Review

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Challenges in Toxicological Risk Assessment of Environmental Cadmium Exposure

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Abstract: Dietary exposure to a high-dose cadmium (Cd) ≥ 100 μg/day for at least 50 years or a lifetime intake of Cd ≥ 1 g causes severe damage to kidneys and bones. Alarmingly, however, exposure to a dose of Cd between 10 and 15 μg/day increases worldwide prevalence of non-communicable diseases, including chronic kidney disease (CKD), non-alcoholic fatty liver disease, fragile bones, diabetes, and cancer. Because such a low-dose Cd exposure, results in urinary Cd excretion rates < 1 μg/g creatinine, it has cast considerable doubt on a "tolerable" Cd exposure of 58 μg/day for a 70 kg person, while questioning a threshold level at urinary Cd excretion rate at 5.24 μg/g creatinine. The present review addresses many unmet challenges in a threshold-based risk assessment for Cd. Special emphasis is given to the benchmark dose (BMD) methodology to estimate the Cd exposure limit that aligns with a no-observed adverse effect level (NOAEL). Reported results of BMDL modeling of Cd exposure levels using different nephrotoxicity endpoints are summarized to identify the most sensitive sign on which exposure guidelines should be based. It also aims to demonstrate that a health-protective exposure guideline for Cd should employ the most recent scientific research data, and the dose-response curves, constructed from an unbiased exposure indicator, and clinically relevant adverse effects such as proteinuria and a decrease in estimated glomerular filtration rate. These are signs of developing CKD and its progression to end stage, when dialysis or a kidney transplant is required for survival.

Keywords: cadmium; benchmark dose; dose-response; eGFR; NOAEL; threshold-based risk assessment

1. Introduction

The conventional toxicological risk assessment for any health hazardous substance is reliant on dose-response curves, constructed from series of experimentation, which typically involves daily administration of 4-5 different doses for 90 days, referred to as sub-chronic exposure conditions in humans [1–5]. The dose-response curves are used to define the lower bound "no observed adverse effect level" (NOAEL) and the upper bound "lowest observed adverse effect level" (LOAEL) from which a point of departure (POD) is established. Subsequently, the POD value forms a basis to estimate health guidance values, which presently are known as a minimal risk level (MRL), a toxicological reference value (TRV), tolerable weekly intake (TWI), tolerable monthly intake (TMI) and a reference dose (RfD) [1–6]. These different terms create unnecessary confusions and stumble blocks.

The NOAEL value derived from experimental animal dosing regimens is the highest dose tested that produces a statistically insignificant effect, compared to controls. In some instances, this NOAEL value is translated to benchmark dose (BMD) with an inclusion of uncertainty factors to compensate for species differences and human variability [1]. Notably the BMD approach has now been applied to human population data from which to the benchmark dose limit (BMDL) value is identified and employed as a replacement of the experimental NOAEL [1–5]. This BMDL methodology overcomes

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the shortcomings of traditional dosing experiments, which requires a compensation for animal-to-human extrapolation.

The POD-based health guidance values; MRL, TRV, TWI, TMI, and RfD all rely on the premise that a threshold level of exposure exists, below which an adverse effect can be discernable [1]. In effect, an exposure level derived from the most sensitive endpoint would be protective against all other adverse effects [1]. A notable limitation is that threshold-based risk assessment is not applicable to cancer endpoints [1,5]. An evaluation of the carcinogenic risk of a suspected entity involves different dosing regimens and an observation over a life-span such as a two-year rodent/murine bioassay [7–9].

The present review has its focus on a metal contaminant cadmium (Cd), which is found in most foodstuffs [10–13], tobacco smoke, and airborne particle pollution [14,15]. An extremely slow excretion rate means that Cd is retained within cells of nearly all tissues and organs in the body [16,17]. Concerningly, Cd is a designated cancer-causing agent in humans; epidemiological studies have linked increased risks of developing cancer in the lung, kidney, pancreas, breast, and liver to chronic Cd exposure [7–9,18]. These data are in line with the two-year bioassay that revealed Cd as a multi-tissue carcinogen [7]. Furthermore, the ability of Cd to induce non-tumorigenic human cells to undergo malignant transformation has been unambiguously demonstrated [18,19].

The first objective of this review is to discuss current health guidance values derived for environmental Cd exposure, and highlight their shortcomings and inadequacy to protect human health. It reiterates a total imprecision in measuring exposure and/or adverse outcomes, which biases dose-response relationships toward the null [20], and consequently leading to an underappreciation of the health effects of Cd by a large magnitude or even a miss. The second objective is to illustrates non-differential errors imposed to dataset, when the urinary excretion of Cd (E_{Cd}), an indicator of body burden, is adjusted to creatinine excretion (E_{cr}). These errors can be eliminated by normalizing E_{Cd} to creatinine clearance (C_{cr}), the surrogate of functioning nephrons. It accentuates a continuing effort to identify the most sensitive non-cancer endpoint to be used as a basis to formulate a meaningful health guideline value for Cd exposure. As a third objective, it provides fundamental and practical knowledges on BMD methodology and together with a summary of reported BMD modeling results and their interpretation.

2. Existing Dietary Cd Exposure Guidelines

This section provides health guidance values for exposure to Cd in the diet together with exposure threshold levels that have been estimated. Because nearly all food types contain Cd as a contaminant, exposure to Cd is through a normal human diet [10–13] and foods which are consumed frequently in a large quantity, like staples, contribute the most to total amount of Cd consumed [11].

Consumption of rice heavily contaminated with Cd is a known cause of “itai-itai” disease with severely damaged kidneys and bones as its dominant pathologies, leading to multiple bone fractures due to osteoporosis and osteomalacia [21,22]. These Cd-induced pathologies have been replicated in ovariectomized cynomolgus monkeys [23], which mimicked the female preponderance feature of the toxicity of a high-dose Cd (≥100 μg /day) for 50 years or longer). Consequently, kidneys and bones have been employed as the critical targets for Cd toxicity for which permissible exposure and threshold levels have been determined [24].

Table 1. Exposure guidelines for Cd in the diet based on kidney and/or bone effects.

Target/ Endpoint	Tolerable Intake/Exposure Threshold Level	Reference
Kidneys, β_2M excretion rate ≥ 300 μg/g creatinine.	A tolerable intake level of 0.83 μg/kg body weight/day (58 μg per day for a 70 kg person). A cumulative lifetime intake of 2 g. Assumed Cd absorption rate of 3–7%. Threshold level of 5.24 μg/g creatinine.	JECFA [25]

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Kidneys, β_2M excretion rate ≥ 300 μg/g creatinine.	A reference dose of 0.36 μg/kg body weight per day (25.2 μg per day for a 70 kg person) Threshold level of 1 μg /g creatinine	EFSA [26,27]
Kidneys, β_2M and NAG excretion rates	A tolerable intake level of 0.28 μg/ kg body weight per day; 16.8 μg/day for a 60 kg person. Threshold levels for the β_2M and NAG effects were 3.07 and 2.93 μg/g creatinine, respectively. An average dietary Cd exposure in China was 30.6 μg/day.	Qing et al. 2021 [28]
Bones, Bone mineral density	A tolerable Cd intake of 0.64 μg/kg body weight per day. Threshold level of 1.71 μg/g creatinine.	Qing et al. 2021 [29]
Bones, Bone mineral density	A tolerable intake level of 0.35 μg/kg body weight per day. Assumed threshold level of 0.5 μg/g creatinine.	Leconte et al. 2021 [30]
Kidneys and bones, Reverse dosimetry PBPK modeling	Toxicological reference values were 0.21 and 0.36 μg/ kg body weight per day, assuming a similar threshold level for effects on kidneys and bones of 0.5 μg/g creatinine.	Schaefer et al. 2023 [31]

NAG, N-acetyl-β-D-glucosaminidase; PBPK, physiologically based pharmacokinetics [32].

As data in Table 1 indicate, there is no consensus on a "safe" exposure level even though the same endpoints were used; the dietary Cd exposure limits range between 0.28 and 0.83 μg/ kg body weight per day with Cd exposure threshold levels varying from 1.0 to 5.24 μg/g creatinine for the β_{2M} and/or E_{NAG} endpoint. In a study on Chinese population data, Qing et al. (2021) reported a tolerable Cd intake to be 0.64 μg/kg body weight per day for the bone mineral density endpoint with a corresponding threshold level of 1.71 μg/g creatinine [29].

In addition to those enlisted in Table 1, POD-based health guidance values for Cd exposure, called MRLs have also been identified for oral and inhalational exposure scenarios. Using experimental dosing data [33–35], Faroon et al. (2017) reported the MRL for oral exposure to Cd in an intermediate exposure duration (15–365 days) to be 0.5 μg/kg body weight per day for decreased bone mineral density endpoint [36]. Based on experimental dosing data from the Fisher rats [37], the MRL for an acute inhalational exposure to Cd for the duration between 1 and 14 days was 0.03 μg/m^3 when alveolar histiocytic infiltration and focal inflammation in alveolar septa were employed as endpoints [36].

3. Imprecisions in Measuring Internal Cd Doses and Adverse Outcomes

The practice of toxicological risk assessment involves measuring two key parameters; exposure and effect indicators. This section focuses on factors which affect the estimation of internal dose of Cd, which account for an underestimation of an effect size. Uses of blood Cd concentrations and urinary excretion rates of Cd are highlighted along with the purposes of adjusting urinary concentrations of Cd and all other excreted biomarkers of Cd effects to creatinine excretion (E_{cr}) and creatinine clearance (C_{cr}).

3.1. Assimilation of Cd and Its Determinants

From foods, Cd enters the bloodstream through multiple mechanisms such as transcytosis [38], receptor-mediated endocytosis [39,40] and specialized transport proteins for essential metals, namely iron (Fe), zinc (Zn), and calcium (Ca) [41–44]. Cd can be expected to be assimilated at rates higher than each individual essential metal Fe, Zn and Ca, consistent with the absorption rate of Cd reported for Japanese women to be between 24 and 45% [45,46]. Conceivably, the internal dose of Cd and health risk imposed will be markedly underestimated, when Cd absorption rate is assumed to be 3 to 7% as in the JECFA provisional tolerable intake model for Cd [25].

Peng et al. (2023) conducted a systematic review and observed inverse associations of zinc and body iron stores with blood Cd concentrations [48]. Higher blood and urinary Cd levels in children

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and adolescent females [49], and women of reproductive age [51,52] have been linked to lower body iron stores, evident from serum ferritin ≤ 30 μg/L. Like iron, marginal dietary zinc intake and subclinical zinc deficiency are highly prevalent worldwide [53–55], which means a significant proportion of population is more likely to experience the nephrotoxicity of Cd.

3.2. Use of Blood Cd Concentration in Toxicological Risk Assessment

Through the gut and lungs, Cd in foodstuffs and airborne particle pollution, enter the systemic circulation. Hence, the blood concentration of Cd can reflect recent exposure to the metal. Because most of Cd in the blood stream is in the cytosol of red blood cells which have a 3-month lifespan, blood Cd concentration reflects exposure in the past three months.

As noted in Section 3.1, and reviewed by Cirovic and Cirovic (2024) [56], the amount of Cd that reaches target tissues and organs depends on many factors, which include absorption rate, nutritional zinc status, and body iron store, not just the amount of Cd in the diet. Consequently, neither blood Cd concentration nor an amount of Cd in the diet can be a precise predictor of an internal dose of Cd. For example, Van Maele-Fabry et al. (2016) reported that breast cancer risk among postmenopausal women was not associated with dietary Cd exposure levels [57]. In comparison, Cd exposure was found to be a strong risk factor for breast cancer in studies in which Cd excretion was used as an exposure indicator [58,59]. In a study by Larsson et al. (2015), risk of having breast cancer increased 66% for each 0.5-μg/g creatinine increase of urinary Cd excretion [58]. Lin et al. (2016) reported that breast cancer risk was not associated with dietary Cd exposure, but it was elevated 2.24-fold among women who had urinary Cd excretion rates in the top quartile, compared to those with urinary Cd in the lowest quartile [59].

Non-association between blood Cd and diabetes has been reported in a recent case-control study from Thailand by Adokwe et al. (2025) [60]. However, in three U.S. population studies, risks of having prediabetes and diabetes both were associated with urinary Cd excretion rates [61–63]. In a study by Schwartz et al. (2003), respective risk of having prediabetes and diabetes rose 48% and 24% at Cd excretion rates of 1–2 μg/g creatinine after smoking and other confounding factors were adjusted [61]. In a study by Wallia et al. (2010), a significant increase in risk of prediabetes was observed at Cd excretion rates ≥ 0.7 μg/g creatinine after adjustment for covariates [62]. In a study by Jiang et al. (2018), risk of having prediabetes was increased 3.4-fold in obese U.S. men who had urinary Cd excretion rate in the top quartile, compared to those with a normal weight and having urinary Cd excretion rate in the bottom quartile [63]. Risks of having break cancer, prediabetes and diabetes all have been found to be associated with urinary Cd excretion rates lower than 5.24 μg/g creatinine, a threshold level identified from the β_2M excretion rate ≥ 300 μg/g creatinine (Section 2.1).

3.3. Urinary Cd Excretion as an Indicator of Body Burden

It is well established that excretion of Cd can be used as a cumulative long-term exposure to the metal [64,65]. Precisely, a urinary Cd concentration reflects kidney burden because most acquired Cd can be found in the proximal tubular cells (PTCs) of kidneys which release Cd complexed with metallothionein (MT) into the lumen and then appears in urine, when they are injured or die from any cause [47].

In human population studies, urine samples are often collected at a single time point (a voided urine sample), and consequently adjusting of the urinary concentrations of Cd and all other urinary biomarkers to creatinine excretion (E_{cr}) has been used as a method to correct for differences in urine dilution among people. However, this E_{cr}-normalization creates a large statistical uncertain to datasets, resulting in an underestimation of an effect size of Cd, detailed further in Section 4. To circumvent such a problem created by E_{cr}-adjustment practice, normalization of Cd and other excreted substances to creatinine clearance (C_{cr}) has been used to simultaneously correct for interindividual differences in urine dilution, and the functioning nephrons. This C_{cr}-normalization has unveiled an unambiguous effect of Cd on eGFR [66] and the excretion of β_2M, albumin and total

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proteins, discussed further in Section 4. Normalization of urinary concentrations of Cd and any excreted substance to E_{cr} and C_{cr} can be undertaken using equations below.

Excretion of x (E_x) was normalized to E_{cr} as $[x]_u/[cr]u$, where x= Cd or any excreted biomarker; $[x]_u$ = 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.

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 any excreted biomarker; $[x]_u$ = 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 [67].

3.4. Use of Urinary β2M in Measuring Cd effect on Tubular Reabsorptive Function

Under normal physiologic conditions, blood perfuses the kidneys at the rate of 1 L per minute, and all renal blood flow is directed through afferent arterioles into glomeruli [68]. The plasma entering the glomerulus is filtered into Bowman's space, and 99.9% of the filtered protein is reabsorbed by tubules in an approximate of 40–50 g each day [68].

The protein β2M with the molecular weight of 11800 Daltons is expressed on the surface of most nucleated cells and is released into the bloodstream [69,70]. As Figure 1 depicts, β2M undergoes glomerular filtration, readily passes through the glomerular membrane to tubular lumen due to its small mass, and is reabsorbed and degraded by proximal tubular cells [69].

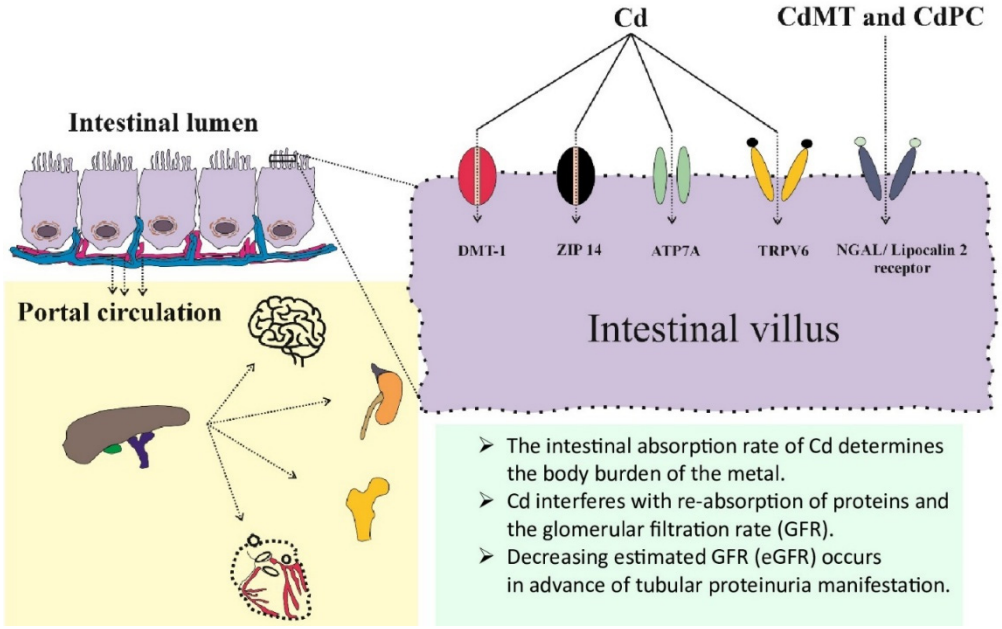

Figure 1. The pathway for cadmium in food to its toxic manifestation in kidneys. From the gut, Cd is delivered to liver via the portal blood system, before reaching the systemic circulation and transported to tissues and organs throughout the body. Due to a lack of excretory mechanism, Cd is retained within cells after entrance, notably the proximal tubular epithelial cells. The manifestation of toxic Cd accumulation in kidneys such as tubulointerstitial inflammation may incapacitate the glomerular filtration rate. Cd appears in urine after being released from injured or dying kidney tubular cells. Thus, it is argued that the excretion rate of Cd (E_{Cd}) should be normalized to creatinine clearance (C_{cr}) to depict the amount of Cd exiting the kidneys per nephron [47].

As previously discussed, β2M excretion rate of 300 μg/g creatinine was used to signify a tubular effect of Cd [25]. Current evidence, however, suggests that excretion of β2M is not a reliable tubular effect marker, and that the fractional tubular degradation of β2M should be used instead of β2M excretion [71]. Thus, the use of β2M as a basis to estimate a Cd exposure limit is inappropriate and a tolerable intake as high as 58 μg/day is not protective of human health.

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The risk of developing CKD, signified by a decrease in eGFR to one third of the normal range or there is albuminuria which persists for at least 3 months [72–74] have been linked to dietary Cd exposure of ≥ 16.7 μg/day [75] and urinary Cd excretion of 0.27-0.37 μg/g creatinine [76–78]. A new health-protective exposure limit for Cd is needed.

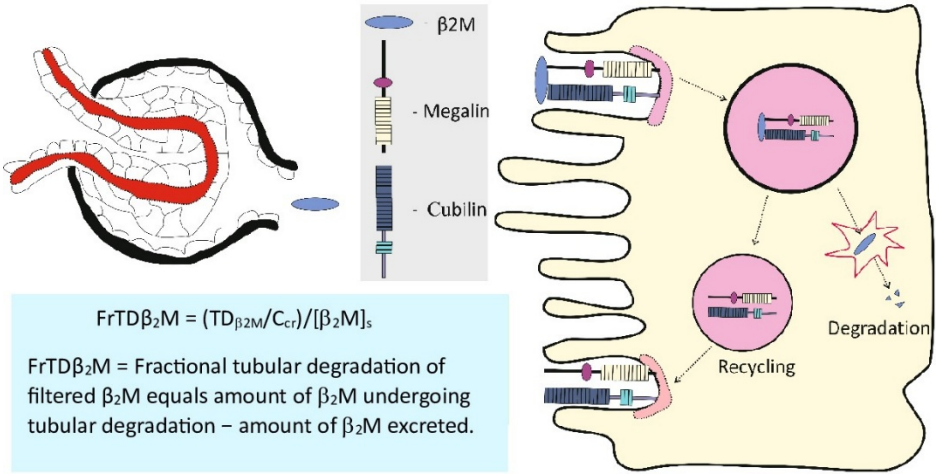

Figure 2. Measuring of an effect of Cd on tubular reabsorption of β_2M. The reabsorption of β_2M occurs mostly in the S1 segment via receptor-mediated endocytosis, involving megalin. Fractional tubular reabsorption of β_2M has emerged as a reliable parameter for assessment of tubular dysfunction [71].

4. Benchmark Dose Modeling of Cd Exposure and Its Nephrotoxicity

In this section, an application the BMD methodology to define a Point of Departure (POD) and a Cd-exposure threshold level is highlighted with a focus on functional kidney outcomes. Its primary aim is to identify the nephrotoxicity endpoint that can be considered as the most sensitive to Cd exposure. Its secondary aim is to illustrate the imprecision in determining internal Cd dose and its effect size, and the underestimation of the severity of an effect of Cd on eGFR and proteinuria, caused by the conventional normalization of excretion rate of nephrotoxicity biomarkers, such as β_2M ($E_{\beta 2M}$), NAG (E_{NAG}), albumin (E_{alb}) and urinary total protein (E_{pro}), to creatinine excretion (E_{cr}).

4.1. Mathematical Models for Dose-Response Relationship Appraisal

Many mathematical dose–response models, namely inverse exponential, natural logarithmic, exponential, and Hill models, can be applied to continuous variables [1,3–5]. The mathematical dose–response models applicable to dichotomized or quantal datasets are two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential, and Hill models [1,2]. Modeling of exposure-effect data can be done manually or using dose-response software programs, like the PROAST software (https://proastweb.rivm.nl) and the U.S. EPA's Benchmark Dose Software (BMDS) (https://www.epa.gov/bmds). Application of the PROAST software for continuous and quantal (prevalence) data are exemplified in Section 4.3.

4.1.1. Identification of POD, BMDL/BMDU, and NOAEL Equivalent of Cd Exposure

The main purpose of BMD modeling of continuous exposure-effect datasets is to define the lower bound (BMDL) and upper bound (BMDU) of the 95% confidence interval (CI) of BMD [1]. The lower bound (BMDL) value derived when the benchmark dose response (BMR) is set at 5% could reflect a Point of Departure (POD) or a reference point [1,3–5]. It is also referred to as the NOAEL equivalent, meaning the level of exposure below which an adverse effect of such exposure can be discernable. The upper bound (BMDU) is for computing the BMDU/BMDL ratio, which reflects the uncertainty in the BMD estimates. The wider difference between BMDL and BMDU values, the higher statistical uncertainty in the dataset [1,3–6].

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4.1.2. Exposure Threshold Identification, $BMDL_5/BMDL_{10}$

The main purpose of BMD modeling of exposure-outcome prevalence datasets is to define the lower bound (BMDL) and upper bound (BMDU) of the 95% confidence interval (CI) of BMD [1,2,6]. The BMDL/BMDU values computed at 5% and 10% prevalence rates of an adverse effect are respectively designated as $BMDL_5/BMDU_5$ and $BMDL_{10}/BMDU_{10}$. The $BMDL_5$ could reflect a threshold level of exposure, defined as an exposure level below which the prevalence of adverse effect to be ≤ 5%.

4.2. Dose-Response Relationship

A significant relationship between exposure doses and outcomes should be first established before any reliable toxicological risk evaluation can be undertaken. However, as Grandjean and Budtz-Jørgensen (2007) noted that non-differential errors in the measurement of exposure and outcomes, termed total imprecision, can result in a failure to establish a dose-response relationship [19], which would otherwise be established, when such errors are eliminated [19]. The concept of imprecision in measurement of Cd exposure levels and its effects on kidneys have already evident from two meta-analyses, published in 2016 [79] and 2021 [80], leading to erroneous conclusion that there was no evidence that Cd exposure produced an effect on eGFR nor it contributed to progressive deterioration of eGFR among Cd-exposed individuals [79,80]. A dose-response relationship between eGFR and Cd has been unveiled in the latest meta-analysis by Doccioli et al. (2024) [81].

Table 3 provides results from an analysis of data from 917 Thai subjects [76], where an effect size of Cd on eGFR was found to be smaller when E_{Cd} was normalized to E_{cr}; doubling of E_{Cd}/E_{cr} increased the risk of having low eGFR by 1.47-fold after adjustment for potential confounding factors. In comparison, the risk of having low eGFR rose 1.96-fold per doubling of and E_{Cd}/C_{cr}. This was after similar adjustments for other variables.

Table 3. Effects of the normalization of Cd excretion rate on risk of having low eGFR.

	[a] Low eGFR			
Model A	**POR**	**95% CI**		***p***
		Lower	**Upper**	
$Log_2[(E_{Cd}/E_{cr}) \times 10^3]$, μg/g creatinine	1.470	1.276	1.692	<0.001
Hypertension	1.632	0.885	3.008	0.117
Gender	1.029	0.528	2.002	0.934
Smoking	1.232	0.637	2.383	0.536
BMI, kg/m²				
12-18	Referent			
19-23	1.058	0.459	2.439	0.894
≥ 24	2.810	1.118	7.064	0.028
Age, years				
16-45	Referent			
46-55	14.23	1.867	108.4	0.010
56-65	28.21	3.538	224.9	0.002
66-87	141.2	17.87	1116	<0.001
Model B	POR	**Lower**	**Upper**	***p***
$Log_2[(E_{Cd}/C_{cr}) \times 10^5]$, μg/L filtrate	1.962	1.589	2.422	<0.001
Hypertension	1.735	0.916	3.287	0.091
Gender	0.840	0.410	1.719	0.633
Smoking	0.944	0.474	1.879	0.869
BMI, kg/m²				
12-18	Referent			
19-23	1.109	0.452	2.717	0.822
≥ 24	3.150	1.181	8.400	0.022
Age, years				
16-45	Referent			

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46-55	9.951	1.305	75.88	0.027
56-65	34.57	4.312	277.2	0.001
66-87	198.6	24.59	1605	<0.001

[a] Low eGFR was defined as eGFR ≤ 60 mL/min/1.73 m². E_{Cd} was normalized to E_{cr} and C_{cr} in models A and B, respectively. Data were from 917 subjects (562 females, 355 males),16–87 years of age [76].

Further evidence that E_{Cd}/E_{cr} created non-differential errors can be found in Table 4, where results from a study on 409 Thai subjects are provided [82]. In this study, effects of Cd on risks of eGFR and proteinuria were both evaluated to compare the impact of E_{cr} and C_{cr} normalization of E_{Cd} and E_{pro}.

For E_{cr}-normalized datasets (model A), risk of having low eGFR was not statistically associated with E_{Cd}/E_{cr} (p = 0.058), while risk of having proteinuria rose 3.7-fold as E_{Cd}/E_{cr} rose 10-fold (p = 0.045). Similar results were obtained in a meta-analysis by Jalili et al. (2021), who found an association of eGFR and E_{Cd}/E_{cr} was 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 [80]. Thus, the risk of having proteinuria was reduced when E_{Cd} and E_{pro} data were normalized to E_{cr}, while the risk of having low eGFR was markedly diminished as such it became statistically insignificantly in E_{cr} normalized data.

For C_{cr}-normalized datasets, (model B), risks of having low eGFR and proteinuria rose 12-fold (p < 0.001) and 7-fold (p = 0.001), when there was a 10-fold increase in E_{Cd}/C_{cr}.

Table 4. Effects of normalization of Cd excretion rate on risk of having low eGFR and proteinuria.

	Low eGFR [a]		**Proteinuria** [b]	
Model A	**POR (95% CI)**	***p***	**POR (95% CI)**	***p***
Age, years	1.121 (1.080, 1.165)	<0.001	1.068 (1.028, 1.110)	0.001
$Log_{10}[(E_{Cd}/E_{cr}) \times 10^3]$, µg/g creatinine	2.638 (0.969, 7.182)	0.058	3.685 (1.027, 13.22)	0.045
Gender	1.082 (0.490, 2.390)	0.845	1.096 (0.475, 2.528)	0.829
Smoking	1.425 (0.596, 3.406)	0.426	1.678 (0.627, 4.486)	0.303
Hypertension	2.211 (1.017, 4.805)	0.045	1.113 (0.432, 2.867)	0.824
Model B	**POR (95% CI)**	***p***	**POR (95% CI)**	***p***
Age, years	1.118 (1.073, 1.165)	<0.001	1.061 (1.022, 1.102)	0.002
$Log_{10}[(E_{Cd}/C_{cr}) \times 10^5]$, mg/ L filtrate	12.24 (3.729, 40.20)	<0.001	7.143 (2.133, 23.92)	0.001
Gender	0.802 (0.346, 1.861)	0.608	1.117 (0.482, 2.587)	0.796
Smoking	1.335 (0.546, 3.262)	0.527	1.947 (0.725, 5.234)	0.186
Hypertension	2.734 (1.204, 6.207)	0.016	1.018 (0.410, 2.530)	0.969

[a] Low eGFR was defined as eGFR ≤ 60 mL/min/1.73 m². [b] Proteinuria was defined as $E_{pro}/E_{cr} \geq 100$ mg/g creatinine and $(E_{pro}/C_{cr}) \times 100 \geq 100$ mg/L filtrate in models A and B, respectively. Data were from 405 subjects (208 females, 197 males) [82].

In summary, adjusting the urinary concentrations of Cd and urinary biomarkers of kidney effects, like total protein to E_{cr} appeared to generate non-differential errors that bias the dose-response relationship toward the null. As data in Table 4 illustrate, a dose-response relationship could not be established between eGFR and E_{Cd}/E_{cr}, while the strength of an association between E_{Pro}/E_{cr} and E_{Cd}/E_{cr} was weak. Consequently, Cd exposure limits cannot not reliably be derived from E_{cr}-adjusted datasets.

4.3. The PROAST Software for BMD Modeling

Typically, a single or two dose-response models are used in manual BMD computation, which is cumbersome. The BMD software program like the PROAST is increasingly been used as it is freely accessible (web-based), and it offers several advantages; there are many dose-response models to choose and it employs the Akaike information criterion (AIC), which objectively compare the relative

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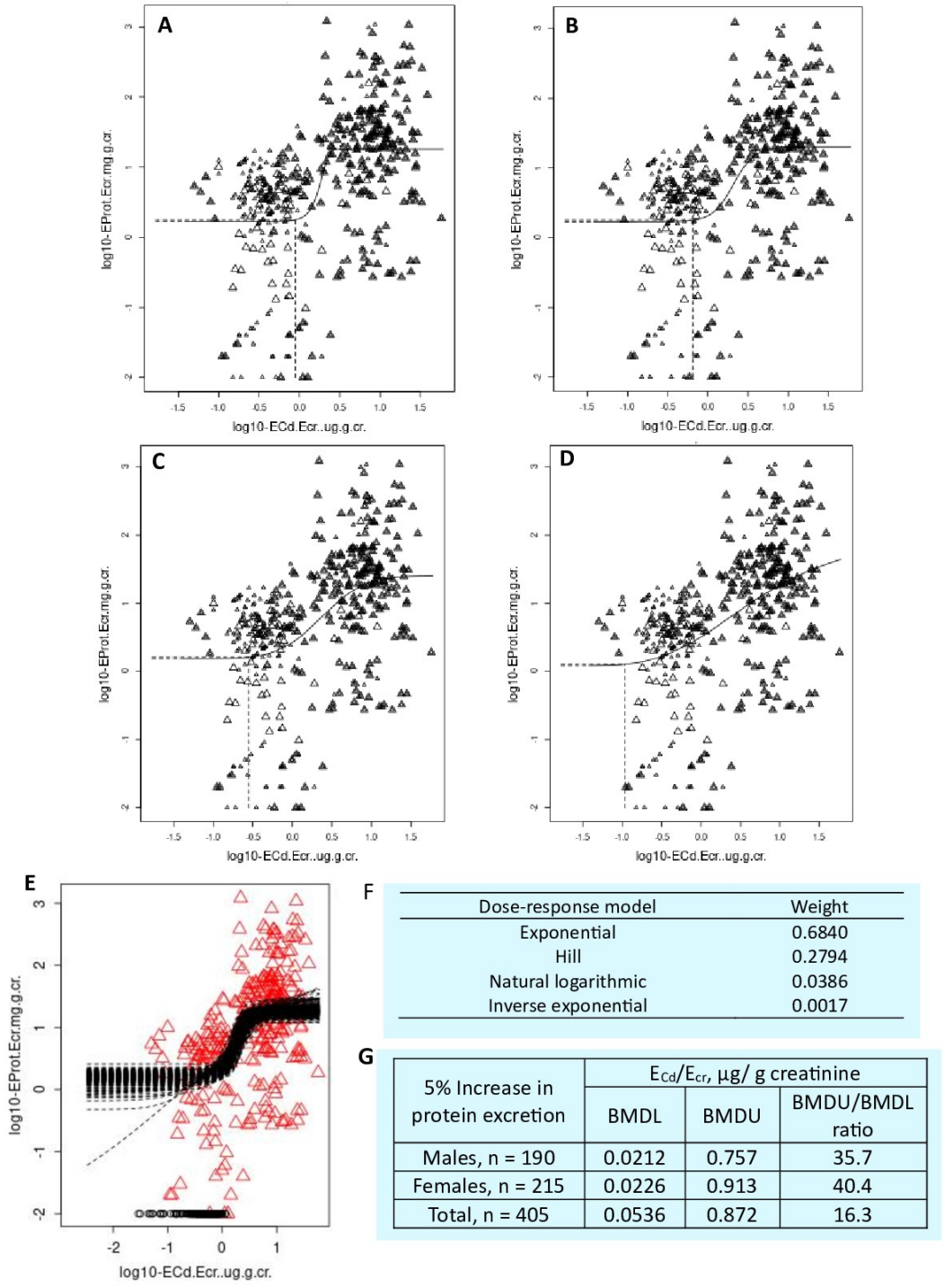
goodness of fit of different models [6]. The dose-response curve in which the data best fit offers an insight into the shape and steepness of the slope describing an effect size of Cd. Outputs from the PROAST software applied to continuous and quantal data from the same 409 individuals [82] shown in Table 4 are recapitulated in Figures 3 and 4.



F

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, n = 190	0.0212	0.757	35.7
Females, n = 215	0.0226	0.913	40.4
Total, n = 405	0.0536	0.872	16.3

Figure 3. Outputs from the PROAST software applied to E_{Cd}/E_{cr} and protein excretion datasets. The mathematical dose-response models applied to datasets are exponential (A), Hill (B), natural logarithmic (C), and inverse exponential (D). Bootstrap model averaging with 200 repeats (E), model weighing (F), BMDL and BMDU values [G]. This figure is adapted from Satarug et al. 2024 [82].

For E_{Cd}/E_{cra} and E_{pro}/E_{cr} datasets (Figure 3), the mathematical dose-response models used were exponential, Hill, natural logarithmic, and inverse exponential. Based on the model weights, the

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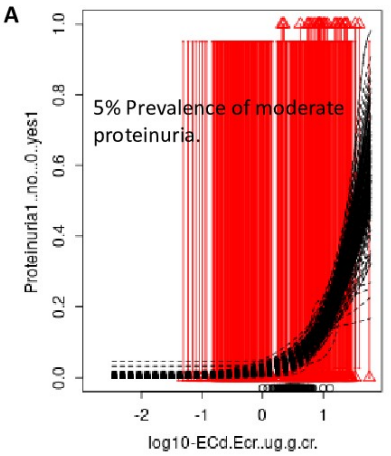
exponential model carried the highest weight (0.6840), followed by Hill model (0.2794), while natural logarithmic model (0.0386) and inverse exponential model (0.0017) carried much less weights. By model averaging, the BMDL value or the NOAEL equivalent of E_{Cd}/E_{cr} was 0.0536 µg/g for E_{pro} endpoint. Notably, the BMDL value of E_{Cd}/E_{cr} for E_{pro} endpoint will be unreliable if only Hill model is applied.

For E_{Cd}/E_{cra} and proteinuria prevalence datasets (Figure 4), the mathematical dose-response models used were two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential, and Hill model. By model averaging, $BMDL_5$ value of E_{Cd}/E_{cr} for proteinuria endpoint was 1.86 µg/g creatinine. This represented a threshold level for proteinuria. The E_{Cd}/E_{cr}-CKD prevalence curve fit moderately logarithmic probability (0.3501), followed by Hill (0.1482) and logarithmic logistic models (0.1452).

The same seven dose-response models were applied to E_{Cd}/E_{cra}-low eGFR (CKD) prevalence datasets (Figure 4). The $BMDL_5$ value of E_{Cd}/E_{cr} for CKD was 1.19 µg/g creatinine. The E_{Cd}/E_{cr}-CKD prevalence curve fit predominantly exponential model (0.8740), meaning that a small change in E_{Cd}/E_{cr} will result in a large increase in CKD prevalence. Thus, CKD prevalence rate was more sensitive to Cd than proteinuria prevalence.

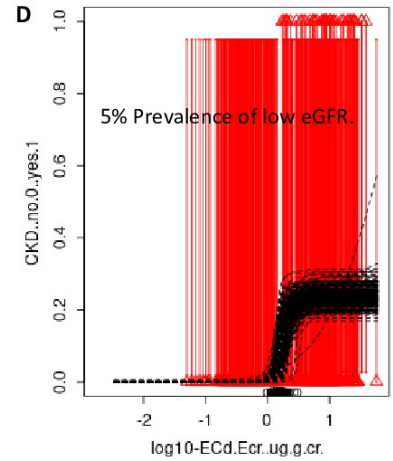


B

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 proteinuria	E_{Cd}/E_{cr}, µg/ g creatinine		
	$BMDL_5$	$BMDU_5$	BMDU/BMDL ratio
Males, n 190	2.07	5.96	2.88
Females, n = 215	1.80	5.98	3.32
Total, n = 405	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, n = 190	1.26	2.37	1.88
Females, n = 215	1.26	2.12	1.68
Total, n = 405	1.19	1.92	1.61

Figure 4. Outputs from the PROAST software applied to E_{Cd}/E_{cr}-proteinuria and E_{Cd}/E_{cr}-low eGFR datasets. The mathematical dose-response models applied to prevalence datasets are two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential, and Hill. This figure is adapted from Satarug et al. 2024 [82].

4.4. Comparing Reposretd BMD Values for Different Nephrotoxic Endpoints

Health-based exposure guidance value for Cd exposure, derived from different "POD" figures like MRL, TRV, TWI, TMI, and RfD, all assumes that a threshold level of exposure exists [1]. In theory, an exposure level derived from the most sensitive endpoint or the one with the lowest BMDL value

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would be protective against all other adverse effects [1]. Thus, the lowest BMDL value of E_{Cd}/E_{cr} should be used to define Cd exposure guidance value. To identify the most sensitive endpoint for an effect of Cd on the functional integrity of kidneys. reported results of BMD modeling of continuous and quantal data; BMDL/BMDU, $BMDL_5/BMDU_5$ and $BMDL_{10}/BMDU_{10}$ of E_{Cd}/E_{cr} are compared.

Current Cd exposure guidelines range from 0.21 and 0.83 µg/ kg body weight per day have been determined (Table 1). These were based on different endpoints and methodologies. However, most countries employ the JECFA "tolerable" exposure level of Cd at 0.83 µg/ kg body weight per day and $BMDL_5$, a threshold level of 5.24 µg/g creatinine. Indeed, the Cd exposure threshold or BMDL5 value of E_{Cd}/E_{cr} of 5.24 µg/g creatinine was based solely on the β_2M endpoint. Qing et al. (2023) reported that average dietary Cd exposure in China was 34.3 µg/day, varying between 22.6 and 54.5 µg/day across regions, and that dietary Cd exposure recorded for 15.4% of study population exceeded the JECFA tolerable intake level of 49.8 µg/day for a 60 kg person [83].

Many $BMDL_5$ values of E_{Cd}/E_{cr} have now been determined using other kidney tubular biomarkers, like excretion of retinal binding protein (RBP) and NAG, together with the β_2M. Findings from two meta-analyses, summarized below showed that $BMDL_5$ values of E_{Cd}/E_{cr} for nephrotoxicity were lower than 5.24 µg/g creatinine.

Liu et al. (2016), applied the BMD modeling to the Cd exposure and NAG data recorded in 30 publications, and they identified $BMDL_5$ value of E_{Cd}/E_{cr} to be 1.67 µg/g creatinine [84]. Based on data from 13 publications, Woo et al. (2015) found $BMDL^5$ value of E_{Cd}/E_{cr} for the β2M endpoint to be 4.88, 3.13 and 1.9 µg/g creatinine, depending on the cut-off values for β_2M used. The $BMDL_5$ value of E_{Cd}/E_{cr} of 1.9 µg/g creatinine was obtained, when $\beta_2M \leq 400$ µg/g creatinine were used as a cut-off value [85].

Many more BMDL, $BMDL_5$ values of E_{Cd}/E_{cr} derived from various nephrotoxicity endpoints can be found in Table 5.

Table 5. BMD modeling of Cd exposure with different nephrotoxicity endpoints.

Endpoints/Population	Results	Reference
NAG and eGFR n = 790 women, 53–64 years, Sweden	BMDL (BMD) values of E_{Cd}/E_{cr} were 0.5 (0.6) and 0.7 (1.1) µg/g creatinine the NAG and eGFR endpoints, respectively.	Suwazono et al. 2006[86]
RBP, β_2M and NAG n = 934 (469 men, 465 women), 10–71+ years, Jiangshan City, Zhejiang, China	BMDL values of E_{Cd}/E_{cr} at 5% (10%) BMR in men were 0.89 (1.59), 0.62 (1.30), 0.49 (1.04) µg/g creatinine for the RBP, β_2M, and NAG endpoints, respectively. Corresponding BMDL values of E_{Cd}/E_{cr} in women were 0.76 (1.53), 0.64 (1.34), 0.65 (1.37) µg/g creatinine for the RBP, β_2M, and NAG endpoints.	Wang et al. 2016 [87]
β_2M, TRβ_2M and eGFR (or C_{cr}) n = 112 (Cd-polluted area, n = 74, non-polluted area, n =38) Japan	BMDL values of E_{Cd}/E_{cr} in men were 1.8, 1.8, and 3.6 µg/g creatinine for the β_2M endpoint and decreases in TRβ_2M by 5% and 10%, respectively. Corresponding BMDL values of E_{Cd}/E_{cr} in women were 2.5, 2.6, and 3.9 µg/g creatinine. BMDL values of E_{Cd}/E_{cr} for the eGFR (C_{cr}) endpoint in men and women were 2.9 and 3.5 µg/g creatinine, respectively	Hayashi et al. 2024 [88]
NAG, β_2M, and eGFR n = 734 (Bangkok, n = 200, Mae Sot, n = 534), 16–87 years, Thailand	BMDL/BMDU values of E_{Cd}/E_{cr} in men were 0.060/0.504 µg/g creatinine for the NAG, while $BMDL_{10}/BMDU_{10}$ values were 0.469/0.973 and 3.26/7.46 µg/g creatinine for the β_2-microglobulinuria and low eGFR [a], respectively. Corresponding BMDL/BMDU values of E_{Cd}/E_{cr} in women were 0.069/0.537 µg/g creatinine for NAG, while $BMDL_{10}/BMDU_{10}$ were 0.733/1.29 and 4.98/9.68 µg/g creatinine for the β_2-microglobulinuria and low eGFR.	Satarug et al. 2022 [89]
Protein excretion and low eGFR n = 405 (Bangkok, n =100,	BMDL/BMDU values of E_{Cd}/E_{cr} for protein loss in men were 0.021/0.757 µg/g creatinine, while $BMDL_5/BMDU_5$ values for proteinuria were 2.07/5.96 µg/g creatinine.	Satarug et al. 2024 [82]

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Mae Sot, n = 215), 19–87 years, Thailand	Corresponding BMDL/BMDU values of E_{Cd}/E_{cr} in women were 0.023/0.913 μg/g creatinine, while $BMDL_5/BMDU_5$ values for proteinuria were 1.80/5.98 μg/g creatinine. In a whole group, BMDL/BMDU values of E_{Cd}/E_{cr} for protein loss were 0.054/0.872 μg/g creatinine, while $BMDL_5/BMDU_5$ values were 1.86/5.72 and 1.19/1.92 μg/g creatinine for proteinuria and low eGFR, respectively.	

NAG, N-acetyl-β-D-glucosaminidase; eGFR, estimated glomerular filtration rate; RBP, retinal binding protein; β2M, β2-microglobulin; TRβ2M, tubular reabsorption of β2M. a Low eGFR was defined as eGFR ≤ 60 mL/min/1.73 m^2, a diagnostic criterion for chronic kidney disease.

As typical, Wang et al. (2016) reported BMDL (BMD) values of E_{Cd}/E_{cr} for markers of tubular toxicity, namely RBP, β_2M and NAG [87]. Surprisingly, a few studies have applied BMD methodology to the data on eGFR although low eGFR is a diagnostic criterion for CKD. There is only one paper involved BMD modeling of total protein excretion although this parameter is a predictor of continued nephron destruction, resulting in progressive decline of eGFR [82]. Interestingly, Cd exposure has been causally related to a rapid fall of eGFR in a prospective cohort study from Switzerland (n = 4704) [90]. Respective $BMDL_5$ value of E_{Cd}/E_{cr} were 1.86 and 1.19 μg/g creatinine, when proteinuria and low eGFR were used as endpoints [82].

It is notable that BMD values of E_{Cd}/E_{cr} for effects on the glomerular filtration rate (GFR) and tubular injury/dysfunction were marginally different, meaning these two effects are intertwined. A study on Swedish women by Suwazono et al. (2006) reported BMD values of E_{Cd}/E_{cr} for effects on eGFR together with E_{NAG}/E_{cr} [86]. The BMDL values of E_{Cd}/E_{cr} in Swedish women were 0.5 and 0.7 μg/g creatinine for the tubular injury (E_{NAG}/E_{cr}) and eGFR endpoints [86]. Satarug et al. (2022) reported BMD values of E_{Cd}/E_{cr} for effects on eGFR, E_{NAG}/E_{cr} plus $E_{\beta 2M}/E_{cr}$ using Thai population data [89]. Hayashi et al. (2024) reported the BMDL values of E_{Cd}/E_{cr} in Japanese women were 3.9 and 3.5 μg/g creatinine for a 10% decrease in tubular reabsorption of β_2M) and C_{cr} effect, respectively [88].

Another notable result comes from Thai population data, suggesting that the nephrotoxicity of Cd occurs at a very low body burden. Respective NOAEL equivalents of E_{Cd}/E_{cr} in men and women were 0.060 and 0.069 μg/g creatinine for a 5% increase in E_{NAG}/E_{cr} [89]. The NOAEL equivalent of E_{Cd}/E_{cr} was as little as 0.054 μg/g creatinine, when a 5% increase in total protein excretion was used as an endpoint [82].

The $BMDL_5/BMDL_{10}$ values of E_{Cd}/E_{cr} for proteinuria were 1.86 and 4.47 μg/g creatinine, meaning that the prevalence of Cd-related proteinuria would increase from 5% to 10% when population mean value of E_{Cd}/E_{Cd} increases from 1.86 to 4.47 μg/g creatinine. For the low eGFR endpoint, $BMDL_5/BMDL_{10}$ values of E_{Cd}/E_{cr} were 1.19 and 1.35 μg/g creatinine, meaning that the prevalence of Cd-related low eGFR would increase from 5% to 10% when population mean value of E_{Cd}/E_{Cd} increases from 1.19 to 1.35 μg/g creatinine. Apparently, an effect size of Cd on eGFR decline was larger than proteinuria.

4.5. BMDL5 and BMDL10 Values of Cd Exposure Derived from E_{cr}- and C_{cr} Normalized Data

To demonstrate that normalization of E_{Cd} and E_{alb} to C_{cr} was superior to a conventional adjustment of E_{Cd} and E_{alb} to E_{cr}, the quantal BMD modeling outputs of the PROAST software can be found in Table 6.

Table 6. $BMDL_5$ and $BMDL_{10}$ of E_{Cd}/E_{cr} versus E_{Cd}/C_{cr} from albuminuria and CKD prevalences.

Prevalence of Adverse Outcome	**E_{Cd}/E_{cr}, μg/ g creatinine**			**(E_{Cd}/C_{cr}) ×100, μg/L filtrate**		
5% Albuminuria [a]	**$BMDL_5$**	**$BMDU_5$**	**$BMDU_5/BMDL_5$**	**$BMDL_5$**	**$BMDU_5$**	**$BMDU_5/BMDL_5$**
Males	3.06×10^{-3}	36.7	1.2×10^2	0.163	13	80

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Females	1.22×10^{-2}	3.05×10^{5}	2.5×10^{7}	0.718	154	60
10% Albuminuria	**$BMDL_{10}$**	**$BMDU_{10}$**	**$BMDU_{10}/BMDL_{10}$**	**$BMDL_{10}$**	**$BMDU_{10}$**	**$BMDU_{10}/BMDL_{10}$**
Males	0.55	337	612	1.65	20	12
Females	2.52	1.74×10^{6}	6.7×10^{5}	3.55	2.12	60
5% CKD [b]	**$BMDL_{5}$**	**$BMDU_{5}$**	**$BMDU_{5}/BMDL_{5}$**	**$BMDL_{5}$**	**$BMDU_{5}$**	**$BMDU_{5}/BMDL_{5}$**
Males	1.47	10.6	7.7	3.22	9.64	2.90
Females	1.93	15.6	8.08	3.33	9.20	2.26
10% CKD	**$BMDL_{10}$**	**$BMDU_{10}$**	**$BMDU_{10}/BMDL_{10}$**	**$BMDL_{10}$**	**$BMDU_{10}$**	**$BMDU_{10}/BMDL_{10}$**
Males	3.92	15.7	4.00	5.61	13.4	2.39
Females	5.31	23.6	4.44	5.88	12.9	2.19

[a] Albuminuria was defined as urinary albumin-to-creatinine ratios ≥ 20 mg/g in men and ≥30 mg/g in women for E_{cr}-normalized data, while it was defined as $(E_{Alb}/C_{cr}) \times 100 \geq 20$ mg/L filtrate in men and ≥ 30 mg/L filtrate in women for C_{cr}-normalized data. [b] CKD was defined as eGFR ≤ 60 mL/min/1.73 m^2. Data were from 603 subjects (203 males, 400 females) [91].

Due to a high degree of statistical uncertainty, indicated by the BMDU/BMDL ratios ≥ 200, the $BMDL_5$ and $BMDL_{10}$ values of E_{Cd}/E_{cr} could not be reliably defined for albuminuria endpoint. However, when 5% and 10% CKD prevalence rates were endpoints, the $BMDL_5$ and $BMDL_{10}$ values of E_{Cd}/E_{cr} were determined with certainty. In women the $BMDL_5$ and $BMDL_{10}$ values of E_{Cd}/E_{cr} for CKD endpoint were 1.93, and 5.31 μg/g creatinine, respectively. Corresponding $BMDL_5$ and $BMDL_{10}$ values of E_{Cd}/E_{cr} in men were 1.47, and 3.92 μg/g creatinine. Lower $BMDL_5$ and $BMDL_{10}$ values of E_{Cd}/E_{cr} in men, compared to women were due to higher creatinine excretion rates in men, attributable to a universally higher muscle mass in men than women of similar age.

In comparison $BMDL_5$ and $BMDL_{10}$ values of Cd exposure levels were determined with certainty for both albuminuria and CKD prevalence endpoints when C_{cr}-normalized data were analyzed. For the CKD (low eGFR) prevalence endpoint, $BMDL_5$ and $BMDL_{10}$ in men and women were not different statistically. In theory, the basic mechanism of the Cd toxicity in PTCs should be the same as such the toxic exposure level of Cd can be expected to be the same for both genders. These data strengthen the superior of C_{cr}-normalization of the urinary Cd concentration because excreted Cd originated from PTCs. Indeed, applying C_{cr}-normalization to urinary Cd and NAG concentrations, independent effects of age and Cd exposure on the rate of loss of tubular cells per nephron has been determined [92].

5. Conclusions

In many populations, Cd exposure level has now reached toxic levels in a significant proportion of people, and yet there is no consensus on a safe exposure level for the metal. The main route of Cd exposure in non-smokers and non-occupationally exposed people is a normal diet. However, current dietary exposure guidelines are not low enough to protect kidney health. An elevation of β_2M excretion used as a basis for derivation of a tolerable Cd exposure level is not a reliable indicator of kidney tubular dysfunction. The fractional tubular degradation of β_2M has been emerged as a measure of tubular dysfunction and thus should be employed for such a purpose.

A practice of adjusting urinary Cd, β_2M, NAG, albumin, and total proteins to creatinine excretion (E_{cr}) incorporates a conceptual flaw, which creates non-differential errors and bias the dose-response relationship toward the null. These errors and total imprecision can be eliminated by adjusting urinary Cd to creatinine clearance (C_{cr}). This C_{cr}-normalization practice does not require timed urine collection. The BMDL (NOAEL equivalent), $BMDL_5$ and $BMDL_{10}$ values for Cd exposure computed from C_{cr}-normalized data should thus be used in health-based exposure guidelines for Cd.

Using E_{NAG}/E_{cr} and E_{pro}/E_{cr} as endpoints, respective NOAEL equivalents of E_{Cd}/E_{cr} identified from Thai population datasets were 0.060 and 0.054 μg/g creatinine. These figures are 10-fold below mean E_{Cd}/E_{cr} recorded for the general populations in many countries of 0.5-0.6 μg/g creatinine. Using population prevalence of CKD as an endpoint, an exposure threshold level of Cd (BMD_5 value of

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E_{Cd}/E_{cr}) was 1.19 μg/g creatinine below which the prevalence of Cd-related CKD is expected to be ≤ 5%.

Based on the above BMD modeling data, and there is no theoretical reason to believe that a decrease in eGFR due to nephron destruction by Cd is irreversible, new dietary Cd exposure guidelines should be established to preserve kidney functional integrity and to minimize disease progression toward kidney failure. Public health measures should be developed to minimize Cd contamination of food chains and maintain the lowest achievable Cd levels in food crops, especially staples. An effective chelation therapy to remove Cd from the kidneys does not exist. Avoidance of foods containing high Cd and smoking cessation are essential preventive measures as is the maintenance of an optimal body content of essential metals, notably zinc and iron to reduce Cd assimilation and kidney burdens to the lowest achievable level.

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