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<http://dx.doi.org/10.1289/ehp.1104769>

Online 22 February 2013



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Modeling Cadmium Exposures in Low- and High-Exposure Areas in Thailand

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Running title: Cadmium exposures and risk assessment

Key words: Cadmium; Computerized predictive model; Diet; Exposure source; Food; Health risk assessment; Smoking; Tolerable intake; Toxicokinetics-based model; Urinary threshold

Acknowledgements: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention Agency for Toxic Substances and Disease Registry. Mention of trade names is not an endorsement of any commercial product.

Competing interest: None.

Abbreviations:

ANOVA	Analysis of variance
Cd	Cadmium
CI	Confidence interval
EFSA	European Food Safety Authority
JECFA	Joint FAO/WHO Expert Committee on Food Additives
NHANES	National Health and Nutrition Examination Survey
PTWI	Provisional Tolerable Weekly Intake
SD	Standard deviation

ABSTRACT

Background: Previous U.S. population modeling studies have reported that urinary cadmium (Cd) excretion patterns differ with age, sex, and dietary exposure, and associations between Cd exposures and health outcomes also have differed by age and sex. Therefore, it is important to test models used to estimate Cd exposures across an expanded Cd exposure range.

Objectives: Estimate relative Cd exposures from both diet and smoking in low- and high-exposure scenarios to provide data for improving risk assessment calculations.

Methods: We used a Cd toxicokinetic-based model to estimate Cd exposures based on urinary Cd levels measured for 399 persons in a low-exposure (Bangkok) area and 6747 persons in a high-exposure (Mae Sot) area in Thailand.

Results: In Bangkok, we estimated dietary Cd exposures of 50–56 $\mu\text{g}/\text{day}$ for males and 21–27 $\mu\text{g}/\text{day}$ for females 20 to 59 years of age who never smoked. In Mae Sot, we estimated dietary Cd exposures of 188–224 $\mu\text{g}/\text{day}$ for males and 99–113 $\mu\text{g}/\text{day}$ for females. In Bangkok, we estimated Cd exposures from smoking of 5.5–20.4 $\mu\text{g}/\text{day}$ for male smokers 20–59 years of age. In Mae Sot, we estimated Cd exposures from smoking of 9.8–26 $\mu\text{g}/\text{day}$ for male heavy smokers and 26 $\mu\text{g}/\text{day}$ for female heavy smokers.

Conclusion: This study provides estimates of Cd exposures from diet and smoking in low- and high-exposure scenarios. Our findings suggest a relatively small safety margin between the established tolerable Cd reference exposure of 62 $\mu\text{g}/\text{day}$ and exposure levels previously associated with evidence of kidney and bone effects in Mae Sot residents, where dietary Cd exposures among women were only 1.6- to 2.1-times the reference value.

INTRODUCTION

Cadmium (Cd) is a food contaminant that poses a real human health hazard (Jarup and Akesson 2009; Satarug et al. 2010; Satarug 2012). For most people, diet is a primary exposure source (Arnich et al. 2012; Amzal et al. 2009; Louekari et al. 1989; Sand and Becker 2012). For a large portion of the general population, tobacco smoke is a secondary source (Mortensen et al. 2011). Cd from dietary and smoking exposures can accumulate in various organs and tissues, but the most extensive accumulation occurs in the kidney cortex. Urinary Cd concentrations correlate more strongly with lung and kidney Cd levels than with age or liver Cd levels (Satarug et al. 2002). In fact, researchers have used urinary Cd as a measure of cumulative lifetime exposure (Slob and Krajnc 1993; Choudhury et al. 2001). The World Health Organization (WHO 1989, 1993, 2010) and the European Food Safety Authority (EFSA 2011) consider the kidney to be the most sensitive target organ for Cd effects. Thus WHO and EFSA have established an intake guideline known as a Provisional Tolerable Weekly Intake (PTWI).

The PTWI is an estimate of the amount of the chemical with no intended function that can be ingested weekly over a lifetime without appreciable health risk (WHO 1989). The original PTWI for Cd was set at 400–500 µg per person per week (WHO 1989), but was later revised to 7 µg per kg body weight per week (WHO 1993). In its latest assessment, WHO adjusted the tolerable intake to 25 µg Cd per kg body weight per month (62 µg per day for a 70-kg person) (WHO 2010). But EFSA (2011) established a tolerable intake of 2.5 µg/kg body weight per week (25 µg per day for a 70-kg person). In addition, WHO set a urinary Cd level of 5.24µg/g creatinine as a threshold to protect against kidney damage, whereas EFSA set a urinary Cd threshold of 1µg/g

creatinine. Mortensen et al. (2011) reported that Cd exposures in the United States resulted in urinary Cd $>1\mu\text{g/g}$ creatinine in 4.8% of nonsmoking adults and 20.8% of smokers.

In an exposure-response analysis, Jarup and Akesson (2009) noted evidence of adverse effects on kidney and bone at urinary Cd below $1\mu\text{g/g}$ creatinine, raising a concern that the established thresholds might not provide sufficient protection. Further, Ciesielski et al. (2012) reported an association between Cd exposure and parental report of a learning disability in a representative sample of U.S. children enrolled in the National Health and Nutrition Examination Survey (NHANES) that persisted even when children with urinary Cd $>1\mu\text{g/g}$ creatinine were excluded from the analysis. This finding raised a further concern that effects may extend beyond kidney and bone, which other studies appeared to corroborate. Cd exposures in representative U.S. adult populations enrolled in NHANES have been reported to be associated with chronic kidney disease and kidney stones (Ferraro et al. 2010, 2011), prediabetes and diabetes (Schwartz et al. 2003), hypertension and cardiovascular disease (Tellez-Plaza et al. 2008, 2010), all-cause mortality (Menke et al. 2009), and overall cancer mortality in both men and women (Adams et al. 2012).

Rather than relying solely on a dietary assessment method known as total diet study (Arnich et al. 2012; Sand and Becker 2012), risk assessments could benefit from an ability to derive Cd exposure levels from population biomonitoring data such as urinary Cd excretion. A previous modeling study using data from NHANES III participants 2–70 years of age reported that estimated urinary excretion of Cd from dietary sources was higher in females than males, and higher in the 6–11 year age range than in older age groups (Ruiz et al. 2010b). In the present

study, we used Thai population-biomonitoring data to estimate Cd exposure from both diet and smoking as a function of age, sex, and locality. In addition, we compared established tolerable-intake and urinary threshold levels derived for average individuals with estimated intakes and urinary concentrations in population subgroups according to age, sex, and smoking status.

MATERIALS AND METHODS

Sample populations

To represent a group with chronic high-dose exposure, we assembled a sample population of over 6500 residents from 12 rural farming villages in Thailand's Mae Sot District, Tak Province. These villages are in an area where environmental Cd contamination had occurred (Swaddiwudhipong et al. 2007, 2010a). Associations of urine Cd concentrations with hypertension and markers of kidney and bone disease in Mae Sot residents have been reported previously (Honda et al. 2010; Limpatanachote et al. 2011; Swaddiwudhipong et al. 2010b; Teeyakasem et al. 2007). The Mae Sot Hospital Ethical Committee approved our study, and the informed participants verbally consented to participate. After obtaining the participants' informed consent, we also obtained information from a low-exposure group of 399 apparently healthy persons who had no exposure to Cd in the workplace and who lived in Bangkok at the time of the study (Satarug et al. 2004a). The Institutional Ethical Committee, Chulalongkorn University Hospital approved the Bangkok protocol. The Bangkok sample provided comparative information for a low-exposure group.

Exposure assessment

For the Bangkok group, urinary Cd concentrations were determined with inductively coupled plasma/mass spectrometry, calibrated with multi-element standards (EM Science, EM Industries, Inc., NJ, USA) (Satarug et al. 2004a). Quality assurance and control were conducted with simultaneous analysis of samples of the reference urine Lyphochek® (Bio-Rad, Australia), which contained low- and high-range Cd levels. A coefficient of variation value of 2.5% was obtained for Cd in the reference urine. Cd concentrations of urine samples below the 0.05µg/L-limit of detection were assigned as the LOD divided by the square root of 2. The automated system at the Chulalongkorn University Hospital, Bangkok, Thailand was used to determine urinary creatinine concentrations based on Jaffe's reaction. For the Mae Sot group, urinary Cd concentrations were determined with an atomic absorption spectrometer (Varian Model AA280Z, USA) in the Thailand Ministry of Public Health's laboratory (Swaddiwudhipong et al. 2010a). Quality assurance and control were conducted with reference urine certified by the German External Quality Assessment Scheme. Urinary creatinine concentrations based on Jaffe's reaction were determined using an auto-analyzer (Konelab 30, Thermo Electron Corp. Finland).

Computerized simulation model of Cd toxicokinetics

The computerized predictive model used in this study is available in the Agency for Toxic Substances and Disease Registry's (ATSDR) Computational Toxicology Laboratory, Physiologically Based Pharmacokinetic (PBPK) toolkit (Ruiz et al. 2010a, b, 2011). The predictive model consists of a series of models recoded in one simulation language: Berkeley-

Madonna software (version 8.01 for Windows, Kagi Shareware, Berkeley, CA) (Ruiz et al. 2010a, b, 2011). The model was based on the Kjellstrom and Nordberg (1978) Cd toxicokinetics model that Choudhury et al. (2001) and Diamond et al. (2003) later modified. The model was validated with data from the Fourth National Report on Human Exposure to Environmental Chemicals as detailed elsewhere by Ruiz et al. (2010a). Briefly, we calculated the percent median absolute performance error (MAPE%) based on estimates of performance error (PE), used root median-square performance error to estimate the prediction's accuracy (RMSPE%), and used a sensitivity ratio (SR) approach to assess the robustness of each recoded model (Ruiz et al. 2010a). The model's ability to simulate urinary Cd measured for nonsmoking populations in NHANES III, using U.S. dietary Cd exposures as the input dataset, has been reported together with complete details on the model structures and parameters (Ruiz et al. 2010b).

Estimates of dietary Cd exposures

For oral route exposure, our initial model input was the amount of dietary Cd ingested per day ($\mu\text{g}/\text{day}$) estimated for age- and sex-specific groups as reported by Choudhury et al. (2001). We iteratively increased the estimated dietary intakes until geometric creatinine-adjusted urinary Cd values ($\mu\text{g}/\text{g}$ creatinine) predicted by the model replicated as closely as possible the geometric mean urinary Cd values measured in Bangkok and Mae Sot study participants who never smoked. In this way we obtained the dietary Cd exposure estimates for the age and sex-specific groups in both Bangkok and in Mae Sot.

Estimates of Cd exposures from smoking

Based on tobacco Cd content data reported for various Asian cigarette brands (O'Connor et al. 2010), we assumed that for every pack of cigarettes, Bangkok smokers inhaled 5.5 μ g of Cd. We assumed Mae Sot smokers inhaled 6.5 μ g Cd per pack of cigarettes, given the potential increase in pulmonary absorption due to anemia (Swaddiwudhipong et al. 2007) which can promote cadmium uptake (Satarug et al. 2002; Satarug et al. 2004b). To estimate overall Cd exposure (i.e., oral plus inhalation) for smokers, we used the model-based age-, sex-, and population-specific estimates of geometric mean dietary Cd exposure derived for those who never smoked, and the number of packs smoked per day reported by participants, as the initial model input for each group of smokers. We then obtained model-based estimates of the number of packs of cigarettes smoked per day by iteratively increasing the number of packs smoked until the geometric mean urinary Cd values predicted by the model replicated geometric mean urinary Cd values measured in the smokers. To estimate Cd exposure from smoking, we multiplied number of packs smoked per day by 5.5 μ g and 6.5 μ g for smokers in Bangkok and Mae Sot, respectively.

Statistical analysis

Statistical analysis was performed with the SPSS statistical package. The Kolmogorov–Smirnov goodness-of-fit test was used to evaluate conformity to normal distributions of measured and base-10 logarithmically transformed data. Differences between the Bangkok and Mae Sot populations were evaluated using the student's "t" test for normally-distributed variables, and the Mann-Whitney test for variables that did not conform to a normal distribution. Differences in logarithmically transformed urinary Cd among three groups or more (e.g., when stratified by age

and smoking habits) were estimated using one-way analysis of variance, followed by the Dunnett post-hoc test. Results were considered statistically significant if $p \leq 0.05$.

RESULTS

Subjects from Bangkok were, on average, in their early to mid-30s, whereas the Mae Sot subjects were in their mid-40s (Table 1). The prevalence of smoking was high in Mae Sot compared with Bangkok, and in males compared with females. About 70% of Mae Sot males smoked, and > 40% were classified as heavy smokers (26–80 cigarettes per day). In Bangkok, about 40% of males smoked, and none were classified as heavy smokers. Bangkok had no female smokers, but 4.4% and 11% of Mae Sot females were light-moderate and heavy smokers, respectively.

As expected, there were pronounced differences in measured urinary Cd between the two communities. Geometric mean values were 0.40 $\mu\text{g/g}$ and 1.65 $\mu\text{g/g}$ creatinine in Bangkok and Mae Sot males, respectively, and 0.50 $\mu\text{g/g}$ and 2.10 $\mu\text{g/g}$ creatinine in Bangkok and Mae Sot females, with significantly higher mean values in females compared with males in both communities (both $p < 0.001$). Among never smokers, 22.5% and 5.9% of females and males in Bangkok, and 76% and 58% in Mae Sot, respectively, had measured urinary Cd $\geq 1\mu\text{g/g}$ creatinine. In Mae Sot, 12% and 4.9% of females and males who never smoked had urinary Cd $\geq 5\mu\text{g/g}$ creatinine, compared with 26.5% and 10.4% of females and males who were current or former smokers.

Measured geometric mean urinary Cd values are shown according to age, sex, smoking status, and location in Table 2. Overall, measured urinary Cd values increased with age, and were

higher in females than males, and in smokers compared with non-smokers. In the Bangkok group, the geometric mean (GM) values for urinary Cd in male smokers in 20–39-year (0.41 $\mu\text{g/g}$ creatinine) and the 40–59-year (0.92 $\mu\text{g/g}$ creatinine) age groups were, respectively, 1.3 times and 1.9 times greater than in males in the same age groups who never smoked (0.33 and 0.49 $\mu\text{g/g}$ creatinine). Similarly, in Mae Sot, the measured urinary Cd for heavy smokers who were 40–59 years of age and those ≥ 60 years were 1.4 times and 1.5 times greater than males in the same age groups who never smoked. The urinary Cd for female heavy smokers in the 40–59-year and ≥ 60 -year groups was 1.6 times and 1.3 times greater than for females in the same age groups who never smoked. In Mae Sot, measured urinary Cd values in older males and females who were heavy smokers were significantly higher ($p > 0.001$ – < 0.002) than in corresponding male and female never smokers.

Age- and sex-specific model-based estimates of dietary Cd exposure among never smokers in Bangkok and Mae Sot are shown in Table 3. In Bangkok, dietary Cd exposures of 56 and 50 $\mu\text{g/day}$ were estimated for males in the 20–39-year and 40–59-year groups, respectively, who never smoked. Dietary Cd exposures of 27 and 21 $\mu\text{g/day}$ were estimated for the 20–39 and 40–59-year females, respectively, who never smoked. Much higher dietary Cd exposures were estimated for all age-, sex-specific groups in Mae Sot compared with their counterpart groups in Bangkok. For Mae Sot, estimates of dietary Cd exposures were 234, 224, 188, and 167 $\mu\text{g/day}$, respectively, for males who never smoked, aged 13–19, 20–39, 40–59, and ≥ 60 years. The corresponding dietary Cd exposures, estimated for females who never smoked, were 132, 113, 99, and 118 $\mu\text{g/day}$, respectively.

Model-based estimates of numbers of packs of cigarettes smoked per day according to age-, sex-, and location among smokers are shown in Table 4. Estimates for current, light-to-moderate male smokers in Bangkok were 1 and 3.7 packs/day for 20–39 and 40–59-year age groups, respectively, resulting in Cd exposure estimates of 5.5 and 20.4 $\mu\text{g}/\text{day}$. For male heavy smokers in Mae Sot, estimates were 1.5, 1.5, 3, and 4 packs/day for 13–19, 20–39, 40–59, and ≥ 60 -year age groups, respectively, resulting in estimated Cd exposures of 9.8, 9.8, 19.5, and 26 $\mu\text{g}/\text{day}$, respectively. For female heavy smokers in Mae Sot, the estimated smoking rate was 4 packs/day for all age groups, resulting in estimated Cd exposures of 26 $\mu\text{g}/\text{day}$.

DISCUSSION

Exposure levels and exposure sources

Among subjects in this study, age, sex, smoking, and locality were sources of urinary Cd variability. A comparison of observed urinary Cd data from males and females who never smoked in the 20–39 and 40–59-year age groups in Mae Sot with respective counterparts in Bangkok indicated overall Cd exposure levels in Mae Sot to be 3- to 3.8-times greater than in Bangkok. Evidence supporting diet as a major source of high Cd exposures in Mae Sot comes from a previous report indicating that Cd levels in most staple food (rice) samples from Mae Sot were above the permissible limit of 0.2 mg/kg (Swaddiwudhipong et al. 2007). In another report, Cd content in 524 rice samples was 0.05–7.7 mg/kg, with over 90% of samples $> 0.2\text{mg}/\text{kg}$ (Simmons et al. 2005). Further, urinary Cd levels were higher among those who consumed locally grown rice compared with those who consumed rice purchased from other areas (Swaddiwudhipong et al. 2007). Urinary Cd levels were also higher in Mae Sot residents who

regularly consumed water from local wells compared with those who did not (Honda et al. 2010). Vegetables and other food crops grown locally in Mae Sot could also be a source of Cd exposure, as was the case of soybeans, all of which samples contained Cd above 0.2mg/kg (Swaddiwudhipong et al. 2007).

Exposure from diet

In this study, estimated dietary Cd exposures were greater in men than in women in both communities. This may be at least partly due to higher food intake in men, as the Cd-toxicokinetics model used to estimate intakes assume that daily Cd exposures increase with caloric intake (Kjellström and Nordberg 1978). Estimated dietary intakes of Cd for all age groups based on 3-day food records were higher in men than women in a previous study of 1348 persons in Finland (13–17µg/day compared with 12–13µg/day) (Louekari et al. 1989) and were higher for men than women according to model-based predictions for U.S. populations (15–22.4µg/day compared with 13.5–16.5µg/day) (Ruiz et al. 2010b). In contrast, Sand and Becker (2012) observed no sex differences in dietary Cd intakes based on 7-day food records from a survey of >1,200 adults in Sweden, and reported that dietary Cd exposure for an average 70-kg consumer was 10µg/day, with 40–50% of dietary Cd coming from staple foods (potatoes and wheat), whereas for high consumers (dietary Cd exposure above 95th percentile) estimated dietary exposure was 22µg/day, with additional Cd coming from seafood and spinach. Tellez-Plaza et al. (2012) reported a decrease in mean values of urinary Cd in the United States from 1988–2008 that may have resulted from reductions in smoking exposure. This suggests diet remains the main Cd exposure source in the U.S. population; that Cd in human urine samples

originates from diet and smoking is well-established (Satarug 2012). Arnich et al. (2012) reported that Cd measured in prepared food samples representing the diet of the French population were higher in total diet samples collected in 2007–2009 compared with 2000–2004.

In the present study, estimated dietary Cd exposures for the Bangkok population were 21 to 27 $\mu\text{g}/\text{day}$ and 50 to 56 $\mu\text{g}/\text{day}$ for 20–59-year women and men, respectively (Table 3). The female dietary Cd exposure data were consistent with GM values of 24.7 μg and 35.7 μg per day based on Cd measured in duplicate diet samples from Japanese women (Ikeda et al. 2000; Shimbo et al. 2000). Reeves and Vanderpool (1997) estimated a daily intake of 36 μg of Cd among frequent consumers of sunflower kernels based on Cd measured in duplicate food samples. Based on telephone interviews, Copes et al. (2008) estimated Cd exposure from oysters among oyster growers on to be 24.8 $\mu\text{g}/\text{day}$. Vahter et al. (1996) analyzed Cd content of duplicate diets collected in four consecutive days and they reported dietary Cd exposure to be 11 $\mu\text{g}/\text{day}$ for Swedish women consuming a mixed diet and 28 $\mu\text{g}/\text{day}$ for those consuming diet high in shellfish. Based on Cd content of duplicate diets and dietary records, Berglund et al. (1994) reported the average dietary Cd exposure ranging from 5 to 38 $\mu\text{g}/\text{day}$ among 57 nonobese, 20–50 year Swedish women.

By comparison, for men and women age 20–59 years in the Mae Sot group, estimated dietary Cd exposures were 188 to 224 $\mu\text{g}/\text{day}$ and 99 to 113 $\mu\text{g}/\text{day}$, respectively (Table 3), consistent with an estimate of > 200 $\mu\text{g}/\text{day}$ for dietary exposure in a Japanese population living in a Cd-contaminated area (Iwata et al. 1993).

Our model may have overestimated dietary Cd exposure because it did not account for water as an additional exposure source. In addition, model estimates do not reflect potential variation in Cd accumulation and urinary excretion (Slob and Krajnc 1993) related to exposure variability, age-related kidney degeneration, changes in exposure over time due to lifestyle changes, and the influence of iron, calcium, and zinc intakes on Cd absorption and excretion. However, Amzal et al. (2009) showed that model performed well when daily exposure is relatively constant because staple foods are the main exposure source. Satarug et al. (2004) reported that urinary Cd concentrations were 3-4 times higher among women who had low iron stores compared with similar-age women whose iron stores were normal. Kippler et al. (2007) reported higher urinary Cd in women who had low iron stores but adequate zinc status compared with women who had both low iron and zinc status. Julin et al. (2011) reported that a model performed well when age, body weight, and body iron store status were incorporated.

Exposure from smoking

We estimated that in Bangkok, male smokers age 20–39 and 40–59 years smoked 1 and 3.7 packs/day, respectively, resulting in estimated Cd exposures of 5.5 and 20.4 μ g/day, assuming an inhaled Cd dose of 5.5 μ g/pack. However, average smoking rates reported by Bangkok males age 20–39 and 40–59 years were only 0.42 and 0.7 packs/day, respectively. Based on the model's assumption of inhaled Cd at 6.5 μ g/pack, estimates of smoking rates in Mae Sot males of 1.5 to 4 packs/day were comparable to the numbers of packs per day reported by the study participants (2-4 packs). Differences between model-based estimates and estimates based on self-reported smoking could include underreporting of smoking, inhalation of Cd in air (e.g., from passive

smoking), and variability in tobacco Cd levels. Pappas et al. (2007) reported that Cd in mainstream smoke varied from 0.02 to 0.35 $\mu\text{g}/\text{cigarette}$, while O'Connor et al. (2010) reported that Cd ranged from 1 to 2.7 $\mu\text{g}/\text{cigarette}$ in Chinese cigarette brands—3 times higher than Canadian brands. In addition, it has been estimated that 2.7 $\mu\text{g}/\text{day}$ Cd could be inhaled from ambient air if 75% of the population smoked an average of 24 cigarettes/day (Kjellström and Nordberg 1978).

It is important to note that Bangkok smokers were light-to-moderate smokers with lower dietary background exposures, in contrast with Mae Sot smokers, most of whom were heavy smokers with high background exposures. Background exposures alone can cause kidney damage and loss of renal proximal epithelial cells, resulting in high urinary Cd. Further, nicotine can also cause of kidney damage among smokers (Hallan and Orth 2011; Jaimes et al. 2007). The current model does not account for nicotine-induced kidney damage.

Implications for risk assessment of dietary Cd exposure

Risk assessments have established tolerable intake and urinary threshold levels to protect against kidney damage. WHO (2010) set the tolerable intake at 62 $\mu\text{g}/\text{day}$ for a 70-kg person, and the urinary threshold at 5.24 $\mu\text{g}/\text{g}$ creatinine. EFSA (2011) set its tolerable intake at 25 $\mu\text{g}/\text{day}$ for a 70-kg person, and the urinary threshold at 1 $\mu\text{g}/\text{g}$ creatinine. Our model-based estimates of dietary Cd for Bangkok never smokers aged 20–39 and 40–60 years were 27 and 21 $\mu\text{g}/\text{day}$ for females, and 56 and 50 $\mu\text{g}/\text{day}$ for males, respectively. These dietary Cd exposure estimates were within the WHO-established tolerable intakes, but Cd exposures for never smokers in Mae Sot (132, 113, 99, and 118 $\mu\text{g}/\text{day}$ for females and 234, 224, 188, and 167 $\mu\text{g}/\text{day}$ for males) all were above

the reference tolerable intake levels. In Mae Sot, the dietary Cd exposures in women who never smoked were 1.6-to 2.1-times greater than the WHO tolerable intake, while the exposures among male counterparts were 2.7-to 3.8-times greater.

These estimates suggest relatively small differences between the WHO tolerable intake level and exposure levels that have been associated with evidence of adverse effects on kidney and bone in cross-sectional studies of Mae Sot residents (Honda et al. 2010; Limpatanachote et al.

2011; Swaddiwudhipong et al. 2010b; Teeyakasem et al. 2007). In addition, we estimated that dietary Cd exposures $\geq 62\mu\text{g}/\text{day}$ (the WHO tolerable intake level) were associated with urine Cd concentrations of $0.70\text{--}1.85\mu\text{g}/\text{g}$ creatinine in men and $0.95\text{--}3.07\mu\text{g}/\text{g}$ creatinine in women, which are substantially lower than the WHO urinary threshold of $5.24\mu\text{g}/\text{g}$ creatinine. Therefore, we conclude that to provide adequate protection, urinary Cd threshold should be $< 1\mu\text{g}/\text{g}$ creatinine and dietary exposure should be $< 62\mu\text{g}/\text{day}$. In Bangkok, dietary Cd intakes were associated with urinary Cd $\geq 1\mu\text{g}/\text{g}$ creatinine in 22.5% of women who never smoked. NHANES data suggest that 4.8% of nonsmokers and 20.8% of smokers in the United States have urinary Cd $\geq 1\mu\text{g}/\text{g}$ creatinine, though the population mean was estimated to be $< 0.5\mu\text{g}/\text{g}$ creatinine (Mortensen et al. 2010; Tellez-Plaza et al. 2012).

Strengths and Limitations

The main strengths of this study include the large population samples of men and women with moderate to high urinary Cd levels, a wide age range (13–92 years), and homogeneous exposure sources (i.e., none were occupationally exposed). Urinary Cd levels, which are a marker of cumulative lifetime Cd exposure, increased steadily with age in both males and females,

reaching a plateau in 60 years or older groups (data not shown). We know of no other studies in any Cd-contaminated areas that cover both men and women in such large numbers and with as wide an age range.

A limitation of the model-based transformation of data on internal dose (urinary Cd concentrations) to external dose levels (intake via diet and smoking) is that the model parameters (body weight, organ weight, and average consumption of different foods) are based on characteristics of an average consumer, and thus does not account for at-risk subpopulations such as females and smokers. A lack of data on Cd in ambient air was also a limitation, although a previous estimate of Cd exposure from passive smoking ($2.7\mu\text{g}/\text{day}$ where 75% of population smoked on an average 24 cigarettes/day) (Kjellström and Nordberg 1978) was substantially lower than our estimates of dietary Cd exposure. Limited smoking data in some groups was a further limitation, as was the assumption that smokers had the same dietary Cd exposures as those who never smoked.

CONCLUSIONS

Our computerized simulation model could be useful in health risk assessments, as it enables the use of measured urinary Cd data to estimate Cd exposures from diet and smoking according to age and sex. For example, we estimated that Cd exposure from dietary sources in Mae Sot females who never smoked was 1.6-to 2.1-times greater than the WHO tolerable intake guideline. This suggests that there may be a relatively small safety margin between the reference level and exposure levels previously associated with adverse health effects in cross-sectional studies of Mae Sot residents. The safety margin may be even lower in smokers, whose Cd

exposures were approximately 1.3- to 1.9-times higher than in never smokers. Smoking exposures thus should to be included in overall risk assessment calculations. Data from the present study also may be relevant in developing risk assessment approaches to improve the protection of subpopulations at particular risk by determining daily tolerable exposures based on both sex and smoking status.

The model on which the WHO PTWI was based did not include an uncertainty factor (WHO 1993) to account for smoking or other non-dietary routes of exposure, or for factors such as age and sex. Our findings suggest the need for a tolerable intake estimate that includes an uncertainty factor of 10 or larger to protect against kidney damage in over 95% of the population, including female smokers, a subpopulation that may be at especially high risk.

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Table 1. Characteristics of Bangkok and Mae Sot groups

Variables	Bangkok		Mae Sot	
	Males	Females	Males	Females
Number of persons	199	200	3021	3726
Age (years)				
Mean \pm SD	32.9 \pm 8.8	36.9 \pm 10*	47.7 \pm 16.6	46.4 \pm 15.2*
Smoking habits				
Never smokers	59.3%	100%	27.2%	77.2%
Former smokers	0	0	20.9%	7.4%
Current smokers				
Light to moderate	40.7%	0	9.2%	4.4%
Heavy	0	0	42.7%	11.0%
Urinary Cd ($\mu\text{g/g}$ creatinine)				
Geometric Mean \pm SD	0.40 \pm 0.46	0.50 \pm 0.46*	1.65 \pm 2.40	2.10 \pm 2.91*
Urinary Cd $\geq 1\mu\text{g/g}$ creatinine				
Never smokers	5.9%	22.5%	58.0%	76.0%
Former and current smokers	13.6%	0	77.2%	94.9%
Urinary Cd $\geq 5\mu\text{g/g}$ creatinine				
Never smokers	0	0	4.9%	12%
Former and current smokers	0	0	10.4%	26.5%

Light to moderate smokers = 10-25 cigarettes/day.

Heavy smokers = 26-80 cigarettes/day.

* $p \leq 0.001$ for differences between males and females in each population.

Table 2. Measured urinary Cd ($\mu\text{g/g}$ creatinine) by age, sex, smoking status, and locality.

Cigarette smoking Status	Bangkok						Mae Sot							
	Males		Females		Males		Females		Males		Females			
	13-19y	20-39y	40-59y	13-19y	20-39y	40-59y	13-19y	20-39y	40-59y	$\geq 60y$	13-19y	20-39y	40-59y	$\geq 60y$
Never smokers	0.30 [0.10]	0.33 [0.36]	0.49 [0.38]	0.35 [0.22]	0.48 [0.43]	0.54 [0.51]	0.70 [0.84]	1.04 [1.61]	1.50 [1.98]	1.85 [2.47]	0.95 [1.36]	1.49 [2.26]	2.08 [2.82]	3.07 [3.79]
Smokers														
Former smokers	–	–	–	–	–	–	0.45 [0.46]	0.99 [1.54]	1.78 [3.11]	2.45 [3.04]	1.93 [0.36]	1.74 [1.24]	2.89 [2.78]	3.70 [3.09]
Current														
Light/moderate Smokers	0.28 [0.32]	0.41 [0.41]	0.92 [0.93]	–	–	–	0.72 [0.54]	1.00 [1.15]	2.07 [1.78]	2.55 [2.53]	–	2.10 [1.48]	2.75 [2.26]	3.13 [3.73]
Heavy smokers	–	–	–	–	–	–	0.79 [0.61]	1.17 [1.51]	2.12* [2.54]	2.84* [4.46]	0.73 [0.08]	1.91 [1.59]	3.41** [2.66]	3.92** [3.46]

Numbers are geometric mean [SD] values for measured urinary Cd. – = <5 subjects

Light to moderate smokers = 10-25 cigarettes/day.

Heavy smokers = 26-80 cigarettes/day.

* $P < 0.001$ for differences between heavy smokers and never smokers of the same sex, age, and location.

** $P > 0.001$ – < 0.002 for differences between heavy smokers and never smokers of the same sex, age, and location.

Table 3. Estimates of dietary Cd exposures from toxicokinetic model for those who never smoked by sex, age and locality.

Age group (years)	No.	Bangkok				Mae Sot			
		Males	Females	Males	Females	Males	Females	Males	Females
		Diet Cd (µg/day)	No.						
13-19	–	–	–	–	152	234	221	132	
20-39	85	56	117	27	191	224	903	113	
40-59	31	50	81	21	327	188	1394	99	
≥60	–	–	–	–	151	167	358	118	

– = Not included because <5 subjects.

Table 4. Estimates of number of packs of cigarettes smoked per day from the toxicokinetic model for current smokers by sex, age and locality.

Age group (years)	Bangkok				Mae Sot			
	Males		Females		Males		Females	
	No.	Packs/day	No.	Packs/day	No.	Packs/day	No.	Packs/day
13-19	–	–	–	–	55	1.5	–	–
20-39	65	1	–	–	296	1.5	38	4
40-59	12	3.7	–	–	663	3	207	4
≥60	–	–	–	–	277	4	162	4

–= Not included because <5 subjects.

For Bangkok, smoking was estimated for current light-moderate smokers only.

For Mae Sot, smoking was estimated for current heavy smokers only.