Article

The NOAEL Equivalent of Cumulative Body Burden of Cadmium: Focus on Proteinuria

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Abstract

Long-term exposure to even low levels of the metal pollutant cadmium (Cd), increases the risk of kidney malfunction and nephron destruction, causing proteinuria and the estimated glomerular filtration rate to fall below 60 mL/min/1.73 m^2 (low eGFR). Proteinuria is a hallmark of kidney disease and its progression toward kidney failure, but has never been applied to Cd health risk assessment. Here, we analyzed data from 405 apparently healthy Thai Nationals, of which 12.6% had low eGFR, while 16.3% and 13.5% had moderate and severe proteinuria, respectively. Exposure to Cd and its adverse effects were assessed by urinary excretion of Cd (E_{Cd}) and total protein (E_{pro}), normalized

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to creatinine clearance (C_{cr}) and creatinine excretion (E_{cr}). The risks of having low eGFR [POR = 12.2, $p < 0.001$] and severe proteinuria [POR = 10.4, $p = 0.001$) were increased markedly per a ten-fold increase in E_{Cd}/C_{cr}. However, due to an imprecision introduced by E_{cr}-normalization, the associations of low eGFR [POR = 2.638, $p = 0.058$] and severe proteinuria [POR =2.97, $p = 0.115$] with a ten-fold increase in E_{Cd}/E_{cr} were statistically insignificant. 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-induced proteinuria was 1.86 µg/g creatinine. The NOAEL equivalent of Cd exposure is 0.0536 µg/g creatinine if an increase in protein excretion is a critical effect.

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, health risk of dietary Cd exposure has been vastly underappreciated because such assessment relied solely on tubular proteinuria, defined as an increase in urinary excretion of the low-molecular weight protein β_2-microglobulin (β_2M) above 300 µg/g creatinine[3-5]. Based on the β_2M endpoint, a tolerable intake level of Cd was 0.83 µg/kg body weight/day (58 µg/day for a 70-kg person) and urinary Cd excretion of 5.24 µg/g creatinine was identified as the exposure level at which 5% of the population had tubular proteinuria, termed a toxicity threshold level[4]. Current evidence, however, suggests that environmental exposure, producing urinary Cd excretion of 0.27–0.32 µg/g creatinine, induced kidney damage, and decreased the estimate glomerular filtration rate to below 60 mL/min/1.73 m^2, termed low eGFR[6,7]. 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 chronic kidney disease (CKD)[8]. These finding cast serious doubt on the utility of the

β_2M endpoint as a basis to define dietary exposure limits and a nephrotoxicity threshold level of Cd.

Reductions in eGFR after Cd exposure are irreversible, and it is likely to decline even further if exposure persists[2,7]. Also, there is compelling evidence that a rise of β_2M above 300 µg/g creatinine is indicative of severe kidney pathologies, including a fall of eGFR at high rates[9,10]. Thus, it is inappropriate to employ the β_2M endpoint as a criterion to judge the nephrotoxicity of Cd, and to define a toxicity threshold level[1]. Like low eGFR, an increased risk of proteinuria has been linked to low environmental Cd exposure in the general populations[11,12]. Proteinuria is a key biomarker of kidney disease and its progression to end-stage kidney disease (eGFR <15 mL/min/1.73m^2)[13-15], when dialysis or a kidney transplant is required to survive, an immense heath care cost.

The present study has three major aims. First aim, is to explore dose-response relationship between environmental Cd exposure and urinary excretion of total protein (E_{pro}). Second aim, is to define the benchmark dose limit (BMDL) of Cd excretion using E_{pro} as a biomarker of Cd effect. The BMDL value derived at 5% benchmark response (BMR) is now a replacement of no-observed-adverse effect level (NOAEL), referred to the highest experimental dose level for which the response does not significantly differ from the response in the control group[16,17]. For comparison, a dose-response relationship between Cd and eGFR reductions were determined simultaneously. Third aim, is to address "unrecognized" imprecision in toxicological assessment of dietary Cd exposure and its effects on kidneys, especially, when the excretion of Cd and urinary biomarkers of adverse effects on kidneys, such as E_{Cd} and E_{pro}, are adjusted customarily to creatinine excretion (E_{cr}) as E_{Cd}/E_{cr} and E_{pro}/E_{cr}. These imprecisions or non-differential errors tend to bias the dose-response relationship toward null[18].

EXPERIMENTAL

Study Design

We prospectively analyzed data from subjects, enlisted from large Thai population-based cohorts that were conducted following the principles outlined in the Declaration of

Helsinki[19-21]. The inclusion and exclusion criterion for cohort participants included apparently healthy, and resided at their current addresses for 30 years or longer. Exclusion criteria were pregnancy, breast-feeding, a history of metal work, and a hospital record or physician's diagnosis of an advanced chronic disease. Details of study objectives, study procedures, benefits, and potential risks were provided to all subjects, who all gave informed consent prior to participation.

Measurement of Exposure and Adverse Effects

We used urinary excretion of Cd (E_{Cd}) as indicative of a cumulative long-term exposure to Cd or body burden of Cd[19-22]. Urinary excretion of total protein (E_{pro}) and the estimated glomerular filtration rate (eGFR) were used to assess the impact of Cd exposure on clinically relevant kidney function measures[21,23]. For these measurements, samples of urine, whole blood, and plasma were collected from all participants after overnight fast, and were stored at -80 ºC for later analysis. Plasma samples were assayed the concentration of creatinine, while urine samples were assayed for the concentrations of creatinine, Cd, and total protein, detailed in previous reports[19-22].

The eGFR was computed with equations of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[24,25]. 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[26]. For dichotomous comparisons, CKD was defined as eGFR $\leq$ 60 mL/min/1.73 m^2[26]. Moderate and severe proteinuria were defined as $E_{pro}/E_{cr} \geq 100$ and 150 mg/g creatinine, respectively[15].

Normalization of cadmium 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[27]. This C_{cr}-normalization corrects for urine dilution and the number of functioning nephrons simultaneously, and it is not influenced by muscle mass.

The urinary excretion of x (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 creatinine excretion among people. Consequently, a clear dose-response relationship cannot be established[18].

Benchmark Dose Computation and Definitions

We employed the web-based PROAST software version 70.1 (https://proastweb.rivm.nl) to identify the lower and upper bounds of the 95% confidence interval of BMD, designated as BMDL and BMDU, respectively[28-31]. For continuous data, the BMDL computed at 5% benchmark dose response (BMR) represents the NOAEL equivalent or the level of exposure below which an adverse effect is negligible[28,29]. For dichotomous data, the BMDL/BMDU computed at 5% and 10% prevalence rates are designated as $BMDL_5$/$BMDU_5$ and $BMDL_{10}$/$BMDU_{10}$, respectively. $BMDL_5$ and $BMDL_{10}$ represent exposure levels at which the prevalence of an adverse effect in the population to be 5% and 10%, respectively[30]. $BMDL_5$ represents a threshold level which defined as an exposure level at which 5% of the general population shows evidence of an adverse effect.

The BMDL/BMDU values of E_{Cd} computed from E_{pro} and eGFR were based on exponential, Hill, inverse exponential, and natural logarithmic dose—response models before subjecting to 200-repeat bootstrap model averaging.

The $BMDL_5$/$BMDU_5$ and $BMDL_{10}$/$BMDU_{10}$ values of E_{Cd} for low eGFR and proteinuria prevalences were based on two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential and Hill dose—response models before subjecting to 200-repeat bootstrap model averaging.

Statistical Analysis

Data were analyzed with 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. The Pearson's chi-squared test was used to determine male-female differences in percentages and prevalences of categorical variables such as 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. Multiple linear regression was conducted to identify determinants of reductions in eGFR and increment of E_{pro}. Logistic regression was conducted to evaluate effects of E_{Cd} on the prevalence odds ratio (POR) for low eGFR and proteinuria with adjustment for potential confounders (age, smoking, gender, hypertension). For all tests, *p*-values ≤ 0.05 were considered to indicate statistical significance.

RESULTS AND DISCUSSION

Study Participants

From a total of 2000 cohort participants, 405 subjects were selected, of which 190 and 215 subjects resided in Bangkok and the Mae Sot district of Tak Province, respectively (Table 1). The overall mean age was 44.6 years, ranging between 16 to 97 years. 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. According to a previous reverse dosimetry modelling of urinary Cd excretion data[19], the Bangkok group was the representative of environmental exposure to low levels of Cd. The Mae Sot group was the representative of moderate-to-high environmental Cd exposure scenarios according to modelling data as well as reported levels environmental Cd contamination and health surveys, detailed below[21,22].

Table 1. Characteristics of study subjects drawn 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 rang, 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)
$(E_{pro}/C_{cr}) \times 100$, µg/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

n, number of subjects; eGFR, estimated glomerular filtration rate; cr, creatinine; pro, protein; Cd, cadmium; Ccr, creatinine clearance; $[x]_p$, plasma concentration of x; $[x]_u$ = urine concentration of x. [a] Low eGFR was defined as eGFR ≤ 60 mL/min/1.73 m^2. Continuous variables are expressed as arithmetic mean and standard deviation (SD) values. For all tests, $p \leq 0.05$ identifies statistical significance, determined with the Pearson 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, §p <0.001.

The paddy soil samples 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 permissible Cd level of 0.1 mg/kg[32]. 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[33].

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} ≥200 mg/g creatinine), tubular proteinuria ($E_{\beta 2M}/E_{cr}$ ≥ 300 µg/g creatinine) and E_{Cd}/E_{cr} ≥ 2 µg/g creatinine, which were found in 32.5, 24.1, 36.1 and 66.7% of the participants[34]. In the present study, cutoff values for moderate and severe proteinuria were 100 and 150 mg/g creatinine and the overall % of low eGFR was 12.6%, while % moderate and severe proteinuria and those who smoked and had hypertension were 16.3, 13.5, 45.9 and 22.3, respectively.

Source of "unrecognized" error in health risk assessment of cadmium

To evaluate an 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 having proteinuria in any model types. 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 both were markedly increased per a 10-fold rise in E_{Cd}/C_{cr} in a type B model. Thus, E_{cr} normalization appeared to be the source of imprecision, which predisposed the dose-response relationship of E_{Cd}/E_{cr} and E_{pro}/E_{cr} to null[18].

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Table 2. Effects of cadmium exposure on the prevalence odds ratio 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
$Log_{10}[(E_{Cd}/C_{cr}) \times 10^5]$, µg/ 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

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

The imprecision of E_{cr} -normalization was also apparent in the logistic regression models of low eGFR (Table 3). Indeed, the impact E_{cr}-normalization on the dose-response relationship of E_{Cd}/E_{cr} and eGFR were even more dramatic than the E_{Cd}/E_{cr} versus E_{pro}/E_{cr} as an increase in POR for low eGFR was not statistically explained by a 10-fold increase in 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 an exposure marker Cd (E_{Cd}) to the markers of its adverse effects (E_{pro} and eGFR). As shown in Figure 1, lower coefficients of determination (R^2) and the wider differences between lower and upper bounds of 95% regression confidence intervals were evident, when E_{Cd} and E_{pro} were adjusted to E_{cr}, compared with the C_{cr}-normalized datasets.

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Table 3. Effects of cadmium exposure on the prevalence odds ratio 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	POR	Lower	Upper	p
Age, years	1.118	1.073	1.165	<0.001
$Log_{10}[(E_{Cd}/C_{cr}) \times 10^5]$, μg/ L filfrate	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

POR, prevalence odds ratio; CI, confidence interval. [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.

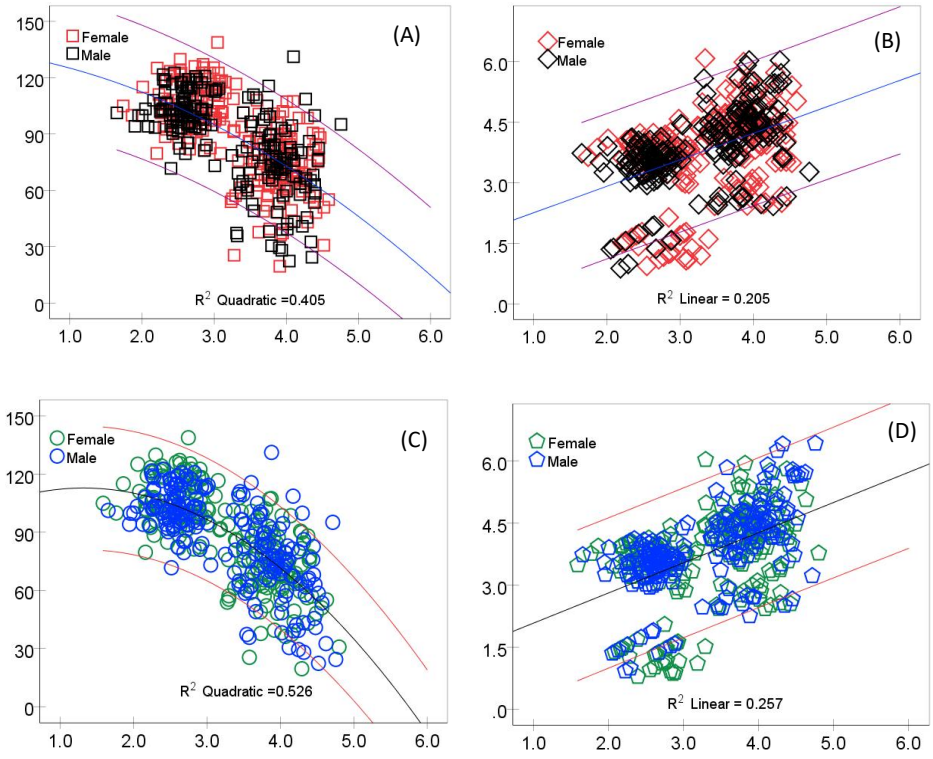

Figure 1. Dose-response relationships of cadmium excretion, eGFR and protein excretion. Scatterplots relate eGFR reduction (A) and $log[(E_{pro}/E_{cr}) \times 10^3]$ increment (B) to $log[(E_{Cd}/E_{cr}) \times 10^3]$ in women and men. Scatterplots relate eGFR reduction (C) and

log[(E_{pro}/C_{cr}) × 10^5] increment (D) to log[(E_{Cd}/C_{cr}) × 10^5] in women and men. Coefficients of determination (R^2) are provided. In each graph, the middle line represents mean regression values. The lower and upper lines represent lower and upper bounds of 95% regression confidence intervals.

A common practice of adjustment of the urinary excretion of Cd and biomarkers of its kidney effects to E_{cr} contributed to erroneous conclusions and vast underestimations of adverse effects of environmental Cd exposure. In a systemic and meta-analysis, Jalili et al. (2021) reported that an association of eGFR and urinary Cd was statistically insignificant, while the risk of proteinuria rose by 35% only, when the top category of Cd dose metrics was compared with the bottom Cd exposure category[12]. In another meta-analysis, Byber et al. (2016) concluded that Cd exposure was not associated with a progressive decline in eGFR[35]. However, in the latest systemic and meta-analysis by Doccioli et al. (2014)[6], an effect of Cd on GFR has now been confirmed. In the present study, the deleterious health effects of environmental Cd exposure have been demonstrated unambiguously, when the measures of exposure and effects (E_{Cd} and E_{pro}) were normalized to creatinine clearance (C_{cr}), discussed above (Tables 2 and 3).

BMD of cadmium exposure identified from protein excretion and GFR 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 identified as the level that had negligible effect on protein reabsorption by kidney tubules, if a 5% increase in protein excretion was a critical effect. By the definition of BMR at 5%[28], this Cd exposure level of 0.0536 µg/g creatinine was the NOAEL for an increase in protein excretion due to Cd. The curves for $E_{pro}/E_{cr}/E_{Cd}/E_{cr}$ pair, in the order of highest to lowest model weights were exponential (0.6840), Hill (0.2794), natural logarithmic (0.0386) and inverse exponential (0.0017) dose-response models.

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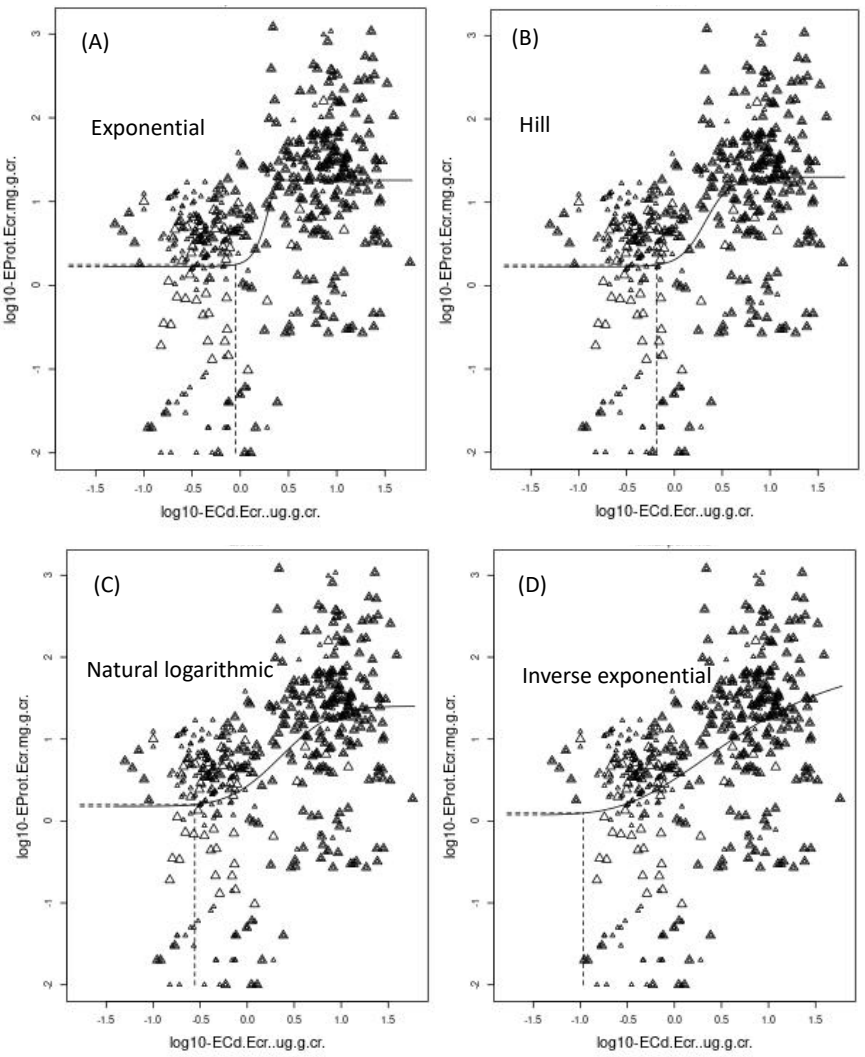
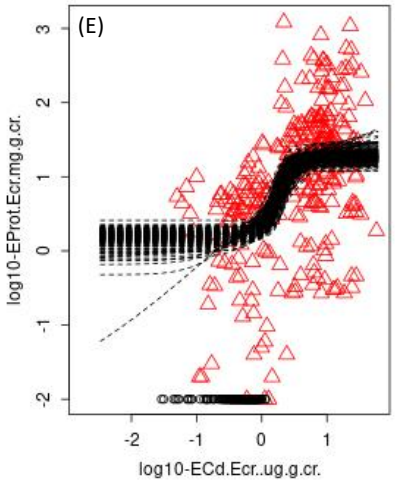




(F)

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

(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

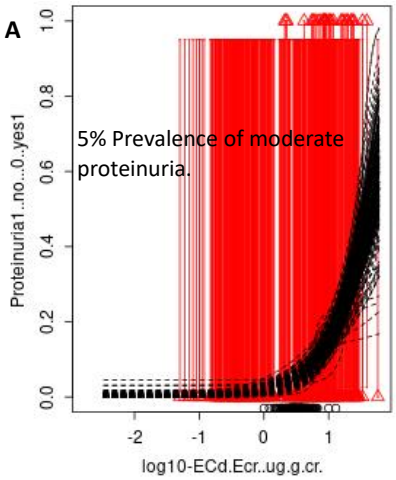
Figure 2. BMDL and BMDU of E_{Cd}/E_{cr} producing a 5% increase in protein excretion. Benchmark dose lower (BMDL) and upper bounds (BMDU) of the 95% confidence

interval of BMD with a 5% increment of protein excretion were based on exponential (A), Hill (B), natural logarithmic (C) and inverse exponential dose-response models (D). BMDL and BMDU values were obtained by bootstrap model weighting and averaging with 200 repeats (E,F,G).

BMD modeling of the prevalence data for moderate proteinuria (Figure 3) indicate 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 due to Cd exposure (Fig. 3 A,B,C) By the definition of $BMDL_5$[28], the Cd exposure level of 1.86 µg/g creatinine was the threshold of Cd effect if proteinuria was an endpoint.

In the BMD modeling of the prevalence data for CKD, defined as eGFR ≤ 60 mL/min/ 1.73 m^2(Fig. 3 D,E,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 definition of $BMDL_5$[28], this Cd exposure level of 1.19 µg/g creatinine was the threshold of Cd effect if CKD was an endpoint. This figure was 36% lower, compared to a proteinuria endpoint, thereby suggesting CKD or low eGFR was a more sensitive endpoint than the proteinuria.

A



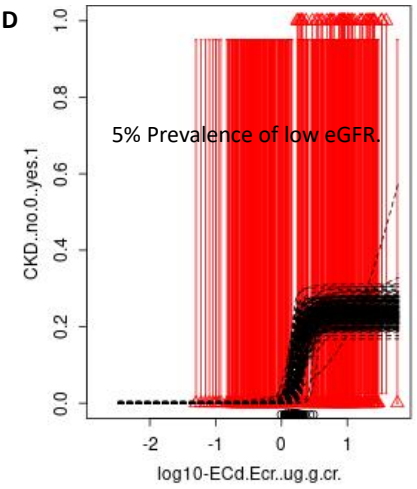
B

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

D



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 benchmark dose lower (BMDL) and upper (BMDU) bounds of the 95% confidence interval of BMD for 5% prevalence of proteinuria (A,B,C) and 5% prevalence of low eGFR (C,D,F). $BMDL_5$ 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.

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 due to Cd was 32% lower than the $BMDL_5$ value of E_{Cd}/C_{cr} for 5% proteinuria prevalence.

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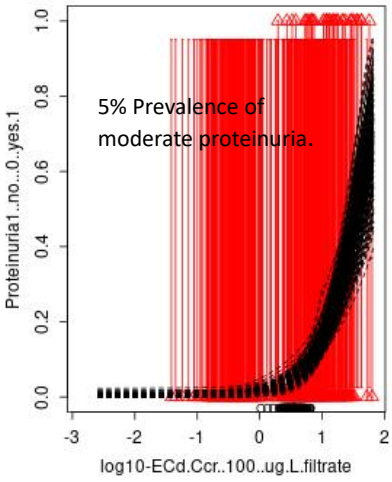
A



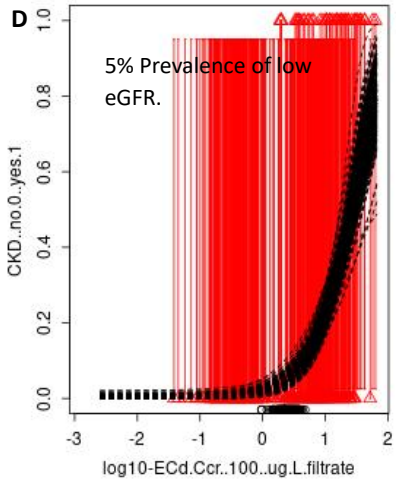
B

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

D



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 benchmark dose lower (BMDL) and upper (BMDU) bounds of the 95% confidence interval of BMD for 5% prevalence of protinuria (A,B,C) and 5% prevalence of low eGFR (D,E,F). 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.

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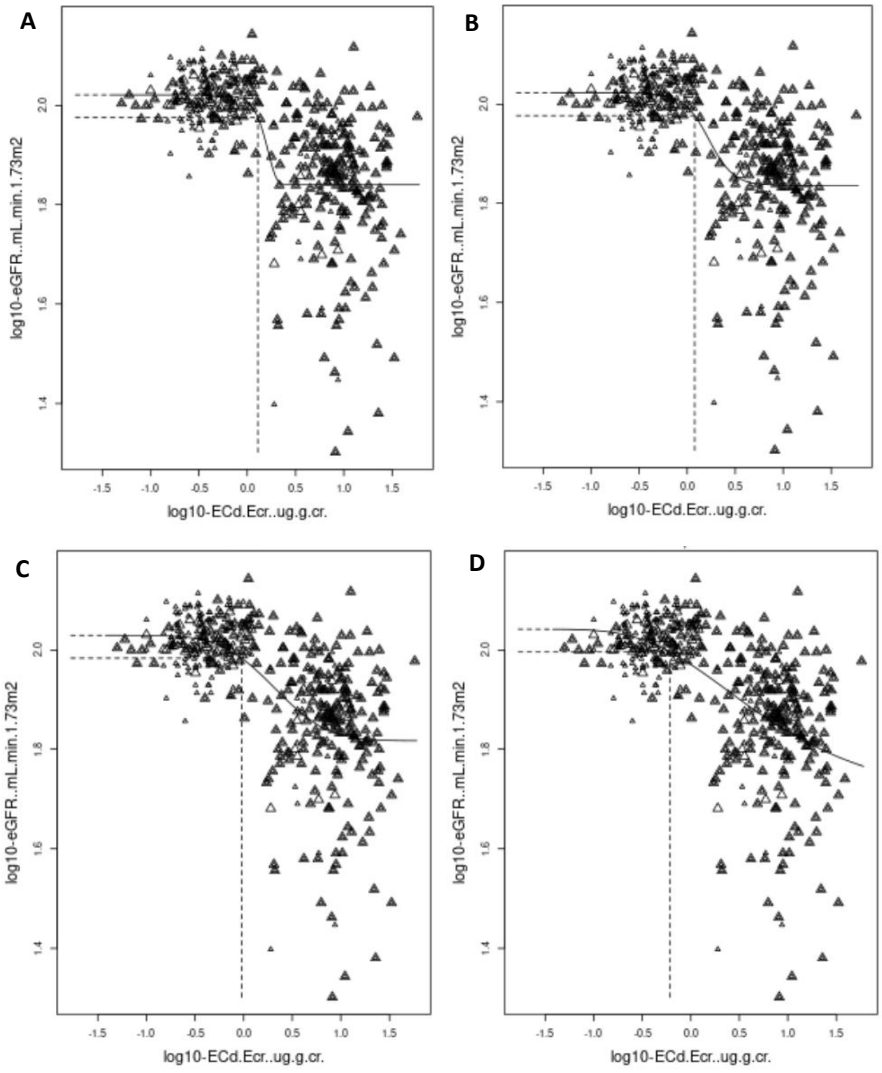
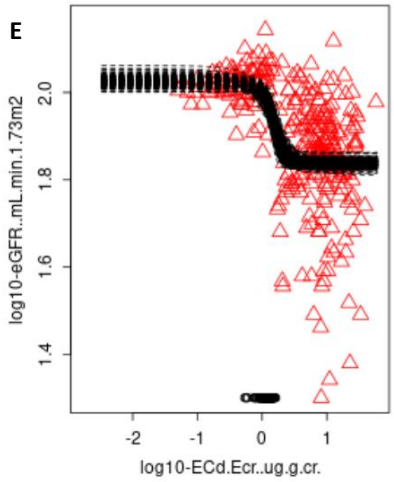
Comparing BMD values of E_{Cd}/E_{cr} versus E_{Cd}/C_{cr} producing 10% reduction in eGFR

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. In effects, additional BMD dose-response models for E_{Cd} versus eGFR were generated and analyzed. As data in Figure 5 indicate, an exposure level of Cd at E_{Cd}/E_{cr} 0.8820 µg/g creatinine was found to be the level at which there was a reduction in eGFR by 10%. The eGFR/E_{Cd}/E_{cr} curves were mostly exponential (0.9535), followed by Hill (0.0417) and natural logarithmic (0.0047) dose-response models.



E



F

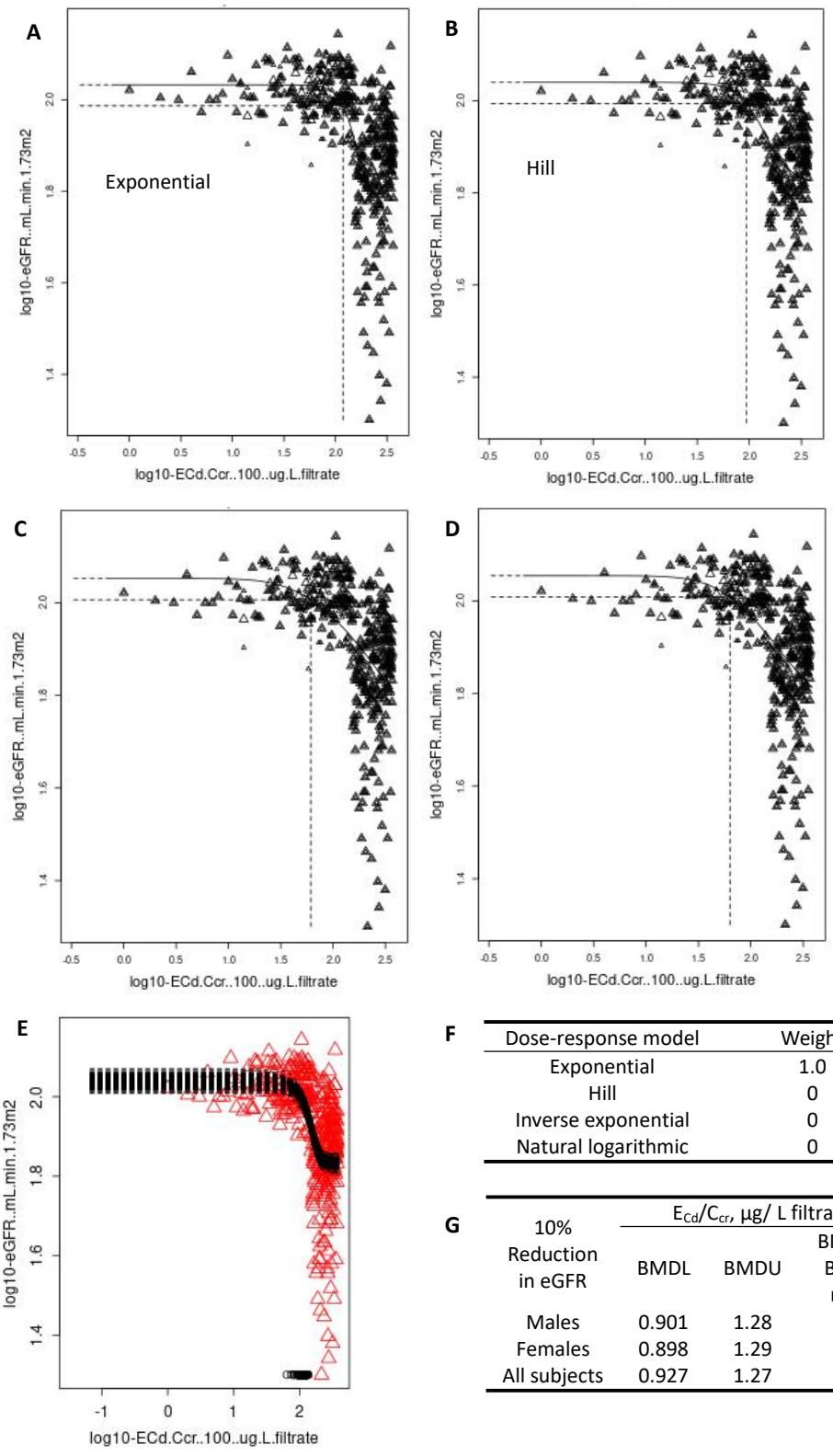
Dose-response model	Weight
Exponential	0.9535
Hill	0.0417
Natural logarithmic	0.0047
Inverse exponential	1×10^{-4}

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 10% reduction in eGFR. Benchmark dose lower (BMDL) and upper bounds (BMDU) of the 95% confidence interval of BMD with a 10% reduction in eGFR were based on exponential (A), Hill (B), natural logarithmic (C) and inverse exponential dose-response models (D). BMDL and BMDU values were obtained by bootstrap model weighting and averaging with 200 repeats (E,F,G).

In the equivalent BMD modeling of eGFR decline and E_{Cd}/C_{cr} (Figure 6), an exposure level of Cd at E_{Cd}/C_{cr} 0.927 µg/L filtrate was found to be the level induced a reduction in eGFR by 10%. The dose-response curve for eGFR versus E_{Cd}/C_{cr} was exclusively exponential (model weight = 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.



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 10% reduction in eGFR. Benchmark dose lower (BMDL) and upper (BMDU) bounds of the 95% confidence interval of BMD

with a 10% reduction in eGFR were based on exponential (A), Hill (B), inverse exponential (C) and natural logarithmic dose-response models (D). BMDL and BMDU values were obtained by bootstrap model weighting and averaging with 200 repeats (E,F,G).

BMDL10/BMDU10 values for proteinuria and CKD prevalence data

Table 4 provide data on Cd exposure levels measured as E_{Cd}/E_{cr} and E_{Cd}/C_{cr} that resulted in 10% prevalence of moderate proteinuria and 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 a more sensitive endpoint than proteinuria. This eGFR endpoint is suitable for use as a basis from which Cd exposure limits can be calcultaed.

Table 4. BMDL and BMDU of cadmium exposure producing 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 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.

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

Table 5. BMDL and BMDU of cadmium exposure producing 5% and 10% prevalences 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 two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential and Hill dose-response models.

Implications for calculating exposure limits

Using the $E_{\beta 2M}/E_{cr} \geq 300$ µg/g creatinine as a critical effect, a provisional tolerable weekly intake (PTWI) of Cd at 7 µg per kg body weight per week was derived by the Food and Agriculture Organization and World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives and Contaminants (JECFA)[4]. Later, the PTWI was amended to a tolerable monthly intake (TMI) of Cd at 25 µg per kg body weight per month, equivalent to 0.83 µg per kg body weight per day, and the E_{Cd}/E_{cr} of 5.24 µg/g creatinine was a threshold level[4]. Notably, however, data in Table 5 indicated that at E_{Cd}/E_{cr} 5.67 µg/g creatinine the prevalence of severe proteinuria in the population was as high as 10%.

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The NOAEL equivalent of a permissible Cd exposure level found in the present study was as low as 0.0536 µg/g creatinine if proteinuria was a critical effect. Thus, a safe exposure level of Cd is extremely low as such in many populations, Cd exposure levels have now exceeded the E_{Cd}/E_{cr} of 1.86 µg/g creatinine, a threshold level for proteinuria endpoint (Figure 3). In theory, to achieve health protection for more than 95% of the population, exposure limits should only be calculated from the most sensitive endpoint, which is the one with the lowest BMDL value[16-18]. Data presented herein suggested that that GFR reduction could be a sensitive endpoint from which Cd exposure limits should be calculated. Previously, the NOAEL equivalent value of E_{Cd}/C_{cr} calculated from eGFR endpoint was 0.010 µg/L filtrate, corresponding to ≈ 0.01-0.02 µg/g creatinine[36]. These figures were about half of the NOAEL calculated from E_{pro} as an endpoint (Figure 2).

CONCLUSIONS

For the first time, the NOAEL equivalent of a permissible Cd exposure level is found to be 0.0536 µg/g creatinine. This NOAEL value is based on proteinuria endpoint. The narrow difference between BMDU and BMDL (0.872/0.0536) implies a high degree of statistical certainty of the identified NOAEL equivalent. However, the practice of adjusting the excretion rates of Cd and biomarkers of kidney injury and malfunction to creatinine excretion (E_{cr}) incorporates non-differential errors that bias the dose-response relationship toward null. Such errors can be eliminated if the excretion rates are normalized to creatinine clearance (C_{cr}). Thus, dietary Cd exposure limits should be derived from the most sensitive endpoint and the BMDL/BMDU values are calculated from C_{cr}- normalized data. At present, no effective chelation therapy exists for the removal of Cd from kidneys. Commonsense therapeutic measures include avoidance of foods containing high Cd and smoking cessation.

DECLARATIONS

Authors' contributions

Conception and design of the study: Satarug S and Vesey DA

BMD modeling and interpretation: Đorđević AB and Satarug S

Data acquisition and analysis: Satarug S

Administrative, technical, and material support: Vesey DA

Availability of data and materials

Not applicable.

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. An informed consent to participate in the study were 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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