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Assessing human exposure risk to cadmium through inhalation and seafood consumption

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HIGHLIGHTS

- Trophically available fraction in seafood and bioaccessibility is linked.
- Human health risk to Cd can *via* inhalation and seafood consumption.
- Female had the higher Cd accumulation in urine and blood than male.
- Cigarette smoking is a major determinant of human Cd intake.

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ABSTRACT

The role of cadmium (Cd) bioaccessibility in risk assessment is less well studied. The aim of this study was to assess human health risk to Cd through inhalation and seafood consumption by incorporating bioaccessibility. The relationships between trophically available Cd and bioaccessibility were constructed based on available experimental data. We estimated Cd concentrations in human urine and blood *via* daily intake from seafood consumption and inhalation based on a physiologically-based pharmacokinetic (PBPK) model. A Hill-based dose–response model was used to assess human renal dysfunction and peripheral arterial disease risks for long-term Cd exposure. Here we showed that fish had higher bioaccessibility (~83.7%) than that of shellfish (~73.2%) for human ingestion. Our results indicated that glomerular and tubular damage among different genders and smokers ranged from 18.03 to 18.18%. Our analysis showed that nonsmokers had 50% probability of peripheral arterial disease level exceeding from 3.28 to 8.80%. Smoking populations had 2–3 folds higher morbidity risk of peripheral arterial disease than those of nonsmokers. Our study concluded that the adverse effects of Cd exposure are exacerbated when high seafood consumption coincides with cigarette smoking. Our work provides a framework that could more accurately address risk dose dependency of Cd hazard.

1. Introduction

Cadmium (Cd) is widely released from industrial, mineral mining, agriculture, and hazardous waste sites [1]. Inhalation of cigarette smoke is one of the major routes for human exposed to Cd. Previous studies indicated that smokers have approximately twice the Cd accumulation of nonsmokers [2,3]. Moreover, consumption of seafood is also one of the dominant routes for human exposed to Cd [4–7]. Seafood can accumulate Cd *via* waterborne and dietborne exposure pathways, posing a potential human health risk [8–10].

In 1992, World Health Organization (WHO) refined the provisional tolerable weekly intake for Cd at 7 $\mu g\ week^{-1}\ kg^{-1}$ body weight, which was based on the effect of renal damage [11]. Besides, the European Food Safety Authority [12] used the benchmark dose derived urinary Cd threshold to strictly estimate the tolerable weekly intake of 2.5 $\mu g\ kg^{-1}$ body weight.

Numerous studies have revealed that the adverse effects on human kidney and bone were related to the environmental Cd exposures [13–17]. Moreover, epidemiological studies also evidenced that Cd exposure was associated with the chronic diseases, such as diabetes, diabetic nephropathy, hypertension, and peripheral artery disease [18–21]. Measuring Cd concentrations in urine and blood are the general and direct method for monitoring the level of Cd exposure [22]. Kidney is the major organ for accumulating Cd that can be eliminated from organisms through urine [23]. Cd can also be absorbed into bloodstream from lung and gastrointestinal tract and binds to blood cell [24].

The bioaccessibility from food to human indicates the portion of total chemical with food digested into solution and is potentially to be assimilated to reach systemic circulation by the alimentary canal

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[25–27]. On the other hand, the bioavailability accounts for the portion that is assimilated by alimentary canal to reach the systemic circulation [25–27]. Bioavailability data must be measured in the blood or target organs with an *in vivo* animal experiment. Generally, bioaccessibility of chemical in food is quantified by an *in vitro* digestion model that simulates based on the gastrointestinal parameters of human [25,28,29]. *In vitro* digestion model is rapid, low-cost, and easy to control in comparison with *in vivo* experiment. In the past decades, human health risk assessment was mostly based on the total Cd intake. However, the bioaccessibility may provide another excellent provision of data in enhancing human health risk assessment [30].

Recent studies on subcellular metal compartmentalization in aquatic organisms have led to conclusions regarding the significance of subcellular fates of metals to potential biological consequences of accumulated metals [31–34]. The fractions of metal can bind to cellular cytosolic and organelles fractions are available for trophic transfer [35,36]. Wallace and Luoma [36] combined heat labile proteins, organelles, and metallothionein-like proteins into a pool, designating as the trophically available metal (TAM). Wallace and Luoma [36] pointed out that different subcellular distributions may lead to different bioaccessibilities in organisms. Yet, the relationship between subcellular partitioning and the bioaccessibility was also less well studied.

Physiologically based pharmacokinetic (PBPK) model has been applied to predict the chemical doses of target organs during the decades [37,38]. Nordberg and Kjellström [39] have developed an eight-compartment kinetic model for predicting human Cd exposure. In this study, we modified that well-established PBPK model to estimate the Cd distributions through both inhalation and seafood consumption exposures [39,40].

Therefore, the purpose of this study was threefold: (i) to construct the relationship between trophically available fraction of Cd in seafood and the Cd bioaccessibility in human; (ii) to use a PBPK model to estimate organ-specific Cd levels in smoking and nonsmoking subgroups; and (iii) to perform a quantitative risk assessment for human health exposed to Cd from inhalation and seafood consumption based on the PBPK-estimated organ-specific Cd burdens incorporating with data on exposure, toxicokinetics and organ toxicity.

2. Materials and methods

2.1. Study data

To estimate the Cd intake from seafood consumption for Taiwanese, we collected the popular seafood in the indigenous markets and adopted the fishery production information from Taiwan Fisheries Administration in 2008 (http://www.fa.gov.tw/userfiles/oldfa//chnn/statistics_publish/statistics/year_book/2008c/97tab08-3.pdf). Seafood products were divided into three groups of freshwater fish, marine fish, and shellfish based on the market shares (Table S1 in Supplementary Materials).

A blanket search was conducted to collect recent publications that focused on Cd accumulations of seafood in Taiwan in the period 1998–2006. The lognormal distribution was used to best fit the accumulation data. Estimates of Cd daily intake *via* seafood consumption were calculated by multiplying species-specific market shares, daily seafood consumption, and Cd concentrations in seafood (Table S1 in Supplementary Materials). Human exposed to Cd *via* inhalation was estimated based on air Cd concentration of 0.004 $\mu g\,m^{-3}$ [41], together with the inhalation rates of 15.3 and 11.3 $m^3\,d^{-1}$ for male and female, respectively [42]. For smoking group, we estimated 1–2 μg Cd per cigarette corresponding to nearly 10% of the Cd content inhaled when the cigarette is smoked [43]. The average smoked cigarettes rates were 13.6 and 8.7 per day for male and female, respectively [44].

To determine the relationship between trophically available Cd in seafood and bioaccessibility to human, a valuable dataset provided by Rainbow et al. [45] and He et al. [27] were used. Rainbow et al. [45] and He et al. [27] conducted the subcellular partitioning experiments to identify the TAM fraction of metal accumulated in seafood and used an *in vitro* digestion method to identify the bioaccessibility of metals. Detailed description of study data is provided in Supplementary Materials.

2.2. PBPK model

The present PBPK model is based on the report by Nordberg and Kjellström (Fig. 1A) [39]. Detailed description of PBPK model is given in (Supplementary Materials). The proposed simulation scheme was based on 1 day interval with the exposure duration of 45 years. The simulated cumulative loads of Cd in urine and blood were calculated by dividing the volumes of urine and blood by 1.4 and 5.18 $L\,d^{-1}$ for male, whereas 1.0 and 4.33 $L\,d^{-1}$ for female, respectively [46].

Validation of PBPK model of Cd was supported by a reasonable agreement between model predictions and data [39,40] for the concentration–time profiles of Cd in a variety of compartments. To compare modeled and observed results, the best fit was

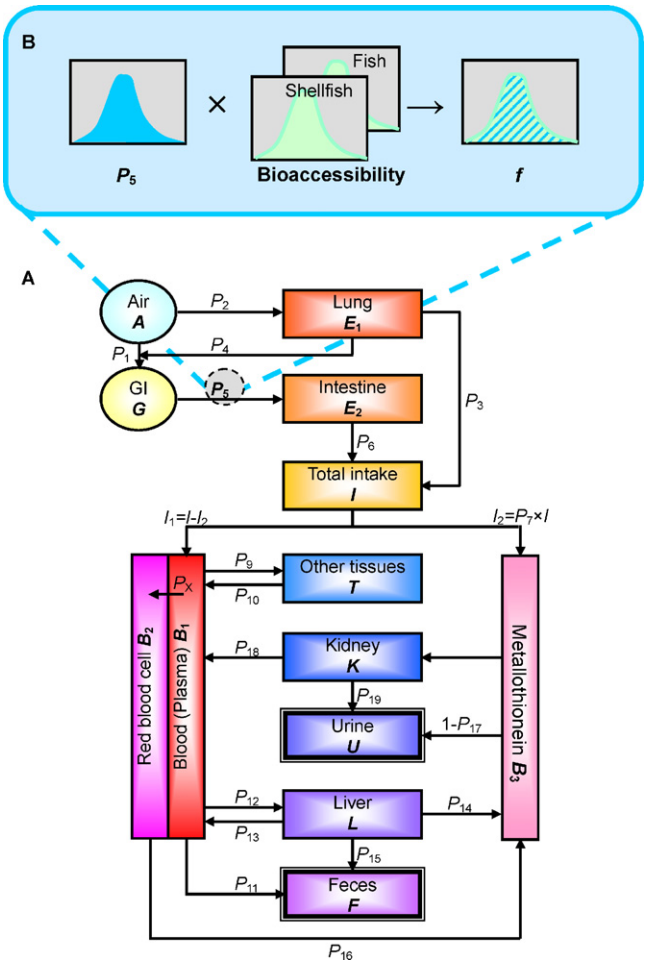

Fig. 1. Schematic of the proposed bioaccessibility-based PBPK model for Cd exposure. (A) Physiological parameter P_5 multiplied by estimated bioaccessibility of fish and shellfish to obtain the bioaccessibility-based parameter *f*. (B) Cd is adsorbed by lung and intestine to tissue compartments of other tissues, kidney, and liver, interconnected by bloodflow, and eliminated by urine and feces.

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evaluated using root-mean-squared-error (RMSE), calculated from $\mathrm{RMSE} = \sqrt{\sum_{n=1}^{N}(C_{m,n} - C_{s,n})^2/N}$ where N denotes the number of measurements, $C_{m,n}$ is the measurement data, and $C_{s,n}$ is the simulation result corresponding to data point n.

To incorporate the concept of bioaccessibility and the individual differences, we performed the Monte Carlo simulation with 10,000 iterations to generate the likely values of bioaccessibility of the 2.5th, 25th, 50th, 75th, and 97.5th percentiles. The generated bioaccessibility values then multiply by the fraction (P_5) that is absorbed to gastrointestinal tract and systemic circulation, to estimate seafood bioaccessibility for obtaining the bioaccessibility-based parameter used in the PBPK modeling scheme (Fig. 1B). We employed five bioaccessibility-based parameters (fs) to simulate a variety of Cd loads in urine and blood (Fig. 1).

2.3. Dose–response analysis

To investigate the relationships between Cd bioaccumulation in urine/blood and Cd-induced damages, the available published data were reanalyzed. Jin et al. [13] performed a study on a general population in China to construct the dose–response relationship between Cd exposure and renal dysfunction.

Briefly, Jin et al. [13] collected urine and blood samples from 5 male and 5 female in a control area and two Cd polluted areas. Jin et al. [13] used the urinary and blood Cd concentrations as the bioindicators of Cd exposure and used concentrations of β_2-microglobulin, retinol binding protein, and albumin to determine the degree of renal dysfunction. The population lived in the polluted areas had significant higher urinary and blood Cd concentrations than those lived in the control area. The relative higher prevalence rate of renal dysfunction was also found in the polluted areas.

On the other hand, Tellez-Plaza et al. [21] studied gender differences in the cross-sectional association of blood and urinary Cd concentrations with peripheral arterial disease by analyzing the data in the period 1999–2004 based on U.S. National Health and Nutrition Examination Survey. They found that the peripheral arterial disease prevalence (PADP) increased with increasing blood Cd levels for male, whereas among the female, Cd levels showed a U-shaped relation with PADP.

We reanalyzed the published data [13,21] and reconstructed two dose–response relationships. The relationships between Cd in urine (C_U) and glomerular and tubular damage (GTD) for whole adult population and Cd in blood (C_B) and PADP for male were described by a 4-parameter Hill model,

$$R(C) = R_{\min} + \frac{(R_{\max} - R_{\min})}{1 + \left(C/\mathrm{EC50}\right)^n} \quad (1)$$

where C is Cd in urine C_U ($\mu g\,g^{-1}$ creatinine) or in blood C_B ($\mu g\,L^{-1}$), $R(C)$ is the C-dependent response measured as GTD (%) or PADP (%), $R_{\min}$ and $R_{\max}$ are the minimum and maximum responses (%), respectively, EC50 is the effective concentration at 50% response, and n is the Hill coefficient.

Due to the U-shaped trend was found in the relationship between Cd in blood (C_B) and PADP for female, we used a nonlinear regression model to obtain the best fitting.

2.4. Risk assessment model

In this study, the dose–response profiles were used as the conditional probabilities. Therefore, the relationship between Cd in urine and GTD can be expressed as $P(\mathrm{GTD}|C_U)$, whereas the relationship between Cd in blood and PADP can be expressed as $P(\mathrm{PADP}|C_B)$. Cd in urine and blood can be predicted by the PBPK model through daily seafood consumption and inhalation in smoking and non-smoking subgroups. The human health risk at each population group can be calculated as the probability density functions of C_U and C_B multiplied by the conditional probabilities of GTD and PADP, respectively. Therefore, a joint probability functions can be used to calculate the human health risk probabilities,

$$P(R_{\mathrm{GTD}}) = P(C_U) \times P(GTD|C_U) \quad (2)$$

$$P(R_{\mathrm{PADP}}) = P(C_B) \times P(PADP|C_B) \quad (3)$$

where $P(R_{\mathrm{GTD}})$ and $P(R_{\mathrm{PADP}})$ represent the human health risk estimates based on two responses of GTD and PADP, respectively.

2.5. Uncertainty and data analyses

TableCurve 2D (Version 5.0, AISN Software Inc., Mapleton, OR, USA) and Statistica® software (Version 6.0, Statsoft, Tulsa, OK, USA) were used to perform the model fittings. We generated 2.5th and 97.5th percentiles as the 95% confidence interval (CI) for all fitted models and explicitly quantified the uncertainty of data by implementing the Monte Carlo technique using Crystal Ball® software (Version 2000.2, Decisionerring Inc., Denver, Colorado, USA). The result showed that 10,000 iterations are sufficient to ensure the stability of results. The PBPK model simulation was performed by Berkeley Madonna: Modeling and Analysis of Dynamic Systems (Version 8.3.9, http://www.berkeleymadonna.com).

3. Results

3.1. Relationship between trophically available Cd and bioaccessibility

We constructed the relationships between trophically available Cd obtained from subcellular partitioning experiment and the bioaccessibility obtained from *in vitro* digestion method with the best-fitting model for fish and shellfish, respectively. The positive relationship is found for fish and shellfish and can be best described by $y = 93.84 - 10328.80/x^2$ ($r^2 = 0.51$, $p = 0.49$) for fish and $y = 47.60 + 0.47x$ ($r^2 = 0.70$, $p < 0.005$) for shellfish. The bioaccessibility of shellfish had stronger correlation with trophically available fraction of Cd than that in fish (Fig. 2). Results showed that fish had higher average bioaccessibility (~83.7%) than that of shellfish (~73.2%) for human ingestion.

3.2. Cd daily intake via seafood and inhalation

Shellfish had the highest Cd concentration than freshwater fish and marine fish for nearly one order of magnitude (Fig. 3). For freshwater fish, other kind of fish showed the highest Cd level with a geometric mean of 0.03 $\mu g\,g^{-1}$ wet wt. On the other hand, the most popular freshwater fish, tilapia, had the Cd concentration of gm 0.02 $\mu g\,g^{-1}$ wet wt (Fig. 3A). Results revealed that marine fish had the similar Cd concentrations with freshwater fish (Fig. 3B). Note, however, that the higher Cd concentrations of geometric mean were found to be 0.25, 0.12, and 0.16 $\mu g\,g^{-1}$ wet wt for oyster, hard clam, and freshwater clam, respectively (Fig. 3C).

Based on the Cd concentrations in respective seafood and seafood consumptions for male and female, the average daily Cd intake from seafood consumption were 7.52 $\mu g\,d^{-1}$ for male and 6.94 $\mu g\,d^{-1}$ for female (Table S5 in Supplementary Materials). Our results showed that nonsmoking groups had the daily Cd intakes *via* inhalation with 0.061 and 0.045 $\mu g\,d^{-1}$ for male and female, respectively, whereas for smoking groups were 2.10 $\mu g\,d^{-1}$ for male and 1.35 $\mu g\,d^{-1}$ for female.

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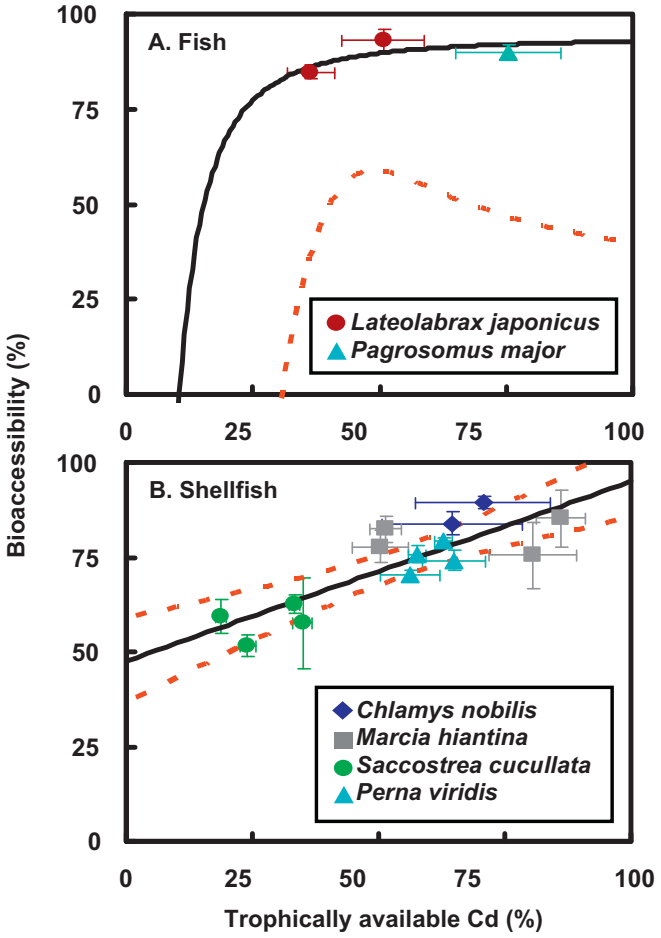

Fig. 2. Relationships between % Cd in TAM and bioaccessibility (%) for (A) fish and (B) shellfish.

3.3. Dose–response profiles

The relationship between Cd in urine and GTD was best described by the Hill model (Eq. (1)) with $n = 2.03 \pm 0.33$ (mean ± SE), minimum response $GTD_{min} = 18.03 \pm 2.46\%$, and EC50 = 15.47 (95% CI: 10.87–20.07) $\mu g\,g^{-1}$ creatinine ($r^2 = 0.99$) (Fig. 4A). The blood Cd concentration-dependent PADP profile for male was showed in a sigmoid curve, whereas a U-shaped fashion was found for female (Fig. 4B, C). Fig. 4B showed that the Hill model can well describe the correlation between Cd in blood and PADP for male with $n = 3.95 \pm 0.36$, maximum response $PADP_{max} = 18.60 \pm 1.99\%$, and EC50 = 0.71 (95% CI: 0.50–0.93) $\mu g\,L^{-1}$ ($r^2 = 0.99$). For female, a nonlinear regression model was used to capture the dose–response relationship of $y = 24.53x^2 - 15.02x + 7.01$ ($r^2 = 0.98$) (Fig. 4C).

3.4. Risk estimates

We used the estimated distributions of daily Cd intake (Table S5 in Supplementary Materials) as the inputs in PBPK model. PBPK modeling used the bioaccessibility-based *fs* and original P_5 that adopted from the report by Kjellström and Nordberg [40] to predict steady-state Cd concentration distributions in urine and blood. The values of *fs* are 0.021, 0.032, 0.044, 0.057, and 0.094 corresponding to the 2.5th, 25th, 50th, 75th, and 97.5th percentiles, respectively. The estimated Cd concentration in urine was creatinine-adjusted and the levels of creatinine for male and female were given in Table S5 (see Supplementary Materials).

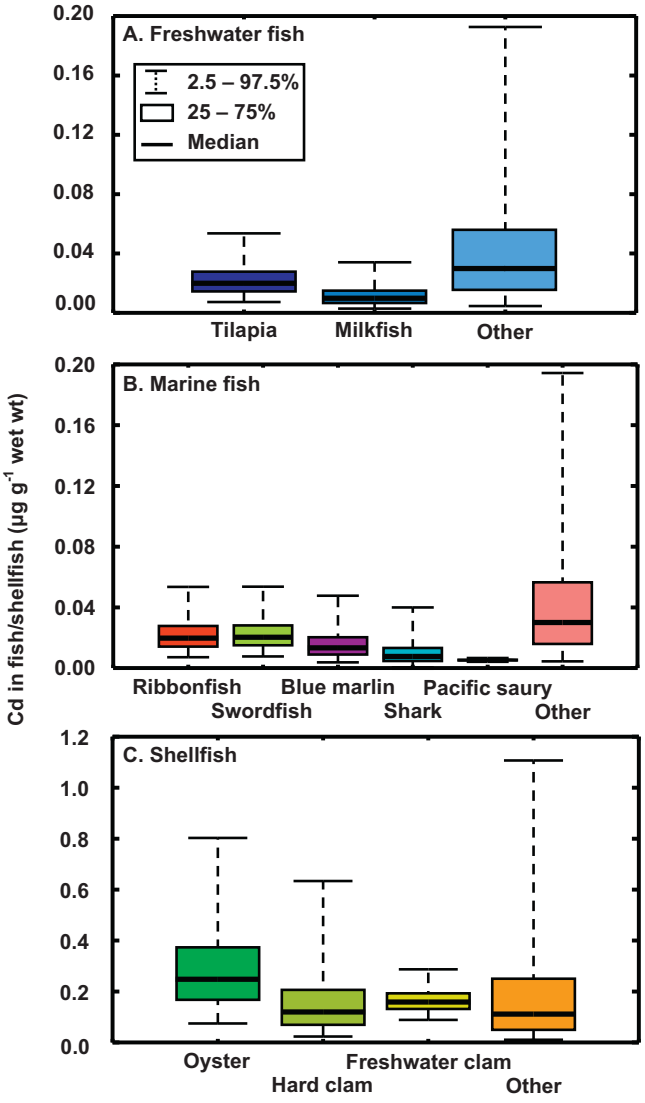

Fig. 3. Box and whisker plot representations of Cd concentrations in (A) freshwater fish, (B) marine fish, and (C) shellfish in Taiwan collected from published literature.

Estimates of Cd concentration distributions in urine and blood were showed under varied bioaccessibility-based *fs* and original P_5 that adopted from the report by Kjellström and Nordberg [40] to investigate the differences among male, female, nonsmoking, and smoking groups (Fig. 5).

In a comparison with gender, the exposure without smoking showed the higher mean Cd in urine for female (0.086–0.335 $\mu g\,g^{-1}$ creatinine) than that for male (0.065–0.259 $\mu g\,g^{-1}$ creatinine). On the other hand, the mean Cd in blood for female (0.177–0.691 $\mu g\,L^{-1}$) was also higher than that for male (0.159–0.624 $\mu g\,L^{-1}$). The smoker had approximately 2–5 times Cd concentrations in urine and blood than the nonsmoker (Fig. 5). Fig. 5 shows that the estimate of bioaccessibility using original P_5 was close to that using *f* at 50th percentile bioaccessibility.

Exceedance risk curves shown in Figs. 6 and 7 indicated the estimated probabilistic of GTD and PADP in different bioaccessibilities for different population groups. Table 1 gives the estimated human health risks for GTD and PADP at 10, 50, and 90% probabilities subjected to Cd intakes from inhalation and seafood consumption in Taiwan. Similar results at various probabilities in GTD can be obtained for different genders and even for smoker (ranging from 18.03 to 18.18%). The level of PADP for nonsmoker had 10, 50, and 90% probabilities exceeding about 3.35–14.10 (95% CI), 3.28–8.80,

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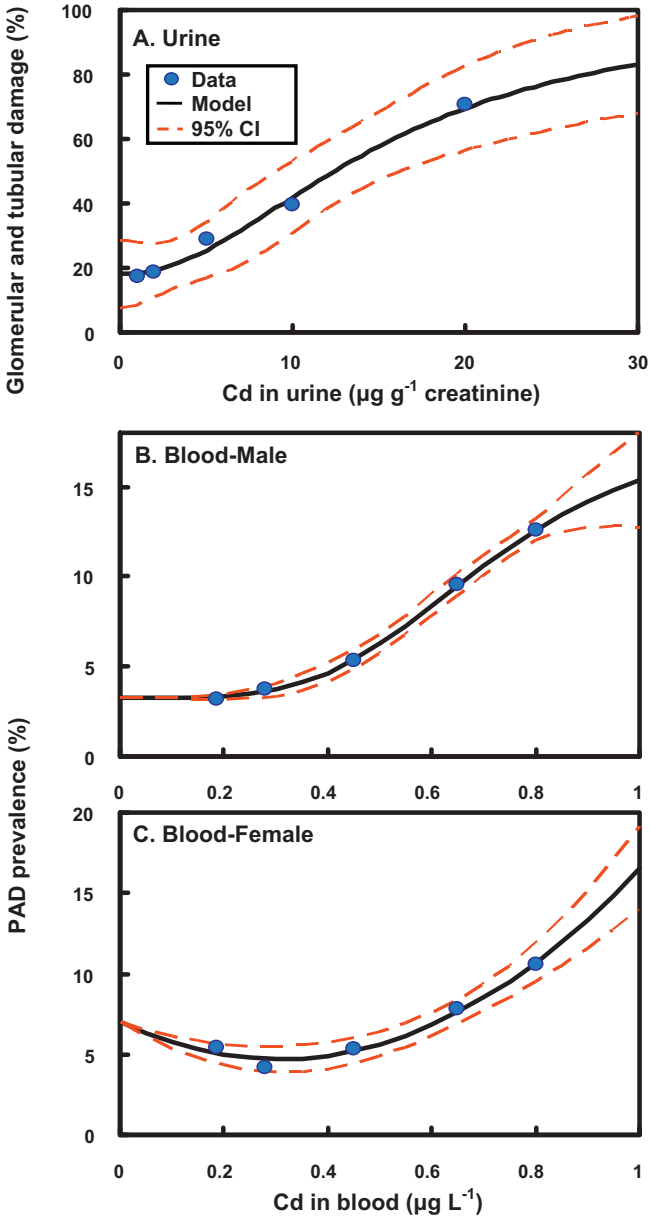

Fig. 4. Reconstructed Hill model-based dose–response profiles for (A) glomerular and tubular damage increasing with Cd in urine. Fitting Hill model and nonlinear regression model describing the relationships between Cd concentration of blood and peripheral arterial disease prevalence for (B) male and (C) female, respectively.

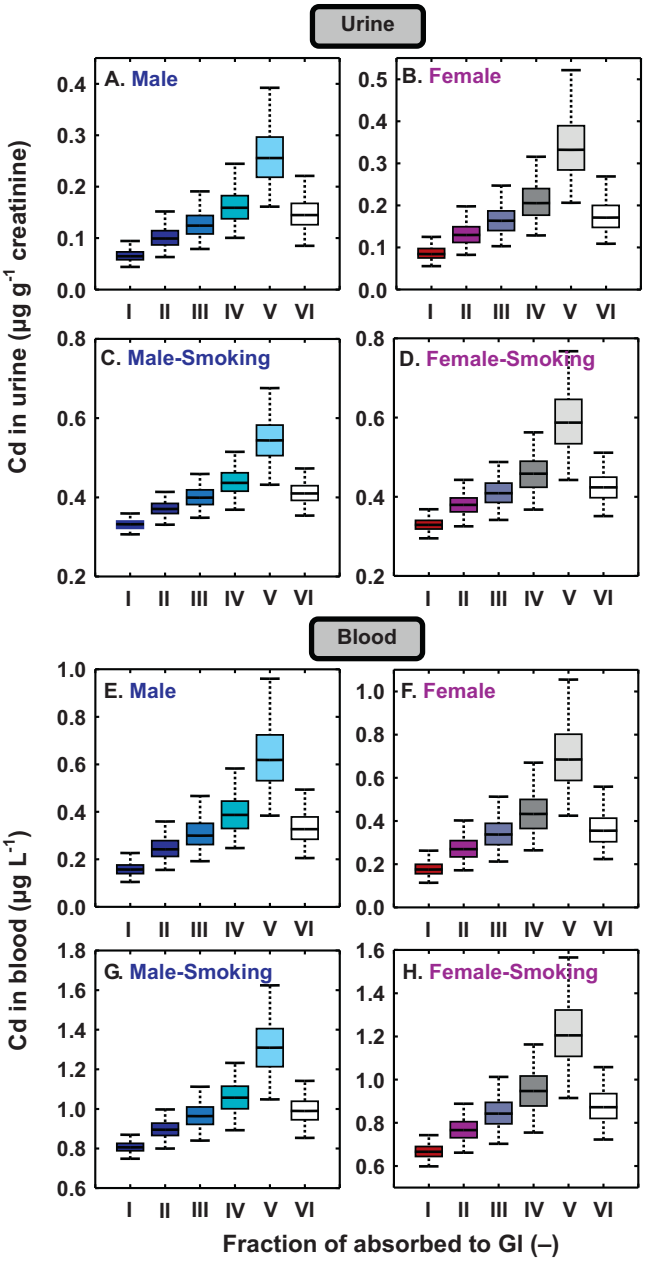

Fig. 5. Box and whisker plot describing distributions of Cd concentrations in (A–D) urine and (E–H) blood in subgroups of nonsmoking male, nonsmoking female, smoking male, and smoking female at six scenarios of bioaccessibility. I–V represent the scenarios of using 2.5th, 25th, 50th, 75th, and 97.5th percentiles bioaccessibility-based parameter f and values of f were 0.021, 0.032, 0.044, 0.057, and 0.094, respectively. VI represents the scenario of using original P_5 adopted from Nordberg and Kjellström [39].

and 3.26–5.68%, respectively, within 2.5th–97.5th percentile level of bioaccessibility. In contrast to nonsmoker, smoking population had nearly 2–4 times of morbidity risk of PADP (Table 1).

3.5. Advise tolerable daily intake (TDI)

To compare the tolerable daily intake with FAO/WHO guidelines (provisional tolerable weekly intake for Cd at 7 μg week^{-1} kg^{-1} body weight based on the renal damage) [11], the dose–response of GTD can be used to estimate EC5 as a surrogate threshold of regulatory endpoint and extrapolated the bioaccessibility-based tolerable daily intake among different population subgroups. Furthermore, to quantify how much the seafood consumption is safe in Taiwan, we transformed the tolerable daily intake with a mean seafood Cd concentration of 0.075 μg g^{-1} wet wt to determine safe seafood intake (SSI) (Table 2). The mean seafood Cd concentrations were estimated by the respective seafood Cd concentration multiplying the realistic market shares. Results indicated that the advised tolerable daily intake of seafood for four population subgroups of nonsmoker-male, nonsmoker-female, smoker-male, and smoker-female were 21.07–91.89, 18.10–79.05, 19.37–85.25, and 16.96–74.01 g d^{-1} kg^{-1} body weight, respectively (Table 2).

4. Discussions

4.1. Linkage of trophically available metal and bioaccessibility

In this study, trophically available Cd and bioaccessibility were obtained from literature for constructing the relationship

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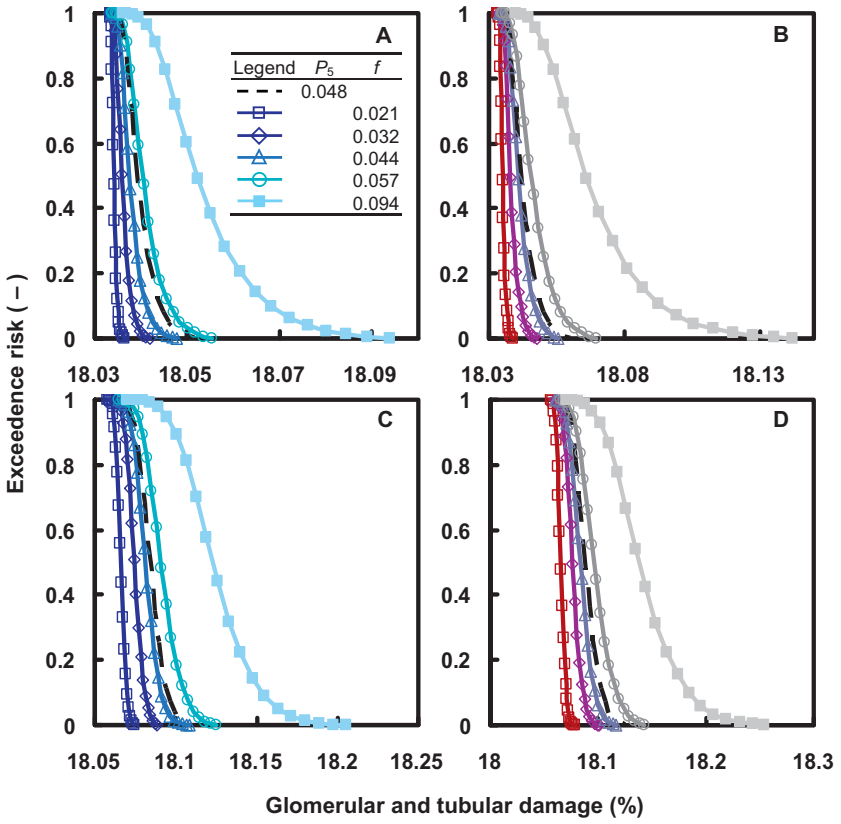

Fig. 6. Exceedence risks of glomerular and tubular damage for (A) nonsmoking male, (B) nonsmoking female, (C) smoking male, and (D) smoking female at six scenarios of bioaccessibility.

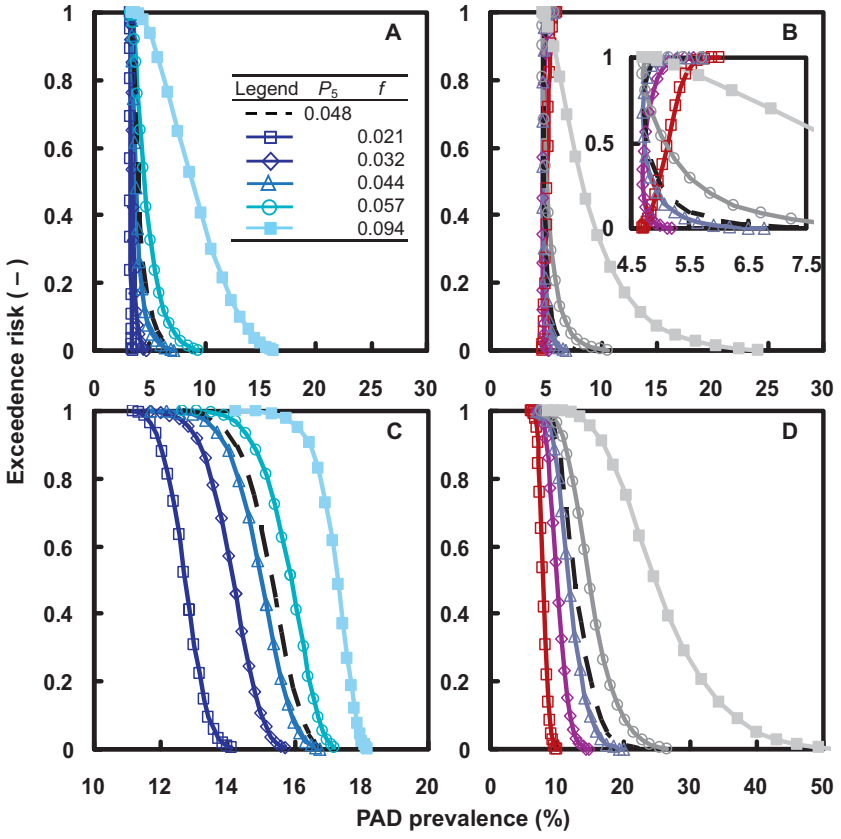

Fig. 7. Exceedence risk of peripheral arterial disease prevalence for (A) nonsmoking male, (B) nonsmoking female, (C) smoking male, and (D) smoking female at six scenarios of bioaccessibility.

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Table 1
Human health risk estimates for glomerular and tubular damage (GTD, %) and peripheral arterial disease prevalence (PADP, %) at 10, 50, and 90% probabilities subject to Cd intakes from inhalation and seafood consumption in Taiwan.

Gender	Exceedance risk		
	0.1	0.5	0.9
Nonsmoker			
Male			
GTD	18.03–18.09[a]	18.03–18.05	18.03–18.04
PADP	3.35–13.21	3.28–8.80	3.26–5.34
Female			
GTD	18.04–18.09	18.04–18.06	18.03–18.05
PADP	4.85–14.10	5.13–8.23	5.45–5.68
Smoker			
Male			
GTD	18.07–18.15	18.07–18.12	18.06–18.10
PADP	13.44–17.83	12.73–17.31	11.98–16.44
Female			
GTD	18.07–18.18	18.07–18.14	18.06–18.11
PADP	8.82–36.53	7.88–24.53	7.10–16.69

[a] Estimates based on 2.5th–97.5th percentiles of bioaccessibility-based fraction absorbed to GI tract and systemic circulation (f).

between the bioaccumulation distribution in seafood and fraction potentially is assimilated by human. In particular, fish had high bioaccessibility ranging from 84.8–93.2%, whereas for trophically available Cd for fish was 36.4–75.6%. Not surprisingly, trophically available Cd of subcellular partitioning is only associated with the cytosol [35].

Metian et al. [47] measured seven metal accumulations of ^{241}Am, Cd, Co, Cs, Mn, Se, and Zn in the Mediterranean mussels *Mytilus galloprovincialis* and found that bioaccessibility estimates were higher than the cellular cytosolic fractions. Our results were consistent with the report by He et al. [27]. He et al. [27] also demonstrated that a significant association between the bioaccessibility and fraction of trophically available metal for marine fish exposed to As, Cd, Cu, Fe, Se, and Zn. In present study, the nonlinear regression model was used to describe the positive correlation in fish and shellfish. Unfortunately, due to the limited fish data, the nonlinear regression equation was not robust enough to well describe the relationship between the bioaccessibility and trophically available metal in fish ($r^2 = 0.51$).

Moreover, the bioaccessibility and trophically available metal can be influenced by many factors, such as species, chemical speciation, type of cooking, and differences in the nature of tissues. Metian et al. [47] assessed the metal intake for a consumer eating mussels would be reduced metal intake by 25% for Mn, 35% for Zn, 40% for Co, 50% for Se, and 65% for Cd and Cs if raw tissues were previously cooked. The reducing in bioaccessibility after cooking might be associated with changes and damages in the structural conformation of the seafood muscle proteins produced by high temperature, which could cause the loss of the native protein structure [48]. However, for food safety concerns, the bioaccessible concentrations in raw flesh have to be interpreted and regulated with caution.

4.2. Cd daily intake via seafood and inhalation

Amzal et al. [49] investigated the 20-year of dietary intake data in 680 nonsmoking females and indicated that participators had daily Cd dietary intake ranging from 7 to 27 μg and Cd in urine ranging from 0.09 to 1.23 $\mu g\,g^{-1}$ creatinine. Our estimates were apparently consistent with these findings with Cd daily intake from seafood of 7.25 and 6.94 $\mu g\,d^{-1}$ for male and female, respectively, and the simulated Cd in urine was 0.07–0.34 $\mu g\,g^{-1}$ creatinine.

When compared to other previous investigation for Taiwan population (295 male with age ≥ 50 years old), Cd in urine and in blood ranged from 0.09–5.96 $\mu g\,g^{-1}$ creatinine and 0.13–3.62 $\mu g\,L^{-1}$, respectively [50]. The discrepancy may due in part to our estimation containing no other food sources, such as bread, cereals and vegetables, and other meat. Here we showed that the smoker had approximately 2–5 times of Cd concentration in urine and blood higher than that nonsmoker. Above results was consistent with the report by Galażyn-Sidorczuk et al. [2]. Galażyn-Sidorczuk et al. [2] found that blood and urinary Cd concentrations in the smokers was 2–4 times higher that in the non-smokers.

Hence, our Cd exposure setting *via* inhalation was close to that in the report by Galażyn-Sidorczuk et al. [2]. Our results of Cd concentrations in urine and blood showed that cigarette smoke was one of the major Cd exposure routes for smoker that compared with nonsmoker, although present study did not take into account Cd contents in different brands of cigarette, the intensity of the habit, and its duration. Strong evidence suggested that the effects of Cd may be different in male and female [51–53]. At similar exposure levels, female had higher blood and urinary Cd concentrations than male. At low level exposure, Cd-induced renal and bone damages have found to be more common and severe in female than in male [51,54].

Vahter et al. [52] showed that the difference between genders resulted from higher gastrointestinal Cd absorption in female. Interestingly, the PBPK model that we applied in the present study did not consider any gender-specific parameter to estimate final outcomes, yet we used different physiological parameters to adjust, such as body weight, volumes of blood and urine, creatinine

Table 2
Advised tolerable daily intakes (TDI, $\mu g\,d^{-1}\,kg^{-1}$ BW) and safe seafood intakes (SSI, $g\,d^{-1}\,kg^{-1}$ BW) estimates for Cd in Taiwan.

Gender	Bioaccessibility-based fraction absorbed from food to GI tract and systemic circulation (f)				
	0.021	0.032	0.044	0.057	0.094
Nonsmoker					
Male					
TDI	6.91	4.29	3.33	2.57	1.59
SSI[a]	91.89	56.96	44.24	34.17	21.07
Female					
TDI	5.95	3.67	2.86	2.21	1.36
SSI	79.05	48.81	38.04	29.33	18.10
Smoker					
Male					
TDI	6.41	3.97	3.09	2.39	1.46
SSI	85.25	52.78	41.01	31.71	19.37
Female					
TDI	5.57	3.45	2.69	2.07	1.28
SSI	74.01	45.83	35.75	27.50	16.96

[a] SSI = TDI/C_b where $C_b = 0.075\ \mu g\,g^{-1}$ wet wt is the mean seafood Cd concentration in Taiwan.

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content, and inhalation rate. Therefore, our estimates were also in a good agreement with the results in that female had relative higher Cd content in urine and blood than male.

4.3. Dose–response relationships

Cd in urine and blood can be used as the bioindicators to reflect long-term and recent Cd exposures [5,22,24]. Single measurement of urine or blood may be limited to completely assess Cd exposure and internal dose. Therefore, this study used urinary and blood Cd as the bioindicators of internal dose in the dose–response relationships. Due to blood Cd can reflect ongoing exposure, Cd in blood can immediately reflect human with high exposure and subsequently take the preventive measures to diminish exposed level before organ damage occurs.

In the recent studies, Cd exposure measured in blood has been associated with cardiovascular diseases, such as stroke and heart failure, ischemic heart disease, and elevation in blood pressure [55–57]. Therefore, we used blood Cd as the dose estimate to relate the PDAP. At low Cd exposure, the relationships between Cd in blood and PDAP were significantly different in genders, indicating a progressively increasing for male and a U-shaped pattern for female. Therefore, the risk assessment should be separated for male and female. Cadmium in urine is mainly used to represent the long-term exposure and is together with metallothionein, by which can significantly represent the accumulation of past exposure, body burden, and renal Cd concentration [13]. Many studies have showed the dose–response relationship between urinary Cd and renal dysfunction [17,51,58,59]. Hence, urinary Cd can be used as an ideal bioindicator of internal dose in respect to the renal damage.

As our knowledge, no published data have been available so far related to Cd-induced health damage in Taiwan. In this study, we attempted to incorporate the mechanistic model of PBPK with the epidemiological data to assess the Cd exposure risk. However, due to the limited data on the epidemiology in Taiwan and some essential data required for the modeling, the predicted risks associated uncertainties and variability would be increased. We recognize that our modeling cannot capture all factors that may affect the results of experiment. Therefore, this study performed the Monte Carlo simulation to obtain all likely effect. However, more epidemiological data in Taiwan are needed to validate the estimated risks induced by the Cd exposures in the future work.

4.4. Implications and limitations

The major application of the present PBPK model included the process of linking long-term exposure measurements of a chemical and bioindicator data at the individual level. Therefore, this study considered the individual linkage between overall intake and urine and blood Cd concentrations and the estimation of the population variations. This study provided predicted average estimates of urinary and blood Cd and total Cd intake among the adult Taiwan population, stratified by smoking groups and genders. Moreover, we used gender-specific creatinine content to adjust the outcomes of PBPK model for reducing the urine dilution effect [60]. Except smokers and women, people having a higher absorption capacity of Cd in the gastrointestinal tract were also belonged to high risk populations for Cd exposure. Further strengths of our study were using of different percentiles of bioaccessibility-based parameters to predict Cd content in urine and blood to completely contain the great variation among food types and individual-specific absorption abilities.

There are some limitations in this study. First, we used the bioaccessibility of Cd in raw flesh to construct the relationship and then assessed the daily intake for human. However, we mostly eat cooked seafood in daily life. Moreover, we only considered the seafood consumption as the single dietary exposure. Risk assessment of exposed to Cd may be underestimated. Thus, further research is needed to examine other food resources, such as meat, dairy products, eggs, vegetables, cereals, fruits, fats, and oil.

Second, the average seafood intake estimates were not based on the consumption data differentiated by age categories. Privalova et al. [61] suggested that children were not the most exposed population, but they were more sensitive to Cd than adults. Thus, the possibility that the daily intakes estimated in the present study may not be representative of the population as whole. In addition, Cd exposure might be affected by several other factors, including body mass index, food habits, and socio-economic status.

5. Conclusions

The results of this study suggested that Cd dietary exposure *via* seafood consumption was low, for male and female, indicating that there was no significant risk posed by Cd weekly intake. We found that Cd in urine is potentially exceeding of 0.5 $\mu g\, g^{-1}$ creatinine in smoking populations with higher bioaccessibility. However, recent studies indicated that population showed adverse effects on bone and increased risk of cancer and mortality with Cd concentration of 0.5 $\mu g\, g^{-1}$ creatinine in urine [62,63]. Although the present estimations were consistent with the recommended PTWI, this study implicated that a plausibly health risk would be posed by long-term exposed to low level Cd among the general populations.

The present study was the first assessment of human exposure to Cd through seafood consumption and inhalation incorporating the concept of the seafood bioaccessibility. The probabilistic risk assessment was applied to estimate the renal damage and prevalence of peripheral arterial disease from seafood consumption of seafood and inhalation. Further study is needed to incorporate all food types and other factors into our model for applying in a realistic scenario. Our work provides a framework that could more accurately address risk dose dependency of Cd hazard.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhazmat.2012.05.060.

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