URINARY AND BLOOD CADMIUM LEVELS IN RELATION TO TYPES OF FOOD AND WATER INTAKE AND SMOKING STATUS IN A THAI POPULATION RESIDING IN CADMIUM-CONTAMINATED AREAS IN MAE SOT

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Abstract. Human exposure to cadmium (Cd) produces a wide variety of toxic effects involving many organs and systems, but the kidney is the main organ affected among long-term Cd-exposed people. In the general population, the primary sources of Cd exposure are cigarette smoke and food (shellfish, offal and certain vegetables). The aims of the study were to investigate the association between urinary and blood Cd levels and personal habits relating to Cd intake (consumption of food stuff, water and tobacco smoking), levels of renal biomarkers in the urine or serum of 314 Thai subjects (85 males, 229 females) who resided in Cd-contaminated areas of Mae Sot District, Tak Province, Thailand. Based on the cut-off levels of 1 μg/g creatinine and 5 μg/l for urinary and blood Cd levels, respectively, nearly all subjects had urinary Cd levels lower than cut-off values for urine and blood (88.2 and 77.7%, respectively). Binary logistic backward stepwise regression analysis with five covariates (gender, residential areas, consumption of bamboo or chicken, and smoking status), and eight covariates (residential areas, consumption of beans, pork, fish or liver, types and sources of rice consumed and smoking status) best predicted urinary and blood Cd levels, respectively. For renal biomarkers, *N*-acetyl-β-glucosaminidase (NAG) best predicted both urinary and blood Cd with good accuracy. A larger sample size with equal distribution of subjects with low (< 2 μg/g creatinine) and high (> 2 μg/g creatinine) urinary Cd levels should be studied to obtain the regression equation that would best predict Cd body burden.

Keywords: cadmium, food intake, smoking personal habits

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INTRODUCTION

Cadmium (Cd) is an environmental pollutant which usually occurs in association with zinc ore and accumulates in water and soil as a by-product of zinc mining. Human exposure to Cd produces a wide

variety of toxic effects involving several organs and systems, but the kidney is the main organ effected in long-term Cd-exposed people (WHO, 1992; Goyer and Clarkson, 2001; Satarug *et al*, 2004; Agency for Toxic Substances and Disease Registry, 2007). At toxic levels, Cd causes nausea, abdominal pain, kidney dysfunction and osteomalacia (Simmons *et al*, 2005). In individuals with chronic exposure, Cd accumulates in the kidney and can cause tubular and glomerular dysfunction (IPCS, 1992; Jarup *et al*, 1998; Akesson *et al*, 2005). In the general population, the primary sources of Cd exposure are cigarette smoke and food intake (shellfish, offal and certain vegetables). Cd is absorbed into the body *via* enteral and pulmonary routes. Unlike organic contaminants whose toxicity decrease with biodegradation, metals cannot be degraded and their toxic effects can be long-lasting. Cd persists in the kidnies of humans for several years (half-life of 30 years), causing Cd toxicity with no additional exposure (Satarug *et al*, 2004). Urinary Cd levels reflect long-term Cd exposure or Cd body burden, while blood Cd levels reflect current Cd exposure (Lauwerys *et al*, 1994; Jarup *et al*, 1998; Choudhury *et al*, 2001).

Since individuals may be exposed to multiple sources of Cd, multivariate analysis of the different variables based on cut-off levels for Cd-induced toxicity are required to predict the relationship between the exposure to these factors and urinary or blood Cd levels. Several renal biomarkers, including β_2-microglobulin (β_2-MG), *N*-acetyl-β-glucosaminidase (NAG), microalbumin, and creatinine, have been used to predict Cd body burden and its effect on renal function. A single biomarker may not accurately predict the extent of Cd accumulation (Marczewski *et al*, 1996; Nishijo *et al*, 1999; Westhuyzen *et al*, 2003). In the present study, we evaluated the relationship between high urinary and blood Cd levels and habits relating to Cd intake (food and water consumption and tobacco smoking), and predictability of the biomarkers β_2-MG, NAG, microalbumin, and creatinine to predict urinary or blood Cd levels, using binary logistic regression analysis. The study was conducted among a Thai population residing in Mae Sot District, an area with a well established Cd-contamination in Thailand.

MATERIALS AND METHODS

Study population

The study was conducted during 2008-2009 among local residents of eleven Cd-contaminated villages in Mae Sot District, Tak Province (Mae Tao, Mae Ku and Phra That Pha Daeng Sub-districts) Thailand. These Cd-contaminated areas were previously determined based on urinary Cd levels among 7,697 inhabitants (Swaddiwudhipong *et al*, 2007). A total of 314 subjects (85 males and 229 females) aged 33 to 68 years who resided in these three areas were included in the study; 131 subjects (36 males, 95 females) from Mae Tao, 132 subjects (38 males, 94 females) from Mae Ku, and 49 subjects (11 males, 38 females) from Phra That Pha Daeng Districts. The participants were randomly recruited from cadmium-contaminated areas in Mae Sot based on a preliminary survey by a Mae Sot Hospital team during 2008-2009. All subjects were interviewed regarding personal habits relating to risk of Cd intake and health history using a questionnaire. Written informed consent was obtained from each of the participants after being informed of the study protocol, which had been approved by the Ethics Committee of the Ministry of

Public Health of Thailand.

Second morning urine samples were collected in polyethylene bottles for analysis of urinary Cd concentrations, renal toxicity biomarkers β_2-MG, NAG, microalbumin, and creatinine. The urine samples were divided into three aliquots (5 ml each). The first aliquot had nitric acid added as a preservative for the Cd analysis. The second aliquot was used to determine for creatinine and albumin levels. The third aliquot was used to determine β_2-MG and NAG levels. If the pH of the urine was ≤ 5, one drop of 0.5 N sodium hydroxide was added to increase the pH of the urine to between 6 and 8 to prevent degradation of β_2-MG. All urine samples were stored at -20°C until analysis.

After an overnight fast, 12 ml of blood was collected from each subject. Whole blood was stored for Cd analysis. Plasma was separated from packed RBC pellets through centrifugation at 2,000*g* for 15 minutes. Two aliquots of 1 ml plasma were kept for β_2-MG analysis. The serum was obtained for creatinine analysis (centrifugation at 2,000*g* for 15 minutes). The aliquots of whole blood, plasma and serum samples were stored at -20°C until analyses.

Determination of cadmium, renal dysfunction biomarkers

Cd concentrations in blood and urine were determined by an electrothermal (graphite furnace) atomic absorption spectrometer, Perkin-Elmer model 4100 ZL with a Zeeman-effect background correction system. Blood and urine controls (ClinChek™, Munich, Germany) were used for quality control and validation. Urinary NAG was determined by a colorimetric assay using a NAG test kit (Diazyme laboratories, Poway, CA). β_2-MG was measured in plasma and urine using a microparticle enzyme immunoassay (Viedma *et al*, 1992). Creatinine and albumin in serum and urine were determined using automated methods (Sylvan *et al*, 1971; Knapp and Hadid, 1987).

Statistical analysis

Statistical analysis was performed using SPSS statistical package (version 12.0). Quantitative data were presented as medians (95% CI) and percentages where appropriate. Binary logistic (forward and backward stepwise) regression analysis was initially performed with all categorical covariates obtained from the 284 subjects in order to find regression model(s) that best predicted high Cd levels in urine (>1 μg/g creatinine) and blood (>5 μg/l). These covariates included personal habits relating to risk of Cd intake (consumption of food and water and tobacco smoking) and levels of renal biomarkers in the urine or serum. In the next step, the applicability of the selected model(s) was then evaluated using data from 30 additional subjects based on the equation: $Y = \beta_1X_1 + \beta_2X_2 + \beta_3X_3..... + \text{constant}$. Y was the prediction of a high Cd level; X_1, X_2, X_3... were covariates included in the model; β_1, β_2, β_3... were slopes in the regression model when each covariate was included; and the constant was the Y-intercept of the regression line. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Of the 314 subjects (85 males, 229 females), 182 were never-smokers, 73 were smokers and 56 were ex-smokers. Median (95% CI) levels of blood and urinary Cd were 2.78 (0.40-19.50) μg/l and 0.41 (0.03-3.12) μg/g creatinine, respectively. Cd levels were classified into two levels (high and low) based on respective cut-off levels of 1 μg/g creatinine and 5 μg/l for urinary

and blood Cd levels, respectively. Two hundred seventy-seven subjects (88.2%) had urinary Cd levels lower than the cut-off value and 244 subjects (77.7%) had blood Cd levels lower than the cut-off value.

Cadmium body burden in relation to consumption of different types of food stuffs, water and smoking status

Table 1 summarizes the frequencies of subjects with high and low levels of urinary and blood Cd in relation to gender, residential areas (Phratad Phadaeng, Mae Ku and Mae Tao Districts), time of staying in the residential areas, types and sources of rice consumed, consumption of beans, rhizome vegetables, vegetables, mushrooms, meat (chicken, pork, fish, duck, beef, shellfish, shrimp, squid and crab), offal (liver and kidney), types of drinking and cooking water and smoking staus (none, current and exsmokers). High urinary Cd levels were observed at high frequencies in female subjects, current smokers, and subjects with regular consumption of vegetables, consumption of sticky rice, rice from self-planting sources, rain or river water (for cooking), duck, liver, shellfish, crab, and those who resided in Mae Tao, or stayed in certain residential areas for at least 10 years. High blood Cd levels were observed in male subjects, current smokers, and subjects with regular consumption of vegetables or bamboo, consumption of beef, liver, kidney, shellfish, fish, squid, sticky rice or rice from self-planting source, rain or river water (for cooking), and those who resided in Mae Tao, or stayed in certain residential areas for at least 10 years.

Based on binary logistic backward stepwise regression analysis, five covariates best predicted urinary Cd levels. These were gender, residential areas of exposure, consumption of bamboo or chicken and smoking status. The logistic regression relationship could be expressed as: Y (urinary Cd) = -3.540+ (-1.008*X1)+(0.981*X2)+(-0.923*X3)+ (-0.989*X4)+(0.627*X5), where X1 = gender, X2 = residential areas, X3 = consumption of bamboo, X4 = consumption of chicken and X5 = smoking status. The model predicted urinary Cd levels with 86.9% and 90.0% accuracy during model building and model evaluation, respectively.

Eight covariates predicted blood Cd levels by binary logistic backward stepwise regression analysis. These included residential areas of exposure (X1), types of rice consumed (X2), source of rice consumed (X3), consumption of beans (X4), consumption of pork (X5), consumption of fish (X6), consumption of liver (X7) and smoking status (X8). The relationship was expressed as: Y (blood Cd) = -5.167 +(0.456*X1)+(0.628*X2)+(0.501*X3)+ (-1.080.*X4)+(-0.721*X5)+(0.699*X6)+(0.8 23*X7)+(0.466*X8). The model predicted blood Cd levels with 75.3%, and 85.2% accuracy during model building and model evaluation, respectively.

Prediction of cadmium body burden by renal markers

Renal dysfunction was defined based on the cut-off values for microalbumin, NAG, β_2-MG, and serum creatinine of 30 mg/g creatinine, 8 U/g creatinine, 0.4 mg/g creatinine, and 1.1 mg/dl (Teeyakasem *et al*, 2007; Swaddiwudhipong *et al*, 2010), respectively. In most subjects these biomarkers were in the normal range. Two, 4, 9, and 27 out of 314 subjects had abnormal microalbumin, NAG, β_2-MG and serum creatinine levels, respectively. Median (95% CI) levels of serum creatinine, microalbumin, NAG and β_2-MG were 0.80 (0.50-2.30) mg/dl, 0.49 (0.06-42.73) mg/g

Table 1
Blood and urinary Cd levels among subjects by variable.

Variables	Type/classification	Urinary Cd[a]		Blood Cd[b]	
		High (*n*, %)	Low (*n*, %)	High (*n*, %)	Low (*n*, %)
(a) Relationship with gender, residential areas of exposure and time of staying					
Gender					
	Male	8, 9.4	77, 90.6	24, 28.6	60, 71.4
	Female	29, 12.7	200, 87.3	45, 19.7	184, 80.3
Residential areas					
	Phra That Pha Daeng	4, 8.2	45, 91.8	7, 14.3	42, 85.7
	Mae Ku	4, 3.0	128, 97.0	24, 18.2	108, 81.8
	Mae Tao	29, 22.1	102, 77.9	38, 29.2	92, 70.8
Length of time in a Cd-contaminated area					
	≥ 10 years	36, 11.9	266, 88.1	69, 22.9	232, 77.1
	< 10 year	0, 0	2, 100	0, 0	2, 100
(b) Relationship with types of food stuff intake					
Type of rice consumed					
	None	0, 0	2, 100	0, 0	2, 100
	Regular (plain) rice	3, 5.0	57, 95.0	2, 3.3	58, 96.7
	Sticky rice	24, 14.3	144, 85.7	47, 28.0	121, 72.0
	Both	10, 11.9	74, 88.1	20, 24.1	63, 75.9
Source of rice					
	Commercial	16, 11.7	121, 88.3	21, 15.4	115, 84.6
	Self-planting	21, 13.1	139, 86.9	46, 28.8	114, 71.3
	Both	0, 0	15, 100	2, 13.3	13, 86.7
Consumption of beans					
	None/rare	33, 13.0	221, 87.0	61, 24.1	192, 75.9
	Regular	4, 7.1	52, 92.9	8, 14.3	48, 85.7
Consumption of rhizome vegetables					
	None/rare	35, 12.0	256, 88.0	65, 22.4	225, 77.6
	Regular	2, 11.8	15, 88.2	3, 17.6	14, 82.4
Consumption of other vegetables					
	None/rare	7, 10.4	60, 89.6	12, 17.9	55, 82.1
	Regular	30, 12.3	214, 87.7	55, 22.6	188, 77.4
Consumption of bamboo					
	None/rare	26, 16.0	136, 84.0	35, 21.7	126, 78.3
	Regular	11, 7.4	138, 92.6	33, 22.1	116, 77.9
Consumption of mushrooms					
	None/rare	33, 12.2	238, 87.8	61, 22.6	209, 77.4
	Regular	4, 10.0	36, 90.0	7, 17.5	33, 82.5
Consumption of chicken					
	None/rare	33, 14.2	199, 85.8	53, 22.9	178, 77.1
	Regular	4, 5.1	74, 94.9	16, 20.5	62, 79.5
Consumption of pork					
	None/rare	14, 14.6	82, 85.4	24, 25.3	71, 74.7
	Regular	23, 10.7	192, 89.3	45, 20.9	170, 79.1
Consumption of fish					
	None/rare	16, 12.1	116, 87.9	22, 16.8	109, 83.2
	Regular	21, 11.9	155, 88.1	46, 26.1	130, 73.9
Consumption of duck					
	None/rare	36, 11.7	273, 88.3	69, 22.4	239, 77.6
	Regular	1, 33.3	2, 66.7	0, 0	3, 100

Table 1 (Continued)

Variables	Type/classification	Urinary Cd[a]		Blood Cd[b]	
		High (*n*, %)	Low (*n*, %)	High (*n*, %)	Low (*n*, %)
Consumption of beef					
	None/rare	33, 12.2	238, 87.8	58, 21.5	212, 78.5
	Regular	4, 10.0	36, 90.0	10, 25.0	30, 75.0
Consumption of liver					
	None/rare	33, 11.7	248, 88.3	56, 20.0	224, 80.0
	Regular	4, 12.1	29, 87.9	13, 39.4	20, 60.6
Consumption of kidneys					
	None/rare	36, 12.3	257, 87.7	62, 21.2	230, 78.8
	Regular	1, 5.6	17, 94.4	6, 33.3	12, 66.7
Consumption of shellfish					
	None/rare	35, 11.7	265, 88.3	66, 22.1	233, 77.9
	Regular	1, 14.3	6, 85.7	2, 28.6	5, 71.4
Consumption of fish					
	None/rare	31, 13.4	200, 86.6	51, 22.2	179, 77.8
	Regular	6, 7.6	73, 92.4	18, 22.8	61, 77.2
Consumption of shrimp					
	None/rare	35, 12.5	245, 87.5	59, 21.1	220, 78.9
	Regular	2, 6.7	28, 93.3	10, 33.3	20, 66.7
Consumption of squid					
	None/rare	36, 12.0	263, 88.0	66, 22.1	232, 77.9
	Regular	1, 9.1	10, 90.9	3, 27.3	8, 72.7
Consumption of crab					
	None/rare	35, 11.6	267, 88.4	67, 22.3	234, 77.7
	Regular	2, 25.0	6, 75.0	2, 25.0	6, 75.0
(c) Relationship with types of water					
Types of drinking water					
	Commercial water	2, 4.9	39, 95.1	5, 12.2	36, 87.8
	Rain water	31, 12.9	210, 87.1	54, 22.5	186, 77.5
	Tap water	1, 25.0	3, 75.0	2, 50.0	2, 50.0
	Well water	3, 17.6	14, 82.4	6, 35.3	11, 64.7
	Rain water + commercial water	0, 0	6, 100	1, 16.7	5, 83.3
	Rain water + well water	0, 0	4, 100	1, 25.0	3, 75.0
	Rain water + well water + commercial water	0, 0	1, 100	0, 0	1, 100
Types of cooking water					
	Commercial water	1, 6.7	14, 93.3	1, 6.7	14, 93.3
	Rain water	17, 12.3	121, 87.7	30, 21.7	108, 78.3
	Tap water	3, 3.8	77, 96.3	11, 13.8	69, 86.3
	Well water	15, 22.7	51, 77.3	23, 35.4	42, 64.6
	Rain water + commercial water	0, 0	3, 100	1, 33.3	2, 66.7
	Rain water + river water	1, 100	0, 0	1, 100	0, 0
	Rain water + well water	0, 0	4, 100	0, 0	4, 100
	Rain water + tap water	0, 0	7, 100	2, 28.6	5, 71.4
(d) Relationship with smoking status					
Smoking					
	Never smoking	15, 8.2	167, 91.8	25, 13.7	157, 86.3
	Current smoking	13, 17.8	60, 82.2	33, 45.8	39, 54.2
	Ex-smoking	9, 16.1	47, 83.9	10, 17.9	46, 82.1

[a] Cut-off = 1 µg/g creatinine; [b] Cut-off = 5 µg/l

Table 2
Urinary and blood Cd levels by renal marker among study subjects.

Renal markers	Level	Urinary Cd[a]		Blood Cd[b]	
		High (*n*, %)	Low (*n*, %)	High (*n*, %)	Low (*n*, %)
Urinary microalbumin[c]					
	Low	34, 12.9	230, 87.1	59, 22.4	204, 77.6
	High	0, 0.0	2, 100.0	1, 50.0	1, 50.0
Urinary NAG[d]					
	Low	34, 11.0	276, 89.0	67, 21.6	243, 78.4
	High	3, 75.0	1, 25.0	2, 66.7	1, 33.3
Urinary β_2-MG[e]					
	Low	34, 11.1	272, 88.9	65, 21.2	241, 78.8
	High	3, 37.5	5, 62.5	4, 57.1	3, 42.9
Serum creatinine[f]					
	Low	30, 10.5	256, 89.5	57, 19.9	229, 80.1
	High	6, 22.2	21, 77.8	12, 44.4	15, 55.6

[a] Cut-off = 1 µg/g creatinine; [b] Cut-off = 5 µg/g creatinine; [c] Cut-off = 30 mg/g; [d] Cut-off = 8 U/l; [e] Cut-off = 0.4 mg/g creatinine; [f] Cut-off = 1.1 mg/dl

creatinine, 1.00 (0-11.33) U/g creatinine, and 0.005 (0-2.16) µg/g creatinine, respectively.

Table 2 summarizes the percents of subjects with high and low levels of urinary and blood cadmium in relation to the levels of various renal biomarkers (microalbumin, NAG, β_2-MG and serum creatinine). High urinary Cd was found at high frequencies in subjects with low microalbumin, high NAG, high β_2-MG and high serum creatinine levels. Based on binary logistic stepwise backward regression analysis, NAG was the only renal biomarker which best predicted urinary Cd level with 88.3% and 90.0% accuracy during model building and model validation, respectively, with the relationship: Y (urinary Cd) = -2.013 + (23.216*NAG). High Cd levels were found in subjects with high microalbumin, NAG, β_2-MG and serum creatinine levels. NAG, β_2-MG and serum creatinine levels were the renal biomarkers which best predicted blood Cd levels with 79.2% and 79.3% accuracy during model building and model evaluation, respectively. These were NAG (X1), β_2-MG (X2) and creatinine (X3). The relationship can be expressed as: Y(urinary Cd) = -1.409+(21.767* X1)+(2.508*X2)+(0.844*X3).

DISCUSSION

The present study was conducted in eleven Cd-contaminated villages in Mae Sot District, Thailand. Blood and urinary Cd levels varied among individuals in the investigated villages. Most of the subjects had urinary Cd excretion less than the tolerable level of 2 µg/g creatinine as defined by the World Health Organization for a non-occupational exposed population (WHO Regional Office for Europe, 2002). This may explain the normal levels of renal dysfuction biomarkers observed. A study by the Department of Agriculture, Ministry of Agriculture and International

Water Management Institute during 1998-2003 reported serious Cd contamination of the soil and rice in a vicinity with a large zinc mine. With varying Cd levels in different residential areas (Simmons *et al*, 2005). Of 7,697 residents, 45.6, 4.9 and 2.3% had urinary Cd levels of < 2, 5-10 and > 10 μg/g creatinine, respectively. Cd concentrations in 69% of sediment samples of creeks passing through those areas were found to exceed the maximum permissible Cd level of 3.0 mg/kg (Unhalekhaka and Kositanont, 2008). Among 524 rice samples, Cd content ranged between 0.05 and 7.7 mg/kg, with over 95% of samples having a Cd content > 0.1 mg/kg (cut-off level for safety) (Satarug *et al*, 2000, 2004).

Results from the present study showed that gender, residential area consumption of bamboo or chicken and smoking status appear to be good predictors of urinary Cd levels (reflects long-term Cd exposure), and residential area, consumption of sticky rice, bean, pork, fish or liver, soucre of rice consumed and smoking status appeared to be good predictors of blood Cd levels (reflects short-term Cd exposure). An increase in soil Cd content generally results in an increase in plant uptake of Cd. Crops grown in Cd-contaminated areas can have Cd levels many times higher than normal, leading to Cd toxicity. Cd accumulates in the muscle tissue of fish and shellfish. The average concentration of Cd in fish species ranged from 0.03 to 0.27 mg/kg weight. The highest Cd concentration was found in the swamp eel (0.27 mg/kg), followed by pond snail, batrachians walking catfish, common climbing perch, and striped snake head fish. The average concentration of Cd found in the swamp eel exceeded the allowable contamination level by the FAO/WHO of 0.2 mg/kg (Krissanakriangkrai *et al*, 2009). A previous study in this area found smokers and people who consumed rice grown in these areas had significantly higher urinary Cd levels (Swaddiwudhipong *et al*, 2007). Both blood and urinary Cd levels were found to increase with age (Sartor *et al*, 1992; Olsson *et al*, 2002). Females were found to have Cd levels higher than males (Olsson *et al*, 2002; Satarug *et al*, 2004; Apinan *et al*, 2009). In the present study, higher urinary Cd levels were seen in females, and higher blood Cd levels were found in males. Age was not found to be associated with high urinary or blood Cd levels in this population based on the present analysis and that previously reported in the same population (Boonprasert *et al*, 2011).

Regarding biomarkers of renal function and toxicity, urinary NAG best predicted urinary Cd and urinary NAG, β_2-MG, and serum creatinine best predicted blood Cd levels. This is in agreement with a previous report that NAG alone appeared to provide a good indication of tubular toxicity from exposure. NAG excretion has been reported to be more sensitive than β_2-MG and microalbumin excretion in the detection of early renal tubular damage (Kawada, 1995; Moriguchi *et al*, 2003; Teeyakasem *et al*, 2007). Elevated urinary NAG is an early sign of renal damage and has been used to screen the general population and certain high-risk groups for the presence of early renal parenchymal damage (Noonan *et al*, 2002).

In conclusion, urinary and/or blood Cd may be used to predict Cd levels in the urine and blood following long- and short-term exposure, respectively. A limitation of the current study was the small sample size and the unbalanced number of subjects in each group (low and high Cd levels). Although all subjects had urinary Cd levels lower than 2 μg/g

creatinine, almost all of them had urinary Cd concentrations classified in the high level group based on the cut-off level of 1 µg/g creatinine. Further study with a larger sample size and equal distribution of subjects with low (< 2 µg/g creatine) and high (> 2 µg/g creatinine) urinary Cd levels should be conducted to obtain the regression equation that would best predict Cd body burden.

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