25	53.64	7825.70	
(ppb)	Smokers	65	1273.43 ± 209.53	23.16	7536.83	0,789
	Total	104	1232.00 ± 202.01	23.16	7825.70	
Cd	Non-Smokers	39	165.00 ± 15.57	27.11	818.75	
(ppb)	Smokers	65	236.31 ± 18.52	37.53	943.36	**0,048***
	Total	104	210.50 ± 17.77	27.11	943.36	

(* p<0.05)

Discussion

Lead and cadmium are known as toxic and carcinogenic metals. In addition to their large-scale toxic effects, there are also a lot of surveys about their cardiovascular effects. It has been thought Pb and Cd have role in atherosclerosis because they increase oxidative stress and inflammation, induces renal dysfunctions, effects endothelial functions and alter the nitric oxide synthesis regulation. High Pb and Cd level is also a risk factor in peripheral arterial diseases and other cardiovascular diseases [14, 17, 18, 27].

Smoking is the main source of Pb and Cd; especially Cd is thought the most effective toxic metal in the smoking induced diseases. In NHANES 1999-2000 that examines more than 2000 people, blood Pb and blood Cd were found higher in smokers than in non-smokers. Pb was higher in men than in women and Cd was higher in women than in men in the same survey [26,28].

Cadmium generally has long half-life and gradually accumulates in liver, kidney and heart. It can bind proteins and other materials in blood via systemic circulation. [29,30]. As a divalent cation having a relatively small atomic radius, Cd can interact with a lot of of biological molecules and this unselective behavior of Cd has made it extremely difficult for investigators to sort out the significant actions of Cd from the insignificant [31]

Environmental exposure to cadmium is toxic for heart and blood vessels and also shown that induce atherosclerosis by increasing free radical generation [32-33]

Generally, effects of Cd and Pb were investigated by measuring the both metals in blood and urine. There have been some autopsy studies assessed their accumulation in some tissues [34], however, there were no studies comparing their gender, age, BMI, settlement and smoking habit with their accumulation in heart tissues.

In this study, metal accumulation assessed with gender firstly (Table 2). Although there were no statistically meaningful results, average Pb level in men heart tissues was found higher than in women and average Cd level was higher in women than in men (p>0.05). These results were parallel to NHANES 1999-2000 study. Cadmium

absorption may increase with iron deficiency, which may contribute to higher absorption of cadmium by women [35]. In order to compare the metal accumulation in heart tissue distribution, cases were divided into three age group as 18-35, 35-60 and over 60 (Table 3). There was no statistical difference for Pb in all age groups ($p>0.05$). Moreover, the highest Pb concentration was measured for 18-35 age group and the lowest, nearly half of 18-35 age group, was measured for 35-60 age group. In contrast to Pb, statistically significant positive correlation with aging was observed for Cd ($p<0.05$). Metal levels associated with body mass index (BMI) also assessed (Table 4) and average values of Cd and Pb level were found higher for overweight group but no statistically significant correlation was observed ($p>0.05$).

In addition to individual factors, environmental effects and smoking habit were also taken into consideration. Autopsy cases were grouped according to their settlements as lived in urban and suburban (Table 5). Both Cd and Pb were found significantly higher in urban than in suburban ($p<0.05$). Accumulation of Pb and Cd in heart tissues of both smokers and non-smokers was evaluated and average Pb was found higher for smokers' than non-smokers but the results were statistically insignificant (Table 6). However, the mean Cd in smokers' heart tissues was significantly greater than non-smokers' ($p<0.05$).

Conclusion

Toxic metal analyses have been done for various autopsy or biopsy tissues in various studies up until now. There are a lot of toxic metal research papers with blood and urine samples of patients with specific diseases but not much with autopsy samples, especially with heart tissue. In most studies show that cardiovascular effects of Cd and Pb are mainly emerged by free radical generation which is also related to level of both metal levels in heart tissue. In this study, the effects of age, gender, BMI, smoking habits and settlement on metal accumulation in the heart tissues of subjects, who without known cardiovascular diseases during lifetime, were investigated.

Resulting data mainly reveals that; (I) accumulation of cadmium in the heart tissue increases by age and smoking; (II) both cadmium and lead levels are higher than in urban areas; (III) gender and BMI does not effect the accumulation level of cadmium and lead in heart tissues.

This study constitutes the first data of future databases on toxic metal accumulation in heart tissue and population cardiovascular risk assesment.

Acknowledgements

This work was financially supported by T. R. Prime Ministry State Planning Organization and Research Fund of Ankara University (Grant number 2003K1201902).

This study is ethically approved by Research Ethics Committee of Medical Faculty-Ankara University (Decision Number: 104-2716/18.12.2006) and authorized by The Council of Forensic Medicine, Ministry of Justice, Ankara (Document Number: B.03.1.ATK.0.01.00.08/242; 15.05.2007).

References

1. 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.
2. ATSDR Agency for Toxic Substances and Disease Registry, Toxicological Profile for Cadmium. U.S. Department of Health and Human Services. Public Health Service 1999a
3. ATSDR Agency for Toxic Substances and Disease Registry, Toxicological Profile for Cadmium. U.S. Department of Health and Human Services. Public Health Service 2012
4. Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure-A review of the literature and a risk estimate. Scand J Work Environ Health. 1998;24(Suppl. 1):1-51.
5. Järup L, Akesson A. Current status of Cd as an environmental health problem. Toxicol Appl Pharmacol. 2009;238:201-8.
6. Peters JL, Perlstein TS, Perry MJ, McNeely E, Weuve J. Cadmium exposure in association with history of stroke and heart failure. Environ Res. 2010;110(2):199-206.
7. Nishijo M, Nakagawa H, Morikawa Y, Tabata M, Senma M, Miura K, Takahara H, Kawano S, Nishi M, Mizukoshi K. Mortality of inhabitants in an area polluted by cadmium: 15 year follow up. Occup Environ Med. 1995;52(3):181-4.
8. Carmignani M, Boscolo P. Cardiovascular responsiveness to physiological agonists of male rats made hypertensive by long-term exposure to cadmium. Sci Total Environ. 1984;34(1-2):19-33.
9. Ronco AM, Montenegro M, Castillo P, Urrutia M, Saez D, Hirsch S, Zepeda R, Llanos MN. Maternal exposure to cadmium during gestation perturbs the vascular system of the adult rat offspring. Toxicol Appl Pharmacol. 2011;251(2):137-45.
10. Zepeda R, Castillo P, Saez D, Llanos MN, Ronco AM. Cardiac tissue injury resistance during myocardial infarction at adulthood by developmental exposure to cadmium. Cardiovas Toxicol. 2012;12(1):64-72.
11. Turdi S, Sun W, Tan Y, Yang X, Cai L and Ren J. Inhibition of DNA methylation attenuates low-dose cadmium-induced cardiac contractile and intracellular Ca^{2+} anomalies. Clinical and Experimental Pharmacology and Physiology. 2013;40(10):706-12.
12. Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. general population. Environ. Health Perspect. 2012;120(7):1017-22.
13. Krantz A, Dorevitch S. Metal exposure and common chronic diseases: a guide for the clinician. Disease-a-Month. 2004;50(5):220-62.
14. Carocci A, Catalano A, Lauria G, Sinicropi MS, Genchi G. Lead Toxicity, Antioxidant Defense and Environment Reviews of Environmental Contamination and Toxicology 2016;238:45-67.
15. Markowitz M. Lead poisoning. Pediatr Rev. 2000;21:327-35.

16. Begovic V, Nozic D, Kupresanin S, Tarabar D. Extreme gastric dilation caused by chronic lead poisoning: a case report. World J Gastroenterol. 2008;14(16):2599-01.

17. Lyn Patrick, ND Lead Toxicity, A Review of the Literature.Part I: Exposure, Evaluation, and Treatment Alternative Medicine Review. 2006;11(1):1-22.

18. Aoki Y, Brody DJ, Flegal KM, Fakhouri THI, Parker JD, Axelrad DA. Blood Lead and Other Metal Biomarkers as Risk Factors for Cardiovascular Disease Mortality. Medicine. 2016:95(1):1-8.

19. Vaziri ND, Lin CY, Farmand F, Sindhu RK. Superoxide dismutase, catalase, glutathione peroxidase and NADPH oxidase in lead induced hypertension. Kidney Int. 2003;63(1):186-94.

20. Fanning D. A mortality study of lead workers, 1926-1985. Arch Environ Health. 1988;43(3):247-51.

21. Sokas RK, Simmens S, Sophar K. Lead levels in Maryland construction workers. Am J Ind Med. 1997;31(2):188-94.

22. Staessen JA, Bulpitt CJ, Fagard R. Hypertension caused by low-level lead exposure: myth or fact? J Cardiovasc Risk. 1994;1(1):87-97.

23. Schwartz J. Lead, blood pressure, and cardiovascular disease in men. Arch Environ Health. 1995;50(1):31-7.

24. Nawrot TS, Tiils L, Den Hond, EM. An epidemiological re-appraisal of the association between blood pressure and blood lead: a metaanalysis. J Hum Hypertens. 2002;16(2):123-31.

25. Lustberg M, Silbergeld E. Blood lead levels and mortality. Arch Intern Med. 2002;162(2):2443-9.

26. Navas-Acien A, Selvin E, Sharrett AR, Calderon-Aranda E, Silbergeld E, Guallar E. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. Circul. 2004;109(25):3196-201.

27. Lukkhananan P, Thawonrachat N, Srihirun S, Swaddiwudhipong W, Chaturapanich G, Vivithanaporn P, Unchern S, Visoottiviseth P, Sibmooh N. Endothelial dysfunction in subjects with chronic cadmium exposure. J Toxicol Sci. 2015;40(5):605-13.

28. National Center for Health Statistics. National Health and Nutrition Examination Survey, 1999–2000. Hyattsville, MD: National Center for Health Statistics, 2004. (http://www.cdc.gov/nchs/about/major/nhanes/nhanes99-00.htm)

29. Bridges CC, Zalups RK. Molecular and ionic mimicry and the transport of toxic metals. Tox Appl Pharm. 2005;204:274-308.

30. Zalups RK. Ahmad S. Molecular handling of cadmium in transporting epithelia. Tox Appl Pharm. 2003;186 (3):163-88.

31. Prozialeck WC, Edwards JR, Woods JM. The vascular endothelium as a target of cadmium toxicity. Life Sci. 2006;79(16):1493-506.

32. Gonick HC, Ding Y, Bondy SC, Ni Z, Vaziri ND. Lead-induced hypertension: interplay of nitric oxide and reactive oxygen species. Hypertension. 1997;30(6):1487-92.

33. Bhatnagar A. Environmental Cardiology:Studying Mechanistic Links Between Pollution and Heart Disease. Circulation Research. 2006;99(7):692-705.

34. Iwao S, Tsuchiya K, Sugita M. Variation of cadmium accumulation among Japanese.Arch Environ Health. 1983;38(3):156-62.

35. CDC. Fourth Report on Human Exposure to Environmental Chemicals. Centers for Disease Control and Prevention. US Department of Health and Human Services. Atlanta, GA. 2009.