Satarug *et al. J Environ Expo Assess* 2024;3:26
DOI: 10.20517/jeea.2024.31

Journal of Environmental Exposure Assessment

Research Article

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The NOAEL equivalent for the cumulative body burden of cadmium: focus on proteinuria as an endpoint

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How to cite this article: Satarug S, Vesey DA, Đorđević AB. The NOAEL equivalent for the cumulative body burden of cadmium: focus on proteinuria as an endpoint. *J Environ Expo Assess* 2024;3:26. https://dx.doi.org/10.20517/jeea.2024.31

Received: 9 Sep 2024 **First Decision:** 6 Nov 2024 **Revised:** 2 Dec 2024 **Accepted:** 6 Dec 2024 **Published:** 17 Dec 2024

Academic Editor: Stuart Harrad **Copy Editor:** Pei-Yun Wang **Production Editor:** Pei-Yun Wang

Abstract

The risk of developing chronic kidney disease (CKD), signified by a decrease in the estimated glomerular filtration rate (eGFR), has been linked to long-term exposure to low levels of the metal pollutant cadmium (Cd). Proteinuria is a hallmark of CKD and predicts continued progressive functional decline of the kidney. The aim of this study was to use the extent of proteinuria for Cd health risk assessment. Data were from 405 apparently healthy Thai nationals, of whom 12.6% had an eGFR below 60 mL/min/1.73 m^2 (low eGFR), and 16.3% and 13.5% had moderate and severe proteinuria. Urinary excretion of Cd (E_{Cd}) and urinary total protein (E_{pro}) were measured and normalized to both creatinine clearance (C_{cr}) and creatinine excretion (E_{cr}). We found that the risk of having a low eGFR [prevalence odds ratio (POR) = 12.2, $P < 0.001$] and severe proteinuria [POR = 10.4, $P = 0.001$) were increased markedly for every ten-fold increase in E_{Cd}/C_{cr}. However, when E_{Cd} was normalized to E_{cr}, the association between eGFR and E_{Cd} was found to be insignificant due to non-differential errors introduced by the E_{cr}-normalization. Respective benchmark dose limit (BMDL) values of E_{Cd}/E_{cr} that increased protein excretion by 5% and 10% were 0.0536 and 0.1140 μg/g creatinine. The E_{Cd}/E_{cr} at which 5% of the population had Cd-related proteinuria was 1.86 μg/g creatinine, respectively. For the first time, a urinary Cd excretion rate of 0.0536 μg/g creatinine has been derived as a Cd exposure level that produces negligible kidney damage.

Keywords: Assessment imprecision, benchmark dose limit, cadmium, GFR, NOAEL equivalent, proteinuria

INTRODUCTION

Dietary exposure to the metal contaminant cadmium (Cd) continues to be one of the most significant public health threats worldwide, given that Cd has no nutritional value or physiological role, and the body burden of Cd increases with age due to a lack of excretory mechanisms[1,2]. Concerningly, the health risk of dietary Cd exposure has been vastly underappreciated because the toxicological risk assessment relied mostly on an increase in urinary excretion of the protein β_2-microglobulin (β_2M) above 300 μg/g creatinine, termed β_2-microglobulinuria[3-6]. Using the β_2M as a toxicity endpoint, the Food and Agriculture Organization and World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives and Contaminants (JECFA) found a tolerable intake level of Cd to be 0.83 μg/kg body weight/day (58 μg/day for a 70-kg person), and they identified urinary Cd excretion of 5.24 μg/g creatinine as a toxicity threshold level[4]. The European Food Safety Authority (EFSA) considered the kidneys to be the critical target of Cd toxicity, and employed the β_2M as an endpoint. The EFSA designated a Cd excretion rate of 1 μg/g creatinine as a threshold level after an uncertainty factor (a safety margin) was included in a model[5,6]. Dietary exposure to Cd at 0.36 μg/kg body weight per day for 50 years was viewed as an acceptable Cd exposure level or a reference dose (R_fD)[5,6].

Current evidence, however, has linked kidney malfunction, reflected by a fall of the estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 (termed a low eGFR) with urinary Cd excretion of 0.27-0.32 μg/g creatinine[7,8], which are much lower than the JECFA's and the EFSA's threshold levels mentioned above. Furthermore, in the China Health and Nutrition Survey, a dietary Cd exposure higher than 16.7 μg/day appeared to be sufficient to increase the risk of having a low eGFR[9]. These findings raise a serious concern that the existing Cd exposure guidelines are not protective of population health. Additionally, they question the utility of the β_2M endpoint as a basis to define a permissible exposure level for Cd and its toxicity threshold level, given that a low eGFR is a pathological sign for the diagnosis of chronic kidney disease (CKD)[2].

Reductions in eGFR after Cd exposure are irreversible, and further decline is likely if exposure persists[2,8]. A β_2M level above 300 μg/g creatinine is indicative of severe kidney pathologies, such as rapid kidney functional deterioration[10,11]. Thus, it is inappropriate to define a toxicity threshold level of Cd based on the β_2M excretion exceeding 300 μg/g creatinine. Chronic environmental Cd exposure has been linked to an increased risk of kidney damage[12-14] concurrently with low eGFR and proteinuria[15,16]. The use of proteinuria as an endpoint in the toxicological risk assessment of Cd has never been explored. Indeed, proteinuria is a key biomarker of kidney disease, as it predicts continued progressive functional decline of the kidney or a rapid drop in eGFR to 15 mL/min/1.73 m^2, which marks end-stage kidney disease[17-19], a condition that requires dialysis or a kidney transplant for survival. The associated healthcare costs are substantial.

The present study has three major objectives. The first is to explore the dose-response relationship between environmental Cd exposure and urinary excretion of total protein (E_{pro}). The second objective is to define the benchmark dose limit (BMDL) of Cd excretion using E_{pro} as a biomarker of an adverse effect of Cd on kidneys. The BMDL value derived at 5% benchmark response (BMR) has increasingly been used as a replacement for the no-observed-adverse-effect level (NOAEL) which has some shortcomings[20,21]. The NOAEL is defined as the highest experimental dose level at which the response does not significantly differ from the control group[20,21]. For comparison, the dose-response relationship between Cd exposure and eGFR reductions was determined simultaneously. The third objective is to address the "unrecognized" imprecision in the toxicological assessment of Cd exposure and its effects on kidneys. This imprecision arises from the practice of adjusting Cd excretion and urinary biomarkers of adverse effects, such as E_{Cd} and

E_{pro}, to creatinine excretion (E_{cr}) as E_{Cd}/E_{cr} and E_{pro}/E_{cr}. These adjustments introduce non-differential errors, which tend to bias the dose-response relationship toward the null[22]. As a result, current dietary Cd exposure limits, which are computed by adjusting the excretion rates of Cd and biomarkers of kidney effects to E_{cr}, underestimate the severity of Cd-induced nephrotoxicity. Consequently, these exposure limits are not low enough to afford health protection.

EXPERIMENTAL

Study design

We assembled archived data from large Thai population-based cohorts of residents in a Cd-contaminated area (Mae Sot District, Tak Province) and a low-exposure area (Bangkok)[23-26]. For the Bangkok group, those aged 19 years or older were selected. The health status was ascertained by physician's examination reports and routine blood and urinary chemistry profiles. For the Mae Sot group, those who had resided at their current addresses for 30 years or longer were selected. Exclusion criteria for both groups were pregnancy, breastfeeding, a history of metal work, and a hospital record or physician's diagnosis of advanced chronic disease. The sociodemographic data, educational attainment, occupation, health status, family history of diabetes, and smoking status were obtained by structured interview questionnaires. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg[27], a physician's diagnosis, or prescription of anti-hypertensive medications.

Measurement of exposure and adverse effects on kidneys

We used urinary excretion of Cd (E_{Cd}) as an indicator of cumulative long-term exposure to Cd or body burden[23-26], while urinary E_{pro} and eGFR were employed as kidney function indicators[26,28]. For these measurements, samples of urine, whole blood, and plasma were collected from all participants after an overnight fast, and were stored at -80 ºC for later analysis. Plasma samples were assayed for the concentration of creatinine, while urine samples were assayed for the concentrations of creatinine, Cd, and total protein, as detailed in previous reports[23-26].

The eGFR was computed with equations of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[29-31]. CKD stages 1, 2, 3, 4, and 5 corresponded to eGFR of 90-119, 60-89, 30-59, 15-29, and < 15 mL/min/1.73 m^2, respectively[31].

Normalization of Cd and protein excretion rates

The urinary excretion of x (E_x) was normalized to creatinine clearance (C_{cr}) as $E_x/C_{cr} = [Cd]_u[cr]_p/[cr]_u$, where x = Cd or pro, $[x]_u$ = urine concentration of x (mass/volume), $[cr]_p$ = plasma creatinine concentration (mg/dL), and $[cr]_u$ = urine creatinine concentration (mg/dL). E_x/C_{cr} was expressed as an amount of x excreted per volume of the glomerular filtrate[32]. This C_{cr}-normalization corrects for urine dilution and the number of functioning nephrons simultaneously, and it is not influenced by muscle mass.

E_x was normalized to E_{cr} as $[x]_u/[cr]_u$, where x = Cd or pro, $[x]_u$ = urine concentration of x (mass/volume), and $[cr]_u$ = urine creatinine concentration (mg/dL). E_x/E_{cr} was expressed as an amount of x excreted per g of creatinine. This E_{cr}-normalization corrects for urine dilution only, but it introduces non-differential errors due to the variability in muscle mass and E_{cr} among people. Consequently, a clear dose-response relationship cannot be established[22].

Benchmark dose computation and definitions

We used the web-based PROAST software version 70.1 [https://proastweb.rivm.nl (accessed on 6 May 2023)] to determine the BMD values for Cd exposure as E_{Cd}/E_{cr} and E_{Cd}/C_{cr} that were linked with eGFR, E_{Pro}, prevalence of a low eGFR (CKD), and proteinuria[20,21,33]. The BMR was set at 5% and 10%[20,21,33-36].

Datasets were fitted to multiple mathematical dose–response models such as inverse exponential, natural logarithmic, exponential, and Hill models[33-35]. The Akaike information criterion (AIC) was applied to model selection and model comparison of the relative goodness of fit of different models[33]. The lower bound (BMDL) and upper bound (BMDU) of the 95% confidence interval (CI) of BMD were determined from model averaging using bootstrap with 200 repeats[36]. The BMDL could serve as a potential reference point[34,35]. The BMDU was used to calculate the BMDU/BMDL ratio, which reflects the uncertainty in the BMD estimates. The wider the BMDL-BMDU difference, the higher the statistical uncertainty in the dataset[33-36].

The BMDL value of E_{Cd} computed at 5% BMR could be considered as the NOAEL equivalent or the level of exposure below which an effect of Cd on eGFR or E_{Pro} was discernable[20,21,33]. The BMDL/BMDU values of E_{Cd} computed at 5% and 10% prevalence rates of CKD and proteinuria were designated as $BMDL_5/BMDU_5$ and $BMDL_{10}/BMDU_{10}$, respectively. The $BMDL_5$ and $BMDL_{10}$ values of E_{Cd} indicated the exposure levels at which the prevalence of CKD or proteinuria reached 5% and 10%, respectively[35]. $BMDL_5$ could reflect a threshold level, defined as an exposure level at which 5% of the general population showed evidence of Cd-linked CKD or Cd-linked proteinuria.

Statistical analysis

Data were analyzed using IBM SPSS Statistics 21 (IBM Inc., New York, NY, USA). The Mann–Whitney U test. was used to assess the differences between males and females in mean values of continuous variables. Pearson's chi-squared test was used to determine male-female differences in percentages and prevalences of smoking, hypertension, low eGFR, and proteinuria. The one-sample Kolmogorov–Smirnov test was used to ascertain the conformity to a normal distribution of continuous variables. Logarithmic transformation was applied to E_{Cd} and E_{pro}, which showed a right-skewed distribution. For eGFR, no data transformation was required because the distribution of eGFR values was left-skewed. Multiple linear regression was conducted to identify factors affecting eGFR and E_{pro}.

Logistic regression was conducted to evaluate the effects of Cd exposure and other independent variables on the prevalence odds ratio (POR) for two Cd toxicity outcomes, namely CKD and proteinuria. The POR values were adjusted for potential confounders (age, smoking, gender, and hypertension). CKD was defined as eGFR ≤ 60 mL/min/1.73 m^2[31]. For E_{cr}-normalized data, moderate and severe proteinuria were defined as E_{pro}/E_{cr} ≥ 100 mg/g creatinine and ≥ 150 mg/g creatinine, respectively[19]. For C_{cr}-normalized data, moderate and severe proteinuria were defined as $(E_{pro}/C_{cr}) \times 100$ ≥ 100 mg/L and ≥ 150 mg/L filtrate, respectively. A *P*-value ≤ 0.05 was considered statistically significant for all tests.

RESULTS AND DISCUSSION

Cohort participants

From a total of 2,000 cohort participants, 405 subjects were selected, of whom 190 and 215 were residents of Bangkok and the Mae Sot district of Tak Province, respectively [Table 1]. The overall mean age was 44.6 years, with a range from 19 to 87 years. The respective overall mean values for E_{Cd}/E_{cr}, eGFR, and E_{Pro}/E_{cr} were 5.81 μg/g creatinine, 87 mL/min/1.73 m^2, and 43.8 mg/g creatinine. For the Bangkok group, the respective mean values for E_{Cd}/E_{cr}, eGFR, and E_{Pro}/E_{cr} were 0.59 μg/g creatinine, 105 mL/min/1.73 m^2, and 4.73 mg/g creatinine. The corresponding mean values for the Mae Sot group were 10.43 μg/g creatinine, 72 mL/min/1.73 m^2, and 78.25 mg/g creatinine. According to a previous reverse dosimetry modeling of E_{Cd}[23], the Bangkok group was representative of environmental Cd exposure. The Mae Sot group was representative of moderate-to-high environmental Cd exposure scenarios according to modeling data, as well as reported levels of environmental Cd contamination and health surveys detailed below[37-39].

Table 1. Characteristics of study subjects from Bangkok residential area and Mae Sot District of Thailand

Parameters	All subjects *n* = 405	Bangkok, *n* = 190		Mae Sot, *n* = 215	
		Male *n* = 97	Female *n* = 93	Male *n* = 100	Female *n* = 115
Age, years	44.6 (16.2)	29.5 (5.8)	31.5 (7.2)*	58.0 (12.4)	56.2 (9.7)
Age range, years	19-87	19-44	19-47	30-87	40-84
Smoking, %	45.9	52.6	0.0§	86.0	42.6§
Hypertension, %	22.3	0.0	0.0	25.0	27.0
$[cr]_p$, mg/dL	0.98 (0.29)	0.99 (0.09)	0.75 (0.08)§	1.21 (0.38)	0.95 (0.26)§
$[cr]_u$, mg/dL	106 (68)	117 (79)	66 (51)§	137 (55)	102 (63)§
$[Cd]_u$, µg/L	6.54 (10.6)	0.61 (1.05)	0.46 (0.47)	14.0 (15.0)	10.0 (9.0)*
$[pro]_u$	4.72 (15.1)	4.64 (4.60)	3.16 (3.49)$^{\#}$	112 (236)	62.7 (158)*
eGFR, mL/min/1.73 m^2	87 (23)	104 (11)	107 (13)	72 (21)	72 (18)
Low eGFR[a], %	12.6	0.0	0.0	26.0	21.7
E_x/E_{cr} normalization					
E_{Cd}/E_{cr}, µg/g creatinine	5.81 (7.64)	0.49 (0.49)	0.69 (0.49)$^{\#}$	10.0 (8.3)	10.8 (7.8)
E_{prot}/E_{cr}, mg/g creatinine	43.8 (133)	4.12 (3.82)	5.36 (5.94)	88.4 (189)	69.4 (162)
$E_{prot}/E_{cr} \geq 100$, %	16.3	0.0	0.0	18.0	14.8
$E_{prot}/E_{cr} \geq 150$, %	13.5	0.0	0.0	15.0%	12.0%
E_x/C_{cr} normalization					
µg/L filtrate	6.21 (9.0)	0.47 (0.42)	0.51 (0.37)	12.3 (10.8)	10.4 (9.0)
$(E_{pro}/C_{cr}) \times 100$, mg/L filtrate	60.2 (236)	4.04 (3.67)	4.11 (4.54)	156 (428)	69.5 (160)
$(E_{Cd}/C_{cr}) \times 100 \geq 100$, %	17.7	0.0	0.0	21.0	14.8
$(E_{Cd}/C_{cr}) \times 100 \geq 150$, %	13.5	0.0	0.0	16.0	11.3

[a]Low eGFR was defined as eGFR ≤ 60 mL/min/1.73 m^2. Continuous variables are expressed as arithmetic mean and SD values. For all tests, $P \leq 0.05$ identifies statistical significance, determined with the Pearson's Chi-Square test for differences in percentages and the Mann-Whitney U for male-female mean differences. $^{*}P$ = 0.041-0.050, $^{\#}P$ = 0.001-0.004, $^{\S}P < 0.001$. *n*: Number of subjects; eGFR: estimated glomerular filtration rate; cr: creatinine; pro: protein; Cd: cadmium; C_{cr}: creatinine clearance; $[x]_p$: plasma concentration of x; $[x]_u$: urine concentration of x; SD: standard deviation.

Environmental samples such as the paddy soils from the Mae Sot district had Cd concentrations above the standard of 0.15 mg/kg, and samples of household storage rice had Cd concentrations four times above the Thailand permissible level of 0.1 mg/kg[37]. A five-year follow-up study of the Mae Sot residents observed progressive deterioration of kidney function, evident from tubular proteinuria and eGFR endpoints, thereby suggesting these Cd effects on kidneys were irreversible[38].

In another health survey of the Mae Sot residents, a high prevalence of low eGFR of 16.1% was noted along with hypertension, proteinuria ($E_{pro}/E_{cr} \geq 200$ mg/g creatinine), tubular proteinuria ($E_{\beta 2M}/E_{cr} \geq 300$ µg/g creatinine), and $E_{Cd}/E_{cr} \geq 2$ µg/g creatinine, which were found in 32.5%, 24.1%, 36.1%, and 66.7% of the participants, respectively[39]. In the present study, the cutoff values for moderate and severe proteinuria were 100 and 150 mg/g creatinine and the overall % of low eGFR was 12.6%, while % of moderate and severe proteinuria and those who smoked and had hypertension was 16.3, 13.5, 45.9, and 22.3, respectively.

Source of "unrecognized" error in toxicological risk assessment of Cd

To evaluate the impact of normalization methods applied to E_{pro} and E_{Cd} [Table 2], we employed two types of models: E_{Cd} was incorporated as log $[(E_{Cd}/E_{cr}) \times 10^3]$ in type A models and log $[(E_{Cd}/C_{cr}) \times 10^5]$ in type B models. All other independent variables in both types of models were identical. The POR values for moderate and severe proteinuria rose by 5% to 6% per every one-year increment of age in both types of models. Gender, smoking, and hypertension did not contribute significantly to the variation in risk of

Table 2. Effects of Cd exposure on the POR for proteinuria

Independent variables/factors	Moderate proteinuria		Severe proteinuria	
	POR (95%CI)	*P*	POR (95%CI)	*P*
Model A[a]				
Age, years	1.068 (1.028, 1.110)	0.001	1.065 (1.023, 1.109)	0.002
$Log_{10}[(E_{Cd}/E_{cr}) \times 10^3]$, µg/g creatinine	3.685 (1.027, 13.22)	0.045	2.973 (0.766, 11.54)	0.115
Gender	1.096 (0.475, 2.528)	0.829	1.137 (0.467, 2.768)	0.778
Smoking	1.678 (0.627, 4.486)	0.303	1.942 (0.656, 5.753)	0.231
Hypertension	1.113 (0.432, 2.867)	0.824	1.343 (0.473, 3.810)	0.580
Model B[b]				
Age, years	1.061 (1.022, 1.102)	0.002	1.051 (1.022, 1.102)	0.018
$Log_{10}[(E_{Cd}/C_{cr}) \times 10^5]$, mg/ L filtrate	7.143 (2.133, 23.92)	0.001	10.36 (2.133, 23.92)	0.001
Gender	1.117 (0.482, 2.587)	0.796	1.204 (0.482, 2.587)	0.695
Smoking	1.947 (0.725, 5.234)	0.186	2.069 (0.725, 5.234)	0.203
Hypertension	1.018 (0.410, 2.530)	0.969	0.902 (0.410, 2.530)	0.839

[a]In type A model, moderate and severe proteinuria were defined as $E_{pro}/E_{cr} \geq 100$ and ≥ 150 mg/g creatinine, respectively. [b]In type B model, moderate and severe proteinuria were defined as $(E_{pro}/C_{cr}) \times 100 \geq 100$ and ≥ 150 mg/L filtrate, respectively. For all tests, *P*-values ≤ 0.05 indicate a statistical significance. Cd: Cadmium; POR: prevalence odds ratio; CI: confidence interval.

having proteinuria in any model type. In a type A model, per a 10-fold increase in E_{Cd}/E_{cr}, there was a significant increase in the POR for moderate proteinuria only. In comparison, the POR values for moderate and severe proteinuria increased markedly per a 10-fold rise in E_{Cd}/C_{cr} in a type B model. Apparently, E_{cr} normalization introduced an imprecision to the measurement of both exposure and effects, which predisposed the dose-response relationship between E_{Cd}/E_{cr} and E_{pro}/E_{cr} to null[22].

The imprecision of E_{cr}-normalization also appeared in the logistic regression models of low eGFR [Table 3]. Indeed, the impact of E_{cr}-normalization on the dose-response relationship between E_{Cd}/E_{cr} and eGFR was even more dramatic than the E_{Cd}/E_{cr} *vs.* E_{pro}/E_{cr}: the POR for low eGFR was not statistically associated with E_{Cd}/E_{cr} (POR = 2.638, $P = 0.058$). In contrast, however, there was a 12.2-fold increase in the POR for low eGFR as E_{Cd}/C_{cr} rose 10-fold. To visualize the source of imprecision, we constructed scatterplots that relate the Cd exposure measure (E_{Cd}) to the markers of its adverse effects (E_{pro} and eGFR). As shown in Figure 1, lower coefficients of determination (R^2) were evident when E_{Cd} and E_{pro} were adjusted to E_{cr}, compared with the C_{cr}-normalized datasets.

Erroneous conclusions on Cd effects resulted from an adjustment of E_{Cd} to E_{cr}, as reported in a 2016 systemic review and meta-analysis, where Cd exposure was not found to be associated with a progressive decline in eGFR[40]. Similarly, another meta-analysis reported that the association between eGFR and urinary Cd was statistically insignificant, while the risk of proteinuria rose by only 35% when comparing the highest category of Cd dose metrics with the lowest Cd exposure category[16]. However, in the latest systemic review and meta-analysis by Doccioli *et al.* (2024), a significant effect of Cd on eGFR was observed[41]. In the present study, we indicate that the effects of Cd exposure on both eGFR and E_{pro} were demonstratable only when E_{Cd} and E_{pr} were normalized to C_{cr} [Tables 2 and 3].

BMD of Cd exposure derived from E_{pro} and eGFR endpoints

By BMD modeling of E_{pro}/E_{cr} and E_{Cd}/E_{cr} [Figure 2], an exposure level of Cd at E_{Cd}/E_{cr} 0.0536 µg/g creatinine was the level that produced a negligible effect on protein reabsorption by kidney tubules. By the definition of BMR at 5%[33], this Cd exposure level of 0.0536 µg/g creatinine was the NOAEL for a significant increase in protein excretion. The curves for $E_{pro}/E_{cr}/E_{Cd}/E_{cr}$ pairs, in the order of highest to lowest model weights,

Table 3. Effects of Cd exposure on the POR for low eGFR

Independent variables/factors	Low eGFR[a]			
	POR	95%CI		*P*
		Lower	Upper	
Model A				
Age, years	1.121	1.080	1.165	< 0.001
$Log_{10}[(E_{Cd}/E_{cr}) \times 10^3]$, μg/g creatinine	2.638	0.969	7.182	0.058
Gender	1.082	0.490	2.390	0.845
Smoking	1.425	0.596	3.406	0.426
Hypertension	2.211	1.017	4.805	0.045
Model B				
Age, years	1.118	1.073	1.165	< 0.001
$Log_{10}[(E_{Cd}/C_{cr}) \times 10^5]$, μg/ L filtrate	12.24	3.729	40.20	< 0.001
Gender	0.802	0.346	1.861	0.608
Smoking	1.335	0.546	3.262	0.527
Hypertension	2.734	1.204	6.207	0.016

[a]Low eGFR was defined as eGFR ≤ 60 mL/min/1.73 m^2.For all tests, *P*-values ≤ 0.05 indicate a statistical significance. Cd: Cadmium; POR: prevalence odds ratio; eGFR: estimated glomerular filtration rate; CI: confidence interval.

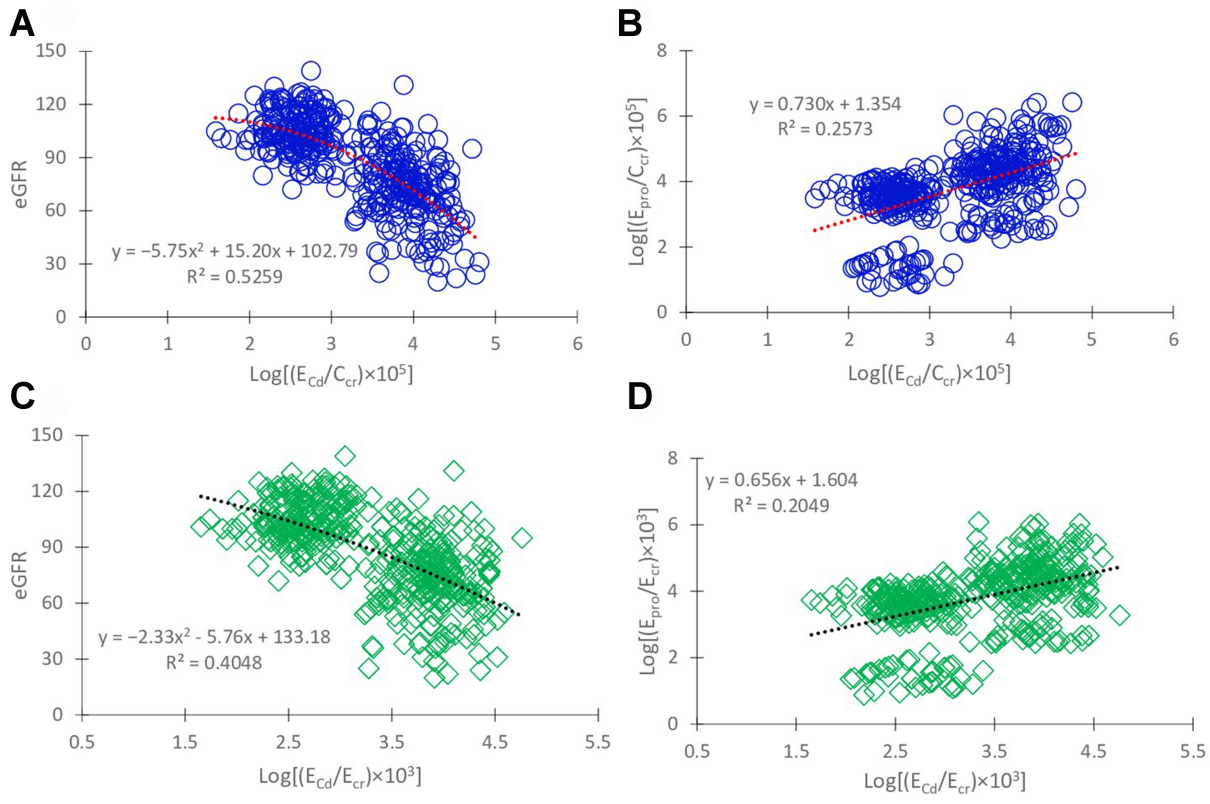
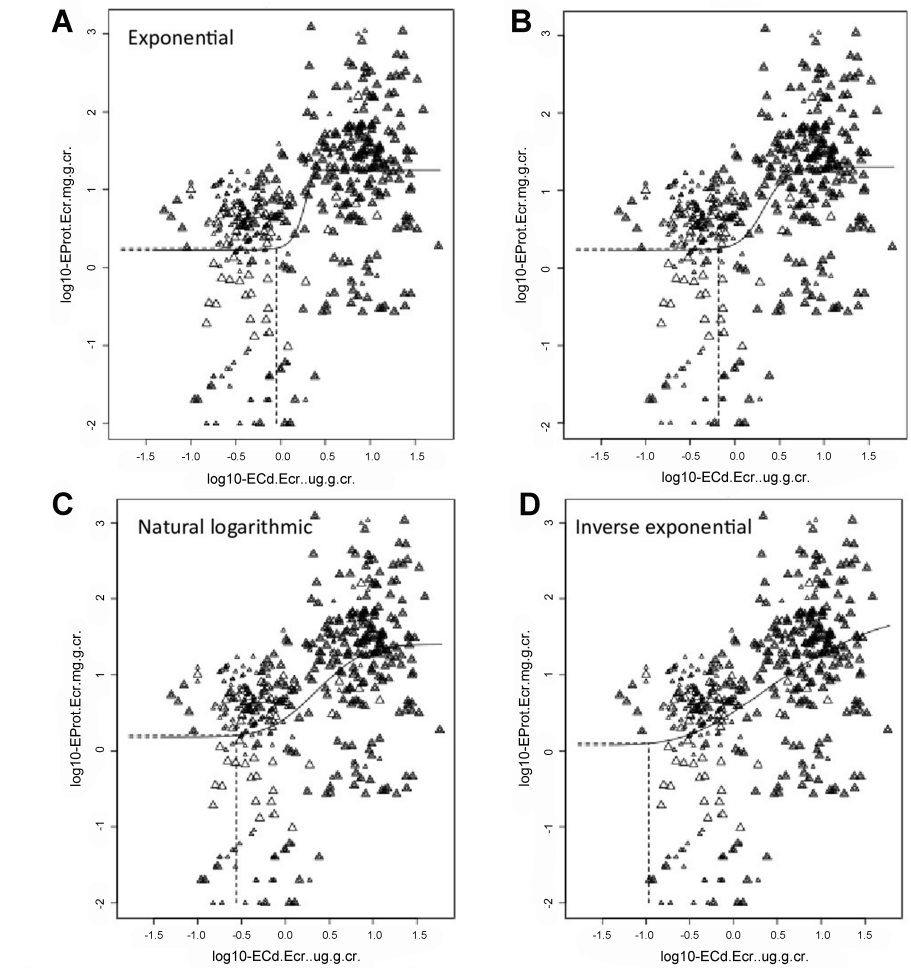


Figure 1. Dose-response relationships of eGFR and protein excretion rate with Cd excretion rate. Scatterplots relate (A) eGFR reduction and (B) $log[(E_{pro}/E_{cr}) \times 10^3]$ to $log[(E_{Cd}/E_{cr}) \times 10^3]$ in all subjects. Scatterplots relate (C) eGFR reduction and (D) $log[(E_{pro}/C_{cr}) \times 10^5]$ to $log[(E_{Cd}/C_{cr}) \times 10^5]$ in all subjects. Coefficients of determination (R^2) are provided. In each graph, the line represents mean regression values. eGFR: Estimated glomerular filtration rate; Cd: cadmium.



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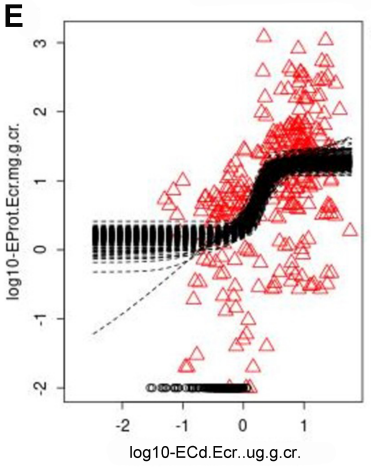

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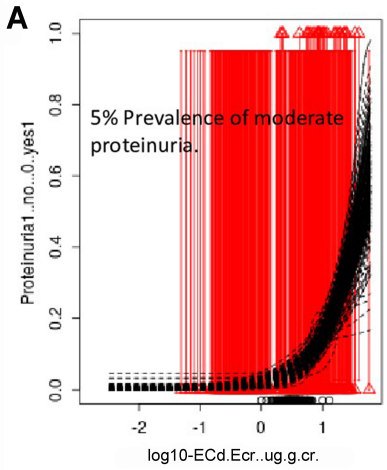
Dose-response model	Weight
Exponential	0.6840
Hill	0.2794
Natural logarithmic	0.0386
Inverse exponential	0.0017

G

5% Increase in protein excretion	E_{Cd}/E_{cr}, µg/ g creatinine		
	BMDL	BMDU	BMDU/BMDL ratio
Males	0.0212	0.757	35.7
Females	0.0226	0.913	40.4
All subjects	0.0536	0.872	16.3

Figure 2. BMDL and BMDU of E_{Cd}/E_{cr} producing a 5% increase in protein excretion. BMDL and BMDU of the 95%CI of BMD with a 5% increment of protein excretion were based on (A) exponential, (B) Hill, (C) natural logarithmic and (D) inverse exponential dose-response models. (E-G) BMDL and BMDU values were obtained by bootstrap model weighting and averaging with 200 repeats. BMDL: Benchmark dose lower; BMDU: benchmark dose upper; CI: confidence interval.

were exponential model (0.6840), Hill model (0.2794), natural logarithmic model (0.0386), and inverse exponential model (0.0017).



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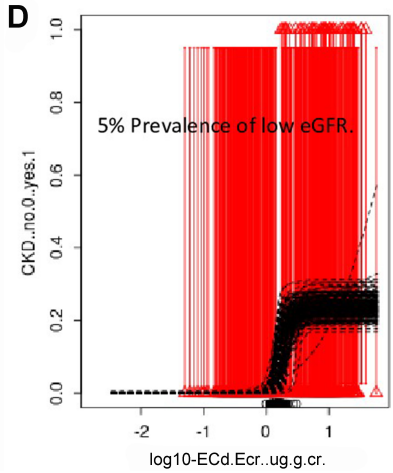
Dose-response model	Weight
Logarithmic probability	0.3501
Hill	0.1482
Logarithmic logistic	0.1452
Weibull	0.1003
Gamma	0.0935
Exponential	0.0838
Two-stage	0.0789

C

5% Prevalence of moderate proteinuria	E_{Cd}/C_{cr}, µg/ L g creatinine		
	$BMDL_5$	$BMDU_5$	BMDU/BMDL ratio
Males	2.07	5.96	2.88
Females	1.80	5.98	3.32
All subjects	1.86	5.72	3.08



E

Dose-response model	Weight
Exponential	0.8740
Hill	0.1231
Logarithmic probability	0.0017
Logarithmic logistic	6×10^{-4}
Gamma	3×10^{-4}
Weibull	4×10^{-4}
Two-stage	1×10^{-4}

F

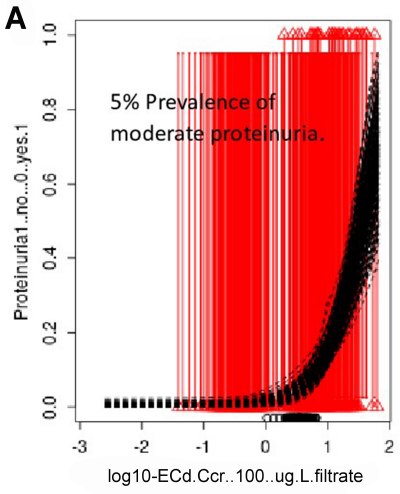
5% Prevalence of low eGFR	E_{Cd}/E_{cr}, µg/ g creatinine		
	$BMDL_5$	$BMDU_5$	BMDU/BMDL ratio
Males	1.26	2.37	1.88
Females	1.26	2.12	1.68
All subjects	1.19	1.92	1.61

Figure 3. $BMDL_5$ values of E_{Cd}/E_{cr} for proteinuria and low eGFR. Bootstrap model weighting and averaging of BMDL and BMDU bounds of the 95%CI of BMD for (A-C) 5% prevalence of proteinuria and (D-F) 5% prevalence of low eGFR. $BMDL_5$ and $BMDU_5$ values of E_{Cd}/E_{cr} were based on two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential and Hill dose-response models. BMDL: benchmark dose lower; eGFR: estimated glomerular filtration rate; BMDU: benchmark dose upper; CI: confidence interval.

BMD modeling of the prevalence of moderate proteinuria [Figure 3] indicates that an exposure level of Cd at E_{Cd}/E_{cr} 1.86 µg/g creatinine was the level at which 5% of the population had moderate proteinuria [Figure 3A-C]. By the definition of $BMDL_5$[33], the threshold of the Cd effect, based on proteinuria prevalence data, was 1.86 µg/g creatinine.

In the BMD modeling of the prevalence of CKD, defined as eGFR ≤ 60 mL/min/1.73 m^2 [Figure 3D-F], an exposure level of Cd at E_{Cd}/E_{cr} 1.19 µg/g creatinine was the level producing 5% prevalence of CKD. By the $BMDL_5$ definition[33], the threshold of the Cd effect on CKD risk was 1.19 µg/g creatinine. This figure was 36% lower compared to a proteinuria endpoint, thereby suggesting eGFR was more sensitive to Cd than E_{pro}.

Figure 4 provides results of BMD modeling of C_{cr}-normalized data, where exposure levels of Cd at E_{Cd}/C_{cr} 0.0224 and 0.0152 µg/L filtrate were the levels resulting in 5% prevalences of proteinuria and 5% prevalences of CKD, respectively. Like E_{cr} normalized data, the eGFR endpoint appeared to be more sensitive than the proteinuria: the $BMDL_5$ value of E_{Cd}/C_{cr} for low eGFR was 32% lower than the $BMDL_5$ value of E_{Cd}/C_{cr} for proteinuria.

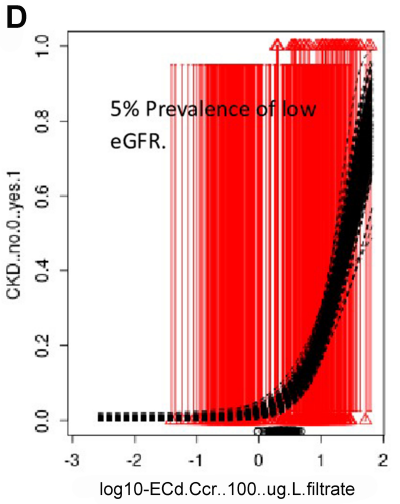


B

Dose-response model	Weight
Logarithmic probability	0.2326
Hill	0.1591
Logarithmic logistic	0.1439
Two-stage	0.1167
Weibull	0.1167
Gamma	0.1178
Exponential	0.1132

C

5% Prevalence of moderate proteinuria	E_{Cd}/C_{cr}, µg/ L filtrate		
	$BMDL_5$	$BMDU_5$	BMDU/BMDL ratio
Males	0.0199	0.0584	2.93
Females	0.0225	0.0560	2.49
All subjects	0.0224	0.0536	2.39



E

Dose-response model	Weight
Two-stage	0.1657
Weibull	0.1561
Gamma	0.1561
Logarithmic probability	0.1412
Hill	0.1412
Exponential	0.1252
Logarithmic logistic	0.1145

F

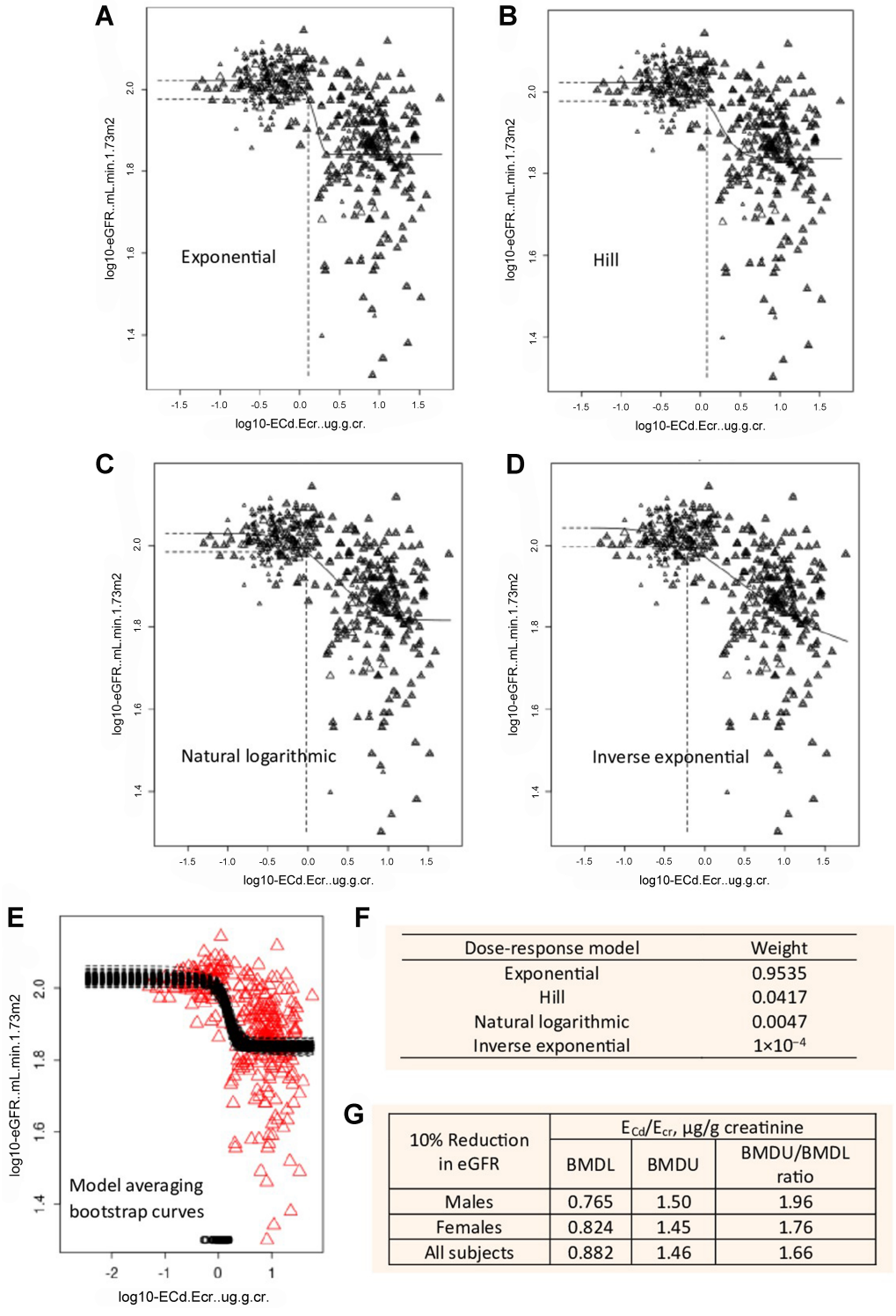
5% Prevalence of low eGFR	E_{Cd}/C_{cr}, µg/ L filtrate		
	$BMDL_5$	$BMDU_5$	BMDU/BMDL ratio
Males	0.0167	0.0457	2.74
Females	0.0168	0.0430	2.56
All subjects	0.0152	0.0378	2.49

Figure 4. $BMDL_5$ values of E_{Cd}/C_{cr} for proteinuria and low eGFR. Bootstrap model weighting and averaging of BMDL and BMDU bounds of the 95%CI of BMD for (A-C) 5% prevalence of protinuria and (D-F) 5% prevalence of low eGFR. BMDL and BMDU values of E_{Cd}/C_{cr} were based on two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential and Hill dose-response models. BMDL: Benchmark dose lower; eGFR: estimated glomerular filtration rate; BMDU: benchmark dose upper; CI: confidence interval.

Comparing BMD values of E_{Cd}/E_{cr} *vs.* E_{Cd}/C_{cr} producing a 10% reduction in eGFR

Given that eGFR is a clinically relevant parameter and a diagnostic criterion of CKD, the results discussed above indicate the potential utility of eGFR in defining Cd exposure limits. Thus, additional BMD dose-response models for E_{Cd} *vs.* eGFR were generated and analyzed. As data in Figure 5 indicate, E_{Cd}/E_{cr} of 0.8820 µg/g creatinine was found to be the level at which there was a 10% reduction in eGFR values. The eGFR/E_{Cd}/E_{cr} curves fit mostly the exponential model (0.9535), followed by Hill model (0.0417) and natural logarithmic model (0.0047).

In an equivalent BMD model of eGFR and E_{Cd}/C_{cr} [Figure 6], E_{Cd}/C_{cr} of 0.927 µg/L filtrate was found to induce a 10% reduction in eGFR. The dose-response curve for eGFR *vs.* E_{Cd}/C_{cr} totally fits the exponential model (1.0). This exponential dose-response curve implies that even a slight increase in E_{Cd}/C_{cr} can result in a significant fall in eGFR, thereby suggesting eGFR to be highly sensitive to Cd.



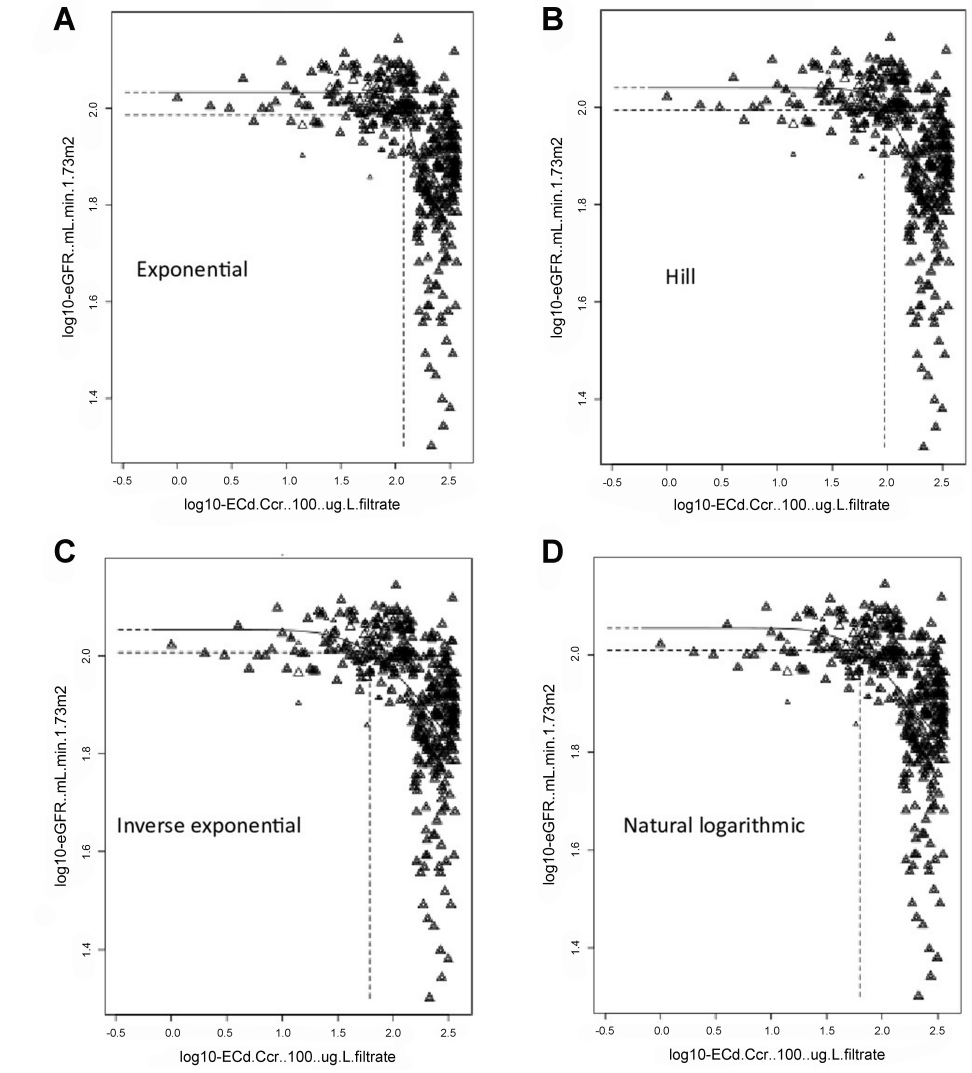
F

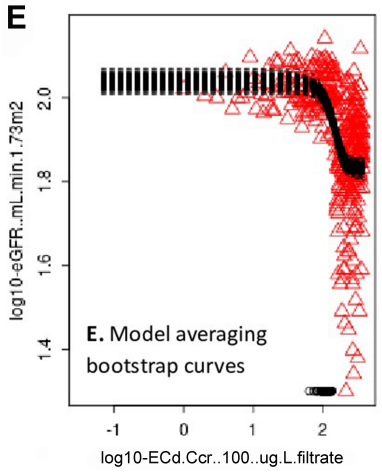
Dose-response model	Weight
Exponential	0.9535
Hill	0.0417
Natural logarithmic	0.0047
Inverse exponential	1×10^{-4}

G

10% Reduction in eGFR	E_{Cd}/E_{cr}, µg/g creatinine		
	BMDL	BMDU	BMDU/BMDL ratio
Males	0.765	1.50	1.96
Females	0.824	1.45	1.76
All subjects	0.882	1.46	1.66

Figure 5. BMDL and BMDU of E_{Cd}/E_{cr} producing a 10% reduction in eGFR. BMDL and BMDU of the 95%CI of BMD with a 10% reduction in eGFR were based on (A) exponential, (B) Hill, (C) natural logarithmic and (D) inverse exponential dose-response models. (E-G) BMDL and BMDU values were obtained by bootstrap model weighting and averaging with 200 repeats. BMDL: Benchmark dose lower; BMDU: benchmark dose upper; eGFR: estimated glomerular filtration rate; CI: confidence interval.





F

Dose-response model	Weight
Exponential	1.0
Hill	0
Inverse exponential	0
Natural logarithmic	0

G

10% Reduction in eGFR	E_{Cd}/C_{cr}, µg/ L filtrate		
	BMDL	BMDU	BMDU/BMDL ratio
Males	0.901	1.28	1.42
Females	0.898	1.29	1.44
All subjects	0.927	1.27	1.37

Figure 6. BMDL and BMDU of E_{Cd}/C_{cr} producing a 10% reduction in eGFR. BMDL and BMDU bounds of the 95%CI of BMD with a 10% reduction in eGFR were based on (A) exponential, (B) Hill, (C) inverse exponential and (D) natural logarithmic dose-response models. (E-G) BMDL and BMDU values were obtained by bootstrap model weighting and averaging with 200 repeats. BMDL: Benchmark dose lower; BMDU: benchmark dose upper; eGFR: estimated glomerular filtration rate; CI: confidence interval.

BMDL10/BMDU10 values for proteinuria and CKD prevalence data

Table 4 provides data on Cd exposure levels, measured as E_{Cd}/E_{cr} and E_{Cd}/C_{cr}, that resulted in a 10% prevalence of moderate proteinuria and a 10% prevalence of CKD. Respective E_{Cd}/E_{cr} values at which 10% of the population had proteinuria and 10% had CKD were 4.7 and 1.35 μg/g creatinine. The corresponding E_{Cd}/C_{cr} were 0.0486 and 0.0324 μg/L filtrate. Thus, CKD (low eGFR) appeared to be more sensitive to Cd than proteinuria. This eGFR is a suitable endpoint from which Cd exposure limits are calculated.

Table 5 provides data on Cd exposure levels, measured as E_{Cd}/E_{cr} and E_{Cd}/C_{cr}, that resulted in 5% and 10% prevalence rates of severe proteinuria, respectively. The % of severe proteinuria rose from 5% to 10% as E_{Cd}/E_{cr} rose by 59% (from 2.30 to 5.67 μg/g creatinine). In comparison, the % of severe proteinuria also increased from 5% to 10% as E_{Cd}/C_{cr} rose by 44% (from 0.0314 to 0.0562 μg/L filtrate). This indicates that a smaller increase in E_{Cd}/C_{cr} than in E_{Cd}/E_{cr} produces the same effect on the prevalence of severe proteinuria. For a more precise risk assessment, C_{cr} normalization should be adopted.

Comparing the existing dietary exposure limits for Cd

Using the $E_{\beta 2M}/E_{cr} \geq 300$ μg/g creatinine as a toxicity endpoint, JECFA assigned a provisional tolerable weekly intake (PTWI) level for Cd at 7 μg per kg body weight per week[4]. Later, the PTWI was amended to a tolerable monthly intake (TMI) of 25 μg per kg body weight per month (0.83 μg per kg body weight per day), and E_{Cd}/E_{cr} of 5.24 μg/g creatinine was assigned as a threshold level[4]. Notably, however, data in Table 5 indicate that at E_{Cd}/E_{cr} of 5.67 μg/g creatinine, the population prevalence of severe proteinuria due to Cd was as high as 10%. This exceeded the 5% prevalence acceptable for any environment-related disease.

The EFSA's tolerable exposure level for Cd was 0.36 μg/kg body weight per day, and a threshold level was 1 μg/g creatinine after a safety margin was included[5,6]. In comparison, a toxicological risk analysis of Chinese population data suggested a tolerable dietary Cd exposure to be 0.28 μg/kg body weight per day or 16.8 μg/day for a 60 kg person[42] and E_{Cd} of 3.07 μg/g creatinine was found to be a threshold level[42]. A tolerable dietary Cd exposure level and its toxicity threshold level computed from Chinese data both differed from the EFSA's and JECFA's figures, although all these assessments employed the same β_2M endpoint. It is noteworthy, however, that health risk assessment for Cd in most countries employs the higher JECFA guidelines. Of further note, BMDL values of urinary Cd were also derived from urinary N-acetyl-β-D-glucosaminidase, a marker of kidney damage[43], but they have not been translated to exposure limits.

Using French population data and bone toxicity as an endpoint, the Cd exposure limit of 0.35 μg Cd per kg body weight per day was derived, and the threshold level of E_{Cd}/E_{cr} was 0.5 μg/g creatinine[44]. In another study using the U.S. population data, Cd exposure limits were found to be between 0.21 and 0.36 μg per kg body weight per day[45]. This study from the U.S. assumed bone and kidney toxicity threshold levels to be similar (0.5 μg/g creatinine)[45]. In summary, existing dietary Cd exposure limits range between 0.21 and 0.83 μg/kg body weight per day[4-6,42,44,45]. These "safe" exposure guidelines assumed Cd excretion rates of 0.5-5.24 μg/g creatinine as the threshold levels for toxicity to kidneys, bones, or both.

Applying the BMD approach to urinary Cd excretion and diabetes prevalence data in the U.S. population, the $BMDL_5$ and $BMDL_{10}$ of E_{Cd}/E_{cr} values for diabetes were 0.198 and 0.365 μg/g creatinine, respectively[46]. These $BMDL_5$ and $BMDL_{10}$ of E_{Cd}/E_{cr} were 3.78% and 6.97% of the JECFA's threshold level of 5.24 μg/g creatinine, respectively. In the present study, the BMDL value of E_{Cd}/E_{cr} (the NOAEL equivalent of E_{Cd}/E_{cr}) was as low as 0.0536 μg/g creatinine. This figure was obtained, if a 5% increase in E_{pro} was a toxicity endpoint [Figure 2].

Table 4. BMDL and BMDU of Cd exposure producing a 10% prevalence of moderate proteinuria and 10% of CKD

Parameters	10% Prevalence of moderate proteinuria			10% Prevalence of CKD		
	$BMDL_{10}$	$BMDU_{10}$	BMDU/BMDL ratio	$BMDL_{10}$	$BMDU_{10}$	BMDU/BMDL ratio
E_{Cd}/E_{cr}, μg/g creatinine						
Males	4.41	10.2	2.31	1.36	2.64	1.94
Female	4.05	10.3	2.54	1.36	2.34	1.72
All subjects	4.47	9.5	2.13	1.35	2.26	1.67
E_{Cd}/C_{cr}, μg/L filtrate						
Males	0.0428	0.0981	2.29	0.0330	0.0710	2.15
Female	0.0442	0.0948	2.14	0.0330	0.0704	2.13
All subjects	0.0486	0.0883	1.82	0.0324	0.0614	1.90

BMDL and BMDU values of E_{Cd}/E_{cr} and E_{Cd}/C_{cr} were based on two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential and Hill dose-response models. CKD was defined as eGFR ≤ 60 mL/min/1.73m^2. BMDL: Benchmark dose lower; BMDU: benchmark dose upper; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

Table 5. BMDL and BMDU of Cd exposure producing 5% and 10% prevalence rates of severe proteinuria

Parameters	5% Prevalence of severe proteinuria			10% Prevalence of severe proteinuria		
	$BMDL_5$	$BMDU_5$	BMDU/BMDL ratio	$BMDL_{10}$	$BMDU_{10}$	BMDU/BMDL ratio
E_{Cd}/E_{cr}, μg/g creatinine						
Males	2.25	7.64	3.40	4.77	14.1	2.96
Females	2.25	6.56	2.92	5.37	13.2	2.46
All subjects	2.30	7.13	3.10	5.67	12.2	2.15
E_{Cd}/C_{cr}, μg/L filtrate						
Males	0.0236	0.0741	3.14	0.0512	0.124	2.42
Females	0.0268	0.0718	2.68	0.0527	0.121	2.30
All subjects	0.0314	0.0741	2.36	0.0562	0.114	2.03

BMDL and BMDU values of E_{Cd}/E_{cr} and E_{Cd}/C_{cr} were based on two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential and Hill dose-response models. BMDL: Benchmark dose lower; BMDU: benchmark dose upper; Cd: cadmium.

Strength, limitation, and recommendation

The strength of our study was that we were able to derive simultaneously the BMDL values of Cd excretion from two clinically relevant endpoints, proteinuria and a low eGFR. The data were obtained from subjects of varying ages and exposure levels, making them representative of the general population. The BMDL values of E_{Cd} were determined for all subjects (n = 405), males (n = 197), and females (n = 208). Additionally, we were able to identify the imprecision, which drove the dose-response relationship between eGFR and E_{Cd} to null, the phenomenon of non-differential errors, well described by Grandjean and Budtz-Jørgensen (2007)[22]. The limitations were a one-time-only assessment of Cd exposure and its effects, and its inability to determine with certainty the relative contribution of Cd from the diet and smoking to the observed outcomes.

In theory, the basic mechanism of Cd cytotoxicity should be similar across populations, as the amount of Cd causing cellular toxicity is expected to be consistent between men and women. However, when E_{Cd} was normalized to E_{cr} (E_{Cd}/E_{cr}), higher BMDL values for Cd were obtained for females compared to males. In a previous study, E_{Cd}/E_{cr} rates of 6.82 and 2.07 μg/g of creatinine were found to be BMDL values that produced a 5% reduction of eGFR in females and males, respectively[47]. The higher E_{Cd}/E_{cr} values in females are most likely due to their universally lower muscle mass and consequently lower urinary E_{cr} in women than men. As C_{cr}-normalization is unaffected by muscle mass and corrects for differences in urine dilution

and functioning nephrons[32], the BMDL values for a toxic Cd level in both sexes can be expected to be identical; the BMDL value of E_{Cd}/C_{cr} leading to a 5% reduction in eGFR was 0.0215 μg/L of filtrate for both men and women[47].

As data in Table 5 indicate, the respective $BMDL_{10}$ values of E_{Cd} that produced a 10% prevalence of severe tubular proteinuria in females and males were 5.37 and 4.77 μg/g of creatinine, if E_{Cd} and E_{pro} were normalized to E_{cr}. The corresponding values obtained from the C_{cr}-normalized data were 0.0527 and 0.0512 μg/L of filtrate in females and males, respectively. Therefore, it is recommended that Cd exposure limits be derived for the most sensitive endpoint using the BMD approach and the BMDL/BMDU values computed from C_{cr}-normalized data.

Current environmental exposure data suggest that a significant proportion of the general population is at risk of Cd toxicity. The main source of Cd exposure in non-smoking and non-occupationally exposed people is their diet. However, the current dietary exposure guidelines are not low enough to provide sufficient health protection. New health-protective exposure guidelines should be established, and public health measures should be developed to help minimize Cd contamination of food chains.

CONCLUSIONS

For the first time, a urinary Cd level as low as 0.0536 μg/g creatinine has been found to be the NOAEL equivalent for Cd. This "safe" body burden of Cd is derived from a 5% increase in protein excretion. The small difference between BMDU and BMDL (0.872/0.0536) implies a high degree of statistical certainty in the estimated values. Adjusting urinary Cd and biomarkers of kidney injury and malfunction to E_{cr} incorporates non-differential errors that bias the dose-response relationship toward the null. Adjusting urinary Cd to C_{cr} can eliminate such errors and imprecisions. Thus, dietary Cd exposure limits should be derived from the most sensitive endpoint and the BMDL/BMDU values calculated from C_{cr}-normalized data. An effective chelation therapy to remove Cd from the kidneys does not exist. Avoidance of foods containing high Cd and smoking cessation are commonsense preventive measures.

DECLARATIONS

Authors' contributions

Conception and design of the study: Satarug S, Vesey DA
BMD modeling and interpretation: Đorđević AB, Satarug S
Data acquisition and analysis: Satarug S
Administrative, technical, and material support: Vesey DA

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The present study involved a retrospective analysis of data from Thai population cohorts that were

conducted following the principles outlined in the Declaration of Helsinki. Informed consent to participate in the study was obtained from participants. The Institutional Ethical Committees of Chulalongkorn University, Chiang Mai University and the Mae Sot Hospital approved the study protocol (Approval No. 142/2544, 5 October 2001).

Consent for publication

Not applicable.

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