Review

Is Chronic Kidney Disease due to Cadmium Exposure Inevitable and Can it be Reversed?

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Is Chronic Kidney Disease due to Cadmium Exposure Inevitable and Can it be Reversed?

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Abstract: Cadmium (Cd) is a metal with no nutritional or physiological value, but is found in most people because it is a contaminant in nearly all food types. The intestinal absorption rate determines the body burden of Cd because humans lack a physiologic mechanism for excretion of the metal. Most acquired Cd accumulates in the kidneys, in which the Cd content increases through age 50 but falls thereafter. The decline from maximal kidney content is probably due to release of Cd from injured tubular cells into urine and replacement of destroyed nephrons by scar tissue. Chronic kidney disease is diagnosed when the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2, or when albuminuria is present. Albuminuria is defined as an albumin-to-creatinine ratio ≥ 30 mg/g creatinine in women or ≥ 20 mg/g creatinine in men that persists for at least 3 months. Generally, Cd-induced reductions in eGFR are not reversible, and Cd nephropathy may progress to end-stage kidney disease. There is no evidence that elimination of current environmental exposure can reverse Cd nephropathy, and no theoretical reason to believe that such a reversal is possible. This review provides an update of knowledge concerning CKD in population environmentally exposed to Cd. Special attention is devoted to mechanisms of Cd-induced albuminuria concurrently with eGFR reductions, and the difficult challenge of exposure guidelines sufficient to eliminate the risk of Cd-induced CKD is addressed.

Keywords: albuminuria; β_2-microglobulin; cadmium; chronic kidney disease; GFR; proteinuria; receptor-mediated endocytosis

1. Introduction

Cadmium (Cd) is a metal pollutant, found in most food types; as such, dietary exposure to the metal is inevitable for most people [1]. Significant sources of Cd in human diet include rice, potatoes, wheat, and leafy salad vegetables [1–5]. Current evidence indicates that the intestinal absorption of Cd and its transport pathways to kidneys and other targets follow closely those for essential metals, notably iron, zinc, and calcium [1,6]. Genetic linkage studies are consistent with the roles of zinc and iron transporters and proteins of iron homeostasis as determinants of blood and urinary Cd levels [7–9], while body iron stores and nutritional status of zinc were found to be inversely related to the body burden of Cd in a meta-analysis [10].

There is also evidence that Cd complexed with phytochelatin (PC) and the metal binding protein metallothionein (MT), denoted respectively as CdPC and CdMT, can be assimilated intact through transcytosis and receptor-mediated endocytosis (RME) [11–13]. The CdMT of dietary origin may be targeted to the distal nephrons, especially when proximal tubules are injured [6,14,15].

Other non-workplace exposure sources of Cd are polluted air, passive and active cigarette smoking [16–18]. Indeed, Cd was found to be the constituent of a cigarette smoke that contributed the most to chronic ailments associated with smoking [19]. This result reflects a typical feature of a toxicant, like Cd, which persists throughout the lifespan of cells due to a lack of excretory mechanism. Studies in humans and rats showed that Cd was excreted in urine, only when kidney tubular cell died, due to the toxic Cd accumulation [20,21].

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In humans, the overall elimination rate of Cd is an extremely slow; only 0.001-0.005% of the body burden is excreted in urine each day [22,23]. The estimated half-life of Cd in the human body varied between 7.4 and 30 years [24–26]. In comparison, other cigarette smoke constituent, such as nicotine, can be eliminated completely in less than 3 hours through hepatic xenobiotic metabolism and urinary excretion [27–29].

The present review aims to provide an update of knowledge on adverse health outcomes of exposure to environmental Cd, focusing on chronic kidney disease (CKD), which is a progressive disease with high morbidity and mortality, affecting 8-16% of the world's population [30–32]. Special emphasis is given to the mechanisms by which Cd causes albuminuria concurrently with a reduction of glomerular filtration rate (GFR). Understanding the pathophysiologic mechanisms underlying Cd-induced albuminuria is of potential significance, given that the global rising incidence of CKD and the escalating treatment costs necessitate screening for an early warning sign of CKD [33]. In addition, this review highlights the implications of Cd-induced GFR reduction for health risk assessment, and benchmark dose calculation of the body burden of Cd that may carry a negligible health risk. Current exposure guidelines are outdated and do not afford a sufficient health protection.

2. Environmental Cadmium and the Increased Prevalence of Chronic Kidney Disease

CKD is diagnosed when the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2, termed low eGFR, or there is albuminuria that persists for at least 3 months [30,31]. Albuminuria is designated, when the excretion of albumin (E_{alb}), measured as albumin-to-creatinine ratio (ACR), rises to levels above 20 and 30 mg/g creatinine in men and women, respectively [30,31]. A higher ACR cutoff value is necessary to define albuminuria in women to adjust for gender differences in muscle mass, which is a principal determinant of creatinine excretion (E_{cr}). This practice simply reflects the fact that women have universally lower muscle mass, and thus lower E_{cr}, compared to men.

For the same reason as ACR, normalization of Cd excretion to E_{cr} yields typically higher E_{Cd}/E_{cr} values in women, compared to men of similar age. The ramification of normalization of excretion rate of Cd to E_{cr} is further discussed in Section 2.4.

2.1. Findings from Systematic Reviews and Meta-Analyses

Doccioli et al. (2024) conducted a systematic review and meta-analysis to evaluate the strength of an association between CKD and Cd exposure [34]. They reported that Cd exposure was associated with increased risk of CKD, only when assessed by eGFR, and the association was more evident for blood than for urinary Cd or dietary exposure [35].

In a previous systematic review and meta-analysis, Jalili et al. (2021) reported that an association of eGFR and urinary Cd was insignificant, but the risk of proteinuria rose 35%, when the top category of Cd dose metrics was compared with the bottom Cd exposure category [35]. In another meta-analysis, Byber et al. (2016) concluded that Cd exposure was not associated with progressive eGFR reductions [36].

Nearly all studies used ACR to define albuminuria, while using E_{Cd}/E_{cr} as an indicator exposure to Cd. However, the E_{cr}-adjustment, introduces variance to datasets and creates a high degree of statistical uncertainty [37]. In effect, associations of E_{Cd}/E_{cr} with eGFR and E_{alb}/E_{cr} (ACR) deemed to be statistically insignificant.

2.2. Exposure Levels of Concern

Dose-responses studies showing Cd exposure levels associated with low eGFR, albuminuria and proteinuria can be found in Table 1.

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Table 1. Associations of enhanced risk of CKD with blood and urinary cadmium.

Study Location	Cadmium Exposure Metrics and Effects Observed	Reference
Thailand, n 1189 16–87 years mean age 43.2 years	Risk of low eGFR[a] increased 6.2-fold and 10.6-fold, comparing urinary Cd levels 0.38–2.49 and ≥ 2.5 μg/g creatinine with ≤ 0.37 μg/g creatinine, respectively.	Satarug et al. 2022 [38].
Korea, n 2992 20–65 years	Increased risk of low eGFR (OR 1.97) in women was associate with blood Cd levels > 1.74 μg/L.	Myong et al. 2012 [39]
Korea, n 2005 ≥ 20 years	Increased risk of low eGFR (OR 1.93) was associated with blood Cd in the top quartile (mean, 2.08 μg/L).	Chung et al. 2014 [40]
Taiwan, n 2447 mean age 55.1 years	Increased risk of proteinuria was associated with urinary Cd (OR 2.67) and copper (OR 1.94). Mean urinary Cd in subjects with proteinuria (1.1 μg/L) was 27.3% higher than those without proteinuria.	Tsai et al. 2021 [41]
China n 683 (64.7% women) mean age 57.4 years	Risk of elevated albumin excretion increased 2.98-fold, comparing urinary Cd levels ≤ 0.32 with > 1.72 μg/g creatinine.	Feng et al. 2022 [42]
Spain, n 1397 age 18–85 years	Increased risks of albuminuria[b] by1.58-fold and 4.54-fold were associated with urinary Cd levels > 0.27 and > 0.54 μg/g creatinine, respectively	Grau-Perez et al. 2017 [43]
United States NHANES 1999 – 2006 n 14,778, ≥ 20 years	Blood Cd levels ≥ 0.6 μg/L were associated with low eGFR (OR 1.32), albuminuria (OR 1.92) and low eGFR plus albuminuria (OR 2.91)	Navas-Acien et al. 2009 [44]
United States NHANES 1999 – 2006 n 5426, ≥ 20 years	Blood Cd levels > 1 μg/L plus urinary Cd levels > 1 μg/g creatinine was associated with albuminuria (OR 1.63). Blood Cd levels > 1 μg/L were associated with low eGFR (OR 1.48) and albuminuria (OR 1.41).	Ferraro et al. 2010 [45]
United States NHANES 2007 – 2012 n 12,577, ≥ 20 years	Blood Cd levels > 0.61 μg/L were associated with low eGFR (OR 1.80) and albuminuria (OR 1.60). eGFR reduction due to Cd was more pronounced in the diabetics, hypertensive, or both	Madrigal et al. 2019 [46]
United States NHANES 2009 – 2012 n 2926, ≥ 20 years	Urinary Cd levels > 0.220 μg/L were associated with elevated albumin excretion, compared with urinary Cd levels < 0.126 μg/L. Blood Cd levels > 0.349 μg/L were associated with elevated albumin excretion, compared with blood Cd levels < 0.243 μg/L	Zhu et al. 2019 [47]

n, sample size; OR, odds ratio; [a]Low eGFR was defined as estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2. [b]Albuminuria was defined as urinary albumin-to-creatinine ratio ≥ 20 and 30 mg/g creatinine in men and women, respectively. NHANES, National Health and Nutrition Examination Survey.

A study from Thailand (n = 1189) reported 6.2-fold and 10.6-fold increases in risk of low eGFR as urinary Cd excretion levels rose from ≤ 0.37 to 0.38–2.49 and ≥ 2.5 μg/g creatinine, respectively [38]. In a study from China, there was a 2.98-fold increase in risk of elevated albumin excretion, as urinary Cd levels rose from ≤ 0.32 to > 1.72 μg/g creatinine [42]. In a study from Spain, 1.58-fold and 4.54-fold increases in risk of albuminuria were associated with urinary Cd levels > 0.27 and > 0.54 μg/g creatinine, respectively [43].

An association of CKD with Cd exposure was observed in U.S. population studies, known as National Health and Nutrition Examination Surveys (NHANES) [44–47]. Specifically, increased risk

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of CKD among U.S. citizens, enrolled in NHANES 1999–2016 was linked to blood Cd levels ≥ 0.6 μg/L and urinary Cd levels ≥ 1 μg/g creatinine.

The median for E_{Cd}/E_{cr} in women enrolled in NHANES 1988–1994 was 0.77 μg/g creatinine, higher than that of men (0.58 μg/g creatinine) [48]. A study from Taiwan, including 977 men and 1470 women (mean age 55), reported a mean urinary Cd concentration was higher in women than men (0.9 vs. 0.7 μg/L) [49]. A study from Swen observed higher blood Cd in women than men of a similar age [50]. In a population-based study of Chinese subjects, aged 2.8 to 86.8 years (n = 1235), urinary Cd levels increased with age, peaking at 50 and 60 years in non-smoking women and men, respectively [51].

Of concern, eGFR decline due to Cd nephropathy has increasingly been observed in both children and adult populations. Lower eGFR values were found to be associated with higher Cd excretion rates in studies from Guatemala [52] and Myanmar [53]. In a prospective cohort study of Bangladeshi preschool children, an inverse relationship between ECd and kidney volume was seen in children at 5 years of age. This was in addition to a decrease in eGFR [54]. ECd was inversely associated with eGFR, especially in girls. In another prospective cohort study, the reported mean for Cd intake among Mexican children was 4.4 μg/d at the baseline and rose to 8.1 μg/d after nine years, when such Cd intake levels showed a marginally inverse association with eGFR [55].

As data in Table 1 indicate, E_{Cd}/E_{cr} values ≥ 0.27-0.32 μg/g creatinine may be sufficient dose levels caused an increase albuminuria excretion and eGFR decline. Thus, eGFR loss and an increased albumin excretion appeared to occur long before E_{Cd}/E_{cr} reached 5.24 μg/g creatinine level at which $E_{\beta 2M}/E_{cr}$ rose to ≥ 300 μg/g creatinine. In theory, for a toxicant with multiple targets, its toxicity threshold level should be based on the most sensitive endpoint [56]. Thus, CKD may serve as a suitable adverse effect, based on which protective exposure guidelines should be formulated (Section 4).

In summary, studies from various countries report disparate levels of urinary and blood Cd, but they are broadly consistent in that they find that urinary Cd levels associated with low eGFR and albuminuria did not exceed 5.24 μg/g creatinine, which was suggested to be the nephrotoxicity threshold level of Cd. This Cd toxicity threshold level was obtained from a risk assessment model that used β_2M excretion as a toxic endpoint, detailed in Section 4.

2.3. Methods of Normalization of Cadmium Excretion Rate

For many years, the custom has been to normalize E_{Cd} to the excretion rate of creatinine, E_{cr}. If V_u is the rate of urine flow, E_{Cd} and E_{cr} equal $[Cd]_u V_u$ and $[cr]_u V_u$, respectively, and E_{Cd}/E_{cr} simplifies to $[Cd]_u/[cr]_u$. Since these two variables, $[cr]_u$ and $[Cd]_u$, are not connected biologically, the ratio does not normalize $[Cd]_u$ to a factor that affects E_{Cd}. The sole virtue of $[Cd]_u/[cr]_u$, as opposed to $[Cd]_u$ alone, is that it adjusts [Cd]u for Vu. However, this adjustment introduces a different and arguably comparable source of imprecision, because Ecr is proportional to muscle mass, which varies by a multiple within some populations [57].

E_{Cd}/C_{cr} is determined by calculation using an equation $[Cd]_u[cr]_p/[cr]_u$, which is algebraically simplified from $[Cd]_u V_u/[cr]_u V_u/[cr]_p$, where p = plasma and u = urine; E_{Cd} = urinary excretion rate of Cd; V_u = urine flow rate; cr = creatinine [58]. E_{Cd}/C_{cr} is expressed as μg/ L of filtrate.

The GFR is the product of nephron number and mean single nephron GFR, while creatinine clearance (C_{cr}) approximates the GFR [30,59–61]. Because C_{cr} varies directly with nephron mass, E_{Cd}/C_{cr} depicts the burden of Cd per surviving nephron. Because most or all excreted Cd emanates from injured or dying tubular cells [62]. E_{Cd}/C_{cr} quantifies the severity of the injury due to Cd accumulation at the present time, not the risk of injury in the future.

Timed urine collections are not required. Variation of $[cr]_u$ with muscle mass does not affect E_{Cd}/C_{cr}, because $[cr]_u$ and $[cr]_p$ are uniformly related at any C_{cr}. At a given tubular cell Cd content, the effect of a reduced nephron number to lower E_{Cd} is offset in the calculation by a rise in $[cr]_p$ as C_{cr} falls, and excretion of Cd per intact nephron is accurately depicted [1,62–64].

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2.5. Demonstrable Dose-Response Relationships

To demonstrate the utility of C_{cr}-normalization in dose-effect relationship evaluation, data on measurement of Cd exposure and its effects in those resided in an Cd-contaminated area of Thailand [63], are recapitulated in Table 2.

Table 2. Comparing excretion rates of various proteins and cadmium in residents of an area of Thailand with endemic cadmium contamination.

Parameters	All Subjects n = 215	eGFR [a], mL/min/1.73 m²			*p*
		> 90, n = 33	61–90, n = 131	≤ 60, n = 51	
Age, years	57.0 ± 11.1	49.4 ± 9.4	55.6 ± 9.6	65.6 ± 10.6	<0.001
BMI, kg/m²	21.4 ± 3.6	21.2 ± 3.2	21.3 ± 3.5	21.7 ± 4.3	0.822
eGFR, mL/min/1.73 m²	71.6 ± 19.4	100.4 ± 8.3	74.6 ± 8.2	45.4 ± 11.3	<0.001
Plasma creatinine, mg/dL	1.07 ± 0.35	0.79 ± 0.13	0.98 ± 0.14	1.50 ± 0.44	<0.001
Urine creatinine, mg/dL	118.4 ± 62.2	99.1 ± 53.1	116.8 ± 60.2	135.2 ± 69.4	0.054
Urine Cd, µg/L	11.85 ± 12.28	11.18 ± 18.70	10.56 ± 8.05	15.61 ± 15.31	0.079
Urine β_2M, mg/L	4.92 ± 17.43	0.20 ± 0.36	1.18 ± 4.02	17.57 ± 32.31	<0.001
Urine α_1M, mg/L	13.09 ± 18.68	5.66 ± 6.17	8.37 ± 7.91	30.04 ± 30.31	<0.001
Urine albumin, mg/L	25.57 ± 70.59	7.62 ± 7.29	22.64 ± 76.57	44.72 ± 73.74	<0.001
Urine protein, mg/L	85.4 ± 199.1	14.9 ± 22.6	56.2 ± 144.6	206.2 ± 307.7	<0.001
Normalized to E_{cr} as E_x/E_{cr} [b]					
E_{Cd}/E_{cr}, µg/g creatinine	10.43 ± 8.02	10.26 ± 10.35	9.98 ± 6.79	11.69 ± 9.20	0.641
$E_{\beta 2M}/E_{cr}$, mg/g creatinine	4.87 ± 16.55	0.23 ± 0.37	1.66 ± 9.72	16.13 ± 27.49	<0.001
$E_{\alpha 1M}/E_{cr}$, mg/g creatinine	11.34 ± 15.00	5.78 ± 4.95	7.53 ± 6.30	24.72 ± 24.57	<0.001
E_{Alb}/E_{cr}, mg/g creatinine	23.21 ± 55.07	10.47 ± 15.68	20.71 ± 59.50	37.88 ± 57.23	<0.001
E_{Prot}/E_{cr}, mg/g creatinine	78.25 ± 174.96	16.73 ± 24.54	57.98 ± 149.26	170.13 ± 246.01	<0.001
Normalized to C_{cr} as E_x/C_{cr} [c]					
$(E_{Cd}/C_{cr}) \times 100$, µg/L filtrate	11.27 ± 9.89	8.10 ± 9.06	9.67 ± 6.60	17.44 ± 14.17	<0.001
$(E_{\beta 2M}/C_{cr}) \times 100$, mg/L filtrate	7.74 ± 29.06	0.18 ± 0.28	1.82 ± 11.58	27.82 ± 52.20	<0.001
$(E_{\alpha 1M}/C_{cr}) \times 100$, mg/L filtrate	15.00 ± 28.25	4.46 ± 3.59	7.45 ± 6.63	41.20 ± 48.68	<0.001
$(E_{Alb}/C_{cr}) \times 100$, mg/L filtrate	29.06 ± 75.93	7.50 ± 9.83	20.23 ± 56.82	65.68 ± 119.75	<0.001
$(E_{Prot}/C_{cr}) \times 100$, mg/L filtrate	109.9 ± 316.8	13.0 ± 19.1	56.3 ± 141.0	310.2 ± 568.2	<0.001

n, number of subjects; eGFR, estimated glomerular filtration rate; E_x, excretion of x; cr, creatinine; C_{cr}, creatinine clearance; Prot, protein; Cd, cadmium; [a] eGFR was determined by equations of the Chronic Kidney Disease Epidemiology Collaboration [65]. [b] $E_x/E_{cr} = [x]_u/[cr]_u$; [c] $E_x/C_{cr} = [x]_u[cr]_p/[cr]_u$, where x = Prot or Cd. Data for all continuous variables are arithmetic means ± standard deviation (SD). For all tests, $p \leq 0.05$ identifies statistical significance, determined by Kruskal–Wallis test for mean differences across three eGFR ranges. Data are from Satarug et al. 2023 [63].

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Among 215 study subjects, 33 (15.3%), 131 (61%), and 51 (23.7%) had eGFR > 90, 61–90, and ≤ 60 mL/min/1.73 m², respectively (Table 2). Relative to the high-eGFR group, the excretion of creatinine tended to rise in the moderate- and the low-eGFR groups. The urinary Cd concentrations (μg/L) and E_{Cd}/E_{cr} in three eGFR groups showed no variation, thereby suggesting a non-association of eGFR decline and Cd exposure, measured as ECd/Ecr. These results in errors were reported in two meta-analyses [35,36].

In comparison, an inverse dose response relationship was observed between with eGFR E_{Cd}/C_{cr}; the mean E_{Cd}/C_{cr} was highest, middle, and lowest in the low-, moderate-, and high-eGFR groups. Those in the low-eGFR group excreted β_2M, α_1M, albumin, total protein, and Cd at the highest rates. Thus, accurate quantification of Cd nephropathy can only be realized, when excretion rates of β_2M, α_1M, albumin, total protein, and Cd itself are normalized to Ccr, which is not superfluous, but it eliminates conceptual flaw in the adjustment of excretion rate to creatinine excretion as noted above.

In summary, Ccr normalization is not affected by muscle mass while it corrects for differences in urine dilution and surviving and functioning nephrons. The utility of Ccr-normalized data in mechanistic dissection of albuminuria in Cd nephropathy, and health risk calculation are indicated also in Tables 3 and 4.

Table 3. Dose-response assessment using E_{cr}-normalized data.

Independent variables	Albuminuria	β2-microglobulinuria	Low eGFR
	POR (95% CI)	POR (95% CI)	POR (95% CI)
Age, years	1.053 (1.024, 1.082) ***	1.008 (0.988, 1.030)	1.143 (1.104, 1.184) ***
BMI, kg/m²	1.009 (0.935, 1.089)	0.987 (0.937, 1.039)	1.073 (0.982, 1.173)
Gender	0.959 (0.534, 1.722)	0.974 (0.640, 1.484)	0.904 (0.438, 1.846)
Smoking	1.903 (1.021, 3.547)	1.087 (0.720, 1.1641)	1.232 (0.583, 2.605)
Hypertension	1.815 (1.051, 3.134)	1.262 (0.867, 1.839)	1.474 (0.750, 2.894)
E_{Cd}/E_{cr}, μg/g creatinine			
< 2	Referent	Referent	Referent
2–4.99	0.799 (0.402, 1.586)	1.120 (0.687, 1.826)	1.959 (0.928, 4.133)
5–9.99	1.080 (0.526, 2.216)	1.417 (0.875, 2.296)	3.463 (1.466, 8.179) **
≥ 10	1.093 (0.380, 3.139)	1.807 (0.910, 3.587)	3.382 (0.862, 13.27)

POR, prevalence odds ratio; CI, confidence interval; eGFR; **p =0.005; ***p <0.001. Data are from Satarug et al. 2024 [64].

Table 4. Dose-response assessment using Ccr-normalized data.

Independent variables	Albuminuria	β2-microglobulinuria	Low eGFR
	POR (95% CI)	POR (95% CI)	POR (95% CI)
Age, years	1.050 (1.021, 1.079) **	1.008 (0.986, 1.030)	1.135 (1.094, 1.178) ***
BMI, kg/m²	1.017 (0.946, 1.093)	0.989 (0.939, 1.043)	1.083 (0.984, 1.192)
Gender	1.196 (0.676, 2.116)	0.962 (0.627, 1.474)	1.258 (0.576, 2.744)
Smoking	2.009 (1.118, 3.619) *	1.011 (0.667, 1.534)	1.280 (0.589, 2.782)
Hypertension	1.912 (1.129, 3.237) *	1.328 (0.907, 1.945)	2.063 (0.992, 4.294)
(E_{Cd}/C_{cr}) × 100, μg/L filtrate			
< 2	Referent	Referent	Referent
2–4.99	1.764 (0.886, 3.514)	1.914 (1.100, 3.330) *	5.704 (2.414, 13.48) ***
5–9.99	1.950 (1.009, 3.766) *	1.744 (1.030, 2.951) *	10.35 (4.160, 25.76) ***
≥ 10	2.849 (1.136, 7.146) *	2.462 (1.320, 4.595) **	18.06 (3.702, 88.15) ***

POR, prevalence odds ratio; CI, confidence interval; eGFR; *p = 0.016–0.047; **p = 0.001–0.005; ***p <0.001. Data are from Satarug et al. 2024 [64].

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No dose-effect relationships were observed between E_{Cd}/E_{cr} and the prevalence odds of albuminuria and β_2-microglobulinuria. There was a 3.5-fold increase in risk of low eGFR in those with Cd excretion rates of 5–9.99 μg/g creatinine, but not the most serverly affected group, compared with Cd excretion rate < 2 μg/g creatinine. In comparison, a clear dose-response relationships were observed for all three adverse outcomes (Table 4). Thus, in subjects with Cd nephropathy, normalization of excretion rates to C_{cr} demonstrated dose-effect relationships that were not evident with normalization to E_{cr}.

Based on C_{cr}-normalized data, all three adverse outcomes of Cd exposure, increases in albumin and β_2M excretion rates, and a reduction in eGFR, appeared to occur simultaneously. Among the three outcomes, eGFR was affected the most, while albumin and β2M were similarly affected. Of note, the eGFR effect of Cd was obscured completely, when E_{Cd} was normalized to E_{cr} (Table 2 vs. Table 3). For C_{cr}-normalized data, respective prevalence odds ratios for low eGFR rose 5.7-fold, 10.3-fold, and 18.1-fold in those with $(E_{Cd}/C_{cr}) \times 100$ values of 2–4.99, 5–9.99 and ≥ 10 μg/L of filtrate, compared with $(E_{Cd}/C_{cr}) \times 100$ values below 2 μg/L of filtrate.

Clearly, E_{cr} normalization of the excretion rate of Cd has dramatically underestimated the severity of Cd nephropathy. As tubular cells and nephrons are lost, an amount of Cd excreted is expected to be reduced. However, the effect of a reduced nephron number to lower E_{Cd} is offset in the C_{cr} normalization by a rise in $[cr]_P$ as C_{cr} falls. Consequently, excretion of Cd per intact nephron is accurately depicted. These scenarios can be found in Tables 2 and 4, thereby enabling a crucial dose-effect analysis and toxic risk calculation to be undertaken with a high degree of certainty (Section 4).

3. Impacts of Cadmium on Tubular Protein Reabsorption

Blood perfuses the kidneys at the rate of 1 L per minute, and all renal blood flow is directed through afferent arterioles into glomeruli [66]. In normal physiologic conditions, 20 % of plasma entering the glomerulus is filtered into Bowman's space. At least 90% of the circulating protein is ultrafilterable, and 99.9% of the filtered load is reabsorbed [67–69]. An approximate 40–50 g of protein can be retrieved each day in the proximal tubule of the kidneys, which is divided into segments S1, S2, and S3 [70–76]. Reabsorption of protein via receptor mediated endocytosis (RME) involving megalin and cubilin occurs mostly in S1, whereas fluid phase endocytosis (FPE) occurs in all three segments [77,78].

Impaired tubular reabsorption of proteins is a known sign of Cd intoxication, which is reflected by an increased excretion of the low-molecular weight proteins, namely retinol binding protein, α_1M, and β_2M, reviewed in Satarug and Phelps, 2021 [79]. Given that Cd intoxication is known to impair reabsorption of β_2M, it was hypothesized that Cd may interfere with reabsorption of albumin as well (Figure 1).

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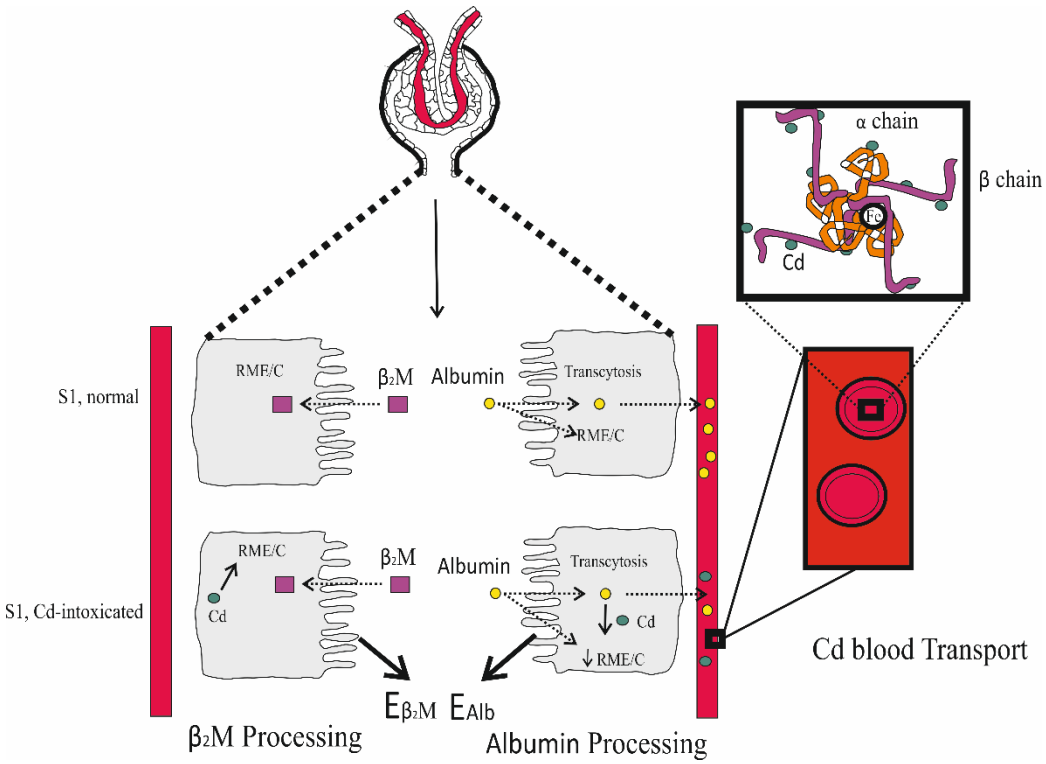

Figure 1. Tubular reabsorption of β2-microglobulin (β2M) and albumin. β2M is reabsorbed by receptor-mediated endocytosis (RME), and is catabolized (C) in lysosomes. Only a small fraction of albumin is reabsorbed through RME. Most albumin is returned to the circulation by transcytosis. Cd intoxication increases excretion of both β2M and albumin. As a carrier of Cd, reabsorption albumin may provide a delivery route for Cd to PTCs.

In normal kidney health, filtered β2M is reabsorbed and degraded mostly in S1 and to a lesser extent in S2 [80]. β2M is a constituent of FcRn, which mediates transcytosis of reabsorbed albumin [81–83]. There is little evidence for transcytosis of β2M. Albumin reabsorption occurs in S1, S2, and S3 [76,84] and FPE is believed to initiate most transcytosis of albumin [70].

In the circulation, most of Cd (90%) are bound to hemoglobin in red blood cells [85–88]. The remainder Cd (10%) is found in plasma, associated with albumin, histidine, and other non-protein thiols, including glutathione, cysteinylglycine, homocysteine, and γ-glutamylcysteine [89–92]. The total plasma concentrations of albumin thiols and non-protein thiols were 0.6 mM and 12–20 μM, respectively [93]. As a principal carrier of plasma Cd, reabsorption albumin complexed with Cd may provide Cd an entry route to PTCs. In an in vitro experiment, cell injury was observed in the rat proximal tubule WKPT-0293 Cl.2 cells, exposed to albumin and β2M complexed with Cd, but the injury was not evident, when cells were exposed to albumin or β2M alone [96].

Because binding of Cd alters the conformational structure of albumin [94,95], Cd-bound albumin probably undergo RME by the megalin-cubilin system and subsequent lysosomal degradation. Cd released during this process may then disrupt megalin homeostasis.

3.1. Cadmium-Induced Albuminuria

Albumin is a globular protein with a molecular weight of 66 kDa, which is synthesized in the liver and secreted into the circulation at a rate of 10–15 g per day [74,75]. Catabolism in muscle, the liver, and the kidney proximal tubular epithelial cells balance synthesis, and homeostasis is continued. Normal plasma concentration of albumin is between 3.5 g/dL and 5 g/dL, and the average half-life in plasma is 19 days [74,75]. Albumin is not normally filtered by glomeruli, due to its large molecular weight and its negative charge. However, by means of transcytosis through endothelial cells and podocyte foot processes, albumin reaches tubular lumen at a rate of 1–10 g per day [97,98].

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In an experimental study, Cd was found to disable the cubilin/megalin RME, leading to albuminuria [99]. In addition, Cd diminished expression of megalin and ClC5 channels [100]. Cd may also increase glomerular permeability to albumin, as shown in other studies, where a non-cytotoxic concentration of Cd (1 μM) increased the permeability of human renal glomerular endothelial cells in monolayers and caused the redistribution of the adherens junction proteins vascular endothelial-cadherin and β-catenin [101,102].

In any mechanistic dissection, a clear dose–response relationship must be first established and a population exposed to a wide range of Cd doses is required to meet this requirement. The Mae Sot District in western Thailand appeared to be ideal because it was an area where environmental Cd pollution was endemic [103–105]. This geographic area provided a well-circumscribed population of people with the same level of exposure that would enable one to discern the health impact of dietary Cd exposure [106–108]. More than 40% of residents aged ≥ 40 years were at risk of Cd-induced toxic injury, and Cd-induced tubular dysfunction [108]. Furthermore, the level of Cd exposure among the Mae Sot residents appeared to be moderate enough to be likely experienced by many populations.

In a logistic regression analysis of data from the Mae Sot residents (Table 4), the risk of albuminuria rose 2.1-7.9% for every one-year increase in age; it also rose 2-fold, and 1.9-fold in smokers and those with hypertension. In comparison, the risk of β_2-microglobulinuria was not affected by age, smoking, or hypertension. However, β_2-microglobulinnura and albuminuria both were related to the excretion of Cd in a dose-dependent manner. Adjustment for age reduced variance, and tightened the correlations of albumin excretion, β_2M excretion and Cd excretion. Consequently, the slope of albumin excretion vs. β_2M excretion regressions approached unity. Apparently, these data indicated that Cd affected a single mechanism, leading to reduction of reabsorption of both albumin and β_2M. Proposed mechanism of Cd-induced albuminuria is depicted in Figure 2.

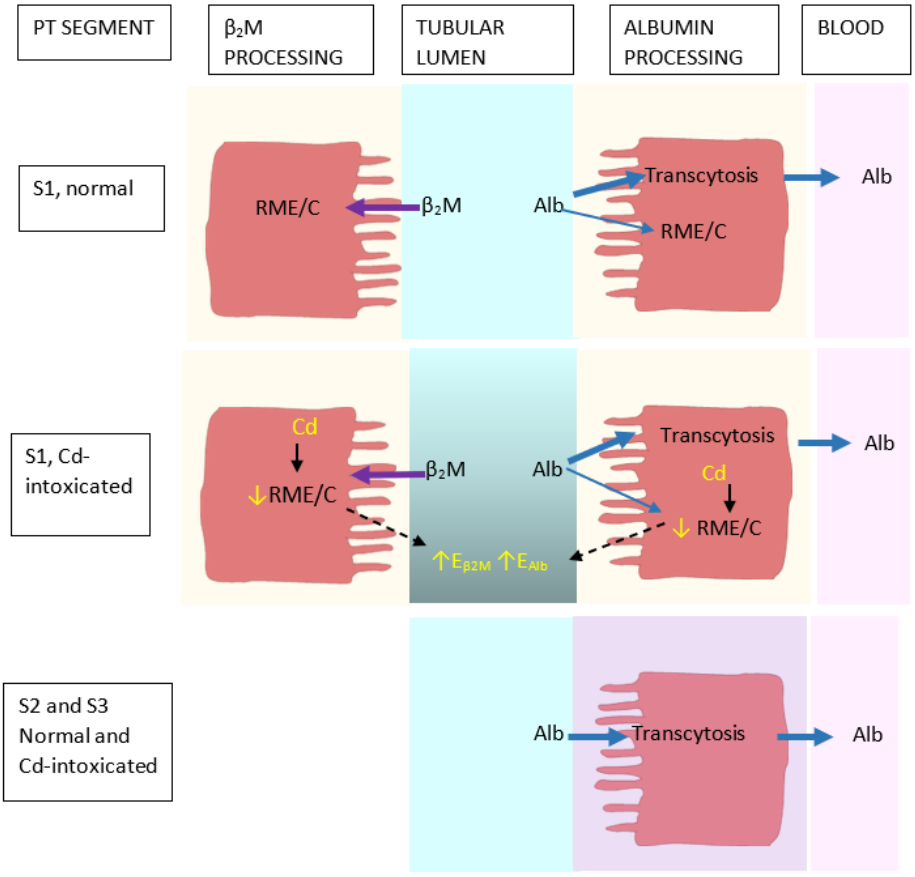

Figure 2. Proposed pathogenesis of reduced proximal tubular reabsorption of albumin and β2-microglobulin in Cd nephropathy. In S1, all β_2M is reabsorbed through receptor-mediated endocytosis (RME) and is catabolized (C) in lysosomes. Albumin is reabsorbed through RME in S1

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and transcytosis in S1, S2 and S3. A small fraction of reabsorbed albumin is subjected to lysosomal catabolism, while most are returned to the blood stream by transcytosis. Cd impairs RME function, which compromises reabsorption and increases excretion of both albumin and β_2M.

In S1, β_2M is reabsorbed by RME, involving the apical protein megalin. β_2M is then degraded in lysosomes. Albumin is reabsorbed by RME in S1, and FPE in S1, S2 and S3, and mostly returned to the circulation by transcytosis. A small fraction of albumin, reabsorbed through RME, undergoes lysosomal degradation. Cd does not disrupt transcytosis of albumin, but it impairs a single mechanism for RME and degradation of both β_2M and albumin. As inferred from the literature reports, it is proposed that Cd disrupts particularly the function of megalin, thereby decreasing reabsorption rates of both proteins [64].

3.2. Fractional Reductions in the Reabsorption of Albumin and β_2M

Fractional reductions in reabsorption of albumin and β_2M were estimated to assess the functional consequences of renal Cd accumulation on protein reabsorption [64].

In the least affected subjects (eGFR > 90 mL/min/1.73 m^2), mean E_{alb}/C_{cr} was 8.57 ×10^{-2} mg/L of filtrate, and mean $E_{\beta 2M}/C_{cr}$ was 5.97 μg/L of filtrate. In the most affected subjects (eGFR < 60 mL/min/1.73 m^2), corresponding values of E_{alb}/C_{cr} and $E_{\beta 2M}/C_{cr}$ were 70.27 ×10^{-2} mg/L of filtrate and 411 μg/L of filtrate, respectively. In the latter group, mean eGFR was 46.6 mL/min, or 67.1 L/d/1.73 m^2.

Fractional excretion of albumin (FE_{alb}; excretion rate/filtration rate of albumin) can be estimated as $(E_{alb}/C_{cr})(eGFR)/(GSC_{alb})([alb]_P])(eGFR)$, or (0.7027 mg/L of filtrate)(67.1 L/d)/(10-2)(40,000 mg/L)(67.1 L/d) = 0.0018, or 0.18%, if a glomerular sieving coefficient for albumin (GSC_{alb}) of 10^{-2} and plasma albumin concentration ($[alb]_P$) of 40 gm/L are assumed. This means that mean fractional tubular reabsorption of albumin (FTR_{alb}) was 99.8% even though a rise in absolute albumin excretion was discernible as eGFR fell. If GSCalb is assumed to have been 10^{-4} instead of 10^{-2}, FE_{alb} was 18%, and FTR_{alb} was 82%.

If $GSC_{\beta 2M}$ of 1 and $[\beta_2M]_P$ of 2.0 mg/L (2000 μg/L) are assumed, mean $F_{E\beta 2M}$ was $(E_{\beta 2M}/C_{cr})(eGFR)/(GSC_{\beta 2M})([\beta_2M]_P)(eGFR)$, or (411 μg/L of filtrate)(67.1L/d)/(1)(2,000 μg/L of plasma)(67.1 L/d) = 0.2055, or 21%. This means that $FTR_{\beta 2M}$ was 79%.

It is noteworthy that although the reductions are likely to have resulted from the same altered mechanism, fractional reductions in reabsorption of albumin and β_2M differed greatly if GSC_{alb} of 10^{-2} is assumed and were similar if GSC_{alb} of 10^{-4} is assumed.

3.3. Overall Effects of Cadmium Burden on Tubular Function

To assess the overall impact of Cd on tubular protein reabsorption function, the amounts of albumin and β_2M that were reabsorbed through RME, and subjected to catabolism in lysosomes were estimated, assuming glomerular sieving coefficients for albumin (GSC_{alb}) and β_2M ($GSC_{\beta 2M}$) to be 0.01 and 1, respectively (Table 5).

Table 5. Representative rates of filtration, excretion, catabolism, and transcytosis in normal and Cd-intoxicated proximal tubular cells.

PTC status	Protein	Filtration rate	Excretion rate	Catabolic rate	Transcytosis rate
Normal	Albumin	60 gm/d	20 mg/d	2.980 gm/d	57 gm/d
	β_2M	300 mg/d	100 μg/d	299.9 mg/d	0
Cd intoxicated	Albumin	60 gm/d	50 mg/d	2.950 gm/d	57 gm/d
	β_2M	300 mg/d	1000 μg/d	299 mg/d	0

Assumptions: plasma albumin is 40 gm/L; plasma β_2M is 2.0 mg/L; GFR is 150 L/d; the glomerular sieving coefficient for albumin (GSC_{alb}) is 0.01; and $GSC_{\beta 2M}$ is 1.

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3.4. Implication of Albumin Reabsorption for Delivery of Cadmium to Proximal Tubules

The evolving concept that proximal tubules reabsorb dozens of grams of albumin per day (Table 5) raises important theoretical possibilities concerning access of Cd to tubular cells. Red blood cells (RBCs) carry at least 90% of circulating Cd [85,86]. In a lysate of rabbit RBCs, the metal associated primarily with hemoglobin and glutathione [87]; in lysates of RBCs from mice pretreated with subcutaneous Cd for six months, the metal was bound to hemoglobin and to a smaller species, probably MT [86,88]. Multiple investigative techniques have shown that Cd binds to specific sites on the globin chains of hemoglobin, represented in Figure 1 [109,110].

The normal mean lifespan of RBCs (and therefore of hemoglobin) is 120 days, but changes in RBC membranes induced by Cd may alter the shape of cells, induce premature hemolysis in the reticuloendothelial system (RES), and thereby shorten cellular lifespan [111–113]. When senescent RBCs are destroyed in the RES, heme porphyrin groups are metabolized to bilirubin, which is taken up by circulating albumin [114,115]. Presumably, Cd is simultaneously released from globin chains as they are broken down to their constituent amino acids, and since albumin is so abundant in plasma, it is speculated that it is the principal scavenger of Cd from the RES. Cd-albumin complexes are continuously presented to hepatocytes and proximal tubular cells at high rates of blood flow, and both cell types store Cd that acquired as CdMT [79,116,117]. The internalization of Cd from albumin complexes has been shown [118].

Because binding of Cd binds alters the conformational structure of albumin [119,120], filtered Cd-albumin complexes probably undergo RME by the megalin-cubilin system and subsequent lysosomal degradation. Cd released during this process may then disrupt megalin homeostasis. If the above proposal is correct, then most Cd assimilated from exogenous sources is destined to interact with albumin eventually even if it is bound to hemoglobin initially.

3.5. Summary on the Impact of Cadmium on Protien Reabsorptuve Function

Accumulation of Cd in kidneys reduced receptor-mediated endocytosis of albumin and β_2M. Estimated fractional reductions in reabsorptions of albumin and β_2M were similar (18 vs 21%), assuming the glomerular sieving coefficients for albumin and β_2M to be 10^{-4} and 0.01, respectively. These impacts of Cd were quantifiable because of the clear dose-effect relationships of E_{alb}/C_{cr}, $E_{\beta 2M}/C_{cr}$, eGFR and the nephron burden of Cd, indicated by E_{Cd}/C_{cr}. In contrast, E_{alb}/E_{cr} (ACR), $E_{\beta 2M}/E_{cr}$ and E_{Cd}/E_{cr} were unrelated, thereby precluding dose-response analysis and nullifying the quantification of Cd effects.

4. CKD and the Health Risk Assessment of Environmental Cadmium

In this section human kidney accumulation of Cd and the excretion of Cd by this organ are addressed together with the estimation of the kidney burden of Cd that may carry discernable health risk using eGFR decline as a representative toxic endpoint and benchmark dose method to calculate benchmark dose limit (BMDL) value of Cd.

To derive exposure guidance values, the BMDL has increasingly been used as a replacement of no-observed-adverse effect level (NOAEL) to reflect the point of departure (POD) from population norm [56,121,122]. BMD method corrects some of the shortcomings of the NOAEL [56,123–125]

4.1 Measurement of Kidney Burden of Cadmium

Cd accumulation in human kidneys can be found in reports of analysis of post mortem and biopsied samples (Table 6).

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Table 6. Cadmium accumulation in human kidneys.

Country of Origin	Cadmium content, μg/g wet tissue weight	Reference
Australia, Autopsy, n 61, 2–89 years	The percentage of kidney Cd content ≥ 50 μg/g was 3.3%.[a] Mean lung, liver and kidney Cd were 0.13, 0.95, and 15.45 μg/g, respectively. Mean kidney Cd was 16 times higher than liver. Peak hepatic and renal Cd levels were 1.5 and 25.9 μg/g.	Satarug et al. [126]
United Kingdom, Autopsy, n 2700, nationwide (1978–1993)	The percentage of kidney Cd content ≥ 50 μg/g was 3.9%. Mean kidney Cd content was 19 μg/g. Peak renal Cd level was 23 μg/g.	Lyon et al. [127]
Canada (Quebec) Autopsy, n 314	Respective mean liver (kidney) Cd in smokers, ex-smokers and non-smokers were 2.5 (34.5), 1.4 (20.3) and 0.7(7.0) μg/g. Mean liver Cd in female smokers was higher than male smokers (3.6 vs. 2.2 μg/g). Peak hepatic and renal Cd levels were 2.2 and 44.2 μg/g.	Benedetti et al. [128]
Greenland [101] Autopsy, n 95, 19–89 years	Mean (range) liver Cd content was 5.3 (0.3–24.3) μg/g. Mean (range) kidney Cd content was 43.8 (6.7–126) μg/g. Peak hepatic and renal Cd levels were 1.97 and 22.3 μg/g.	Johansen et al. [129]
Sweden Kidney transplant donors, n 109, 24–70 years, median age 51.	Median kidney Cd was 12.9 μg/g. In non-smokers, renal Cd accumulation rate was 3.9 μg/g in every 10-year increase in age. An additional 3.7 μg/g accumulation rate in every 10-year smoking. In women who had serum ferritin levels ≤ 20 μg/L (depleted iron stores), renal Cd accumulation rate was 4.5 μg/g in every 10-year increase in age.	Barregard et al. [130]

[a] Kidney Cd content of 50 μg/g was used as a toxicological reference value [131].

It is noteworthy that Australian study measured lung Cd content, which was used to assess contribution of inhalational exposure, where females were found to have higher hepatic and renal cortical Cd levels than males of after adjustment for age and inhalational exposure. Renal cortical Cd content increases progressively to age 50 years and declines sharply thereafter. Peak kidney Cd content was 25.9 μg/g [126].

Hepatic Cd content increased gradually with age without interruption, and it was higher in women than in men. It is speculated that iron depletion due to menstrual losses promoted intestinal Cd absorption in women during the premenopausal years, and we speculate that nephron loss and interstitial scarring due to aging and Cd toxicity caused the observed decline in cortical Cd content after age 50 [132,133].

4.4. Cadmium Excretion and Glomerular Filtration Rate

A paradox is evident in reported relationships of GFR to environmental Cd exposure. Some investigators found that E_{Cd} rose with GFR when exposure was low [134–136]. On the other hand, many investigators associated tubular dysfunction with low environmental exposure [137–140], and at least two groups found that GFR fell from normal values as ECd rose minimally [141–143].

To reconcile these observations, we speculate that Cd nephropathy begins with a transitory phase in which cell injury is releasing Cd to filtrate but has not yet led to cell death; during that phase, the number of nephrons determines ECd. As Cd begins to destroy cells, E_{Cd} increases further even though nephrons drop out and GFR begins to decline. Lending support to this speculation is a recent study in which that eGFR rose with ECd at low kidney burden (E_{Cd}/C_{cr}) < 0.01 μg/L filtrate, and this parameter (eGFR) showed an inverse association with E_{Cd} as E_{Cd}/C_{cr} levels > 0.01 μg/L filtrate.

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A large body of work shows that GFR fell as a consequence of intense occupational or environmental exposure to Cd. Nephron loss was most extreme in polluted regions of Japan [144], but it was also documented in other Asian countries and in Europe. Progression of CKD often continued after cessation of exogenous exposure [145–147].

Reductions in GFR due to Cd nephropathy are sometimes attributed to glomerular injury. Although this inference may be at least partially correct, it is not necessary. Sufficient tubular injury disables glomerular filtration and ultimately leads to nephron atrophy, glomerulosclerosis, and interstitial inflammation and fibrosis [148].

Cd that eludes MT complexation promotes synthesis of ROS that inflict injury. That injury induces autophagy, apoptosis, and necrosis of tubular cells, and it undermines adhesion of cells to one another. Cellular injury also leads to the release of proteins and CdMT into filtrate; compromises reabsorption of filtered proteins and substances co-transported with sodium; and ultimately reduces GFR through destruction of nephrons.

4.3. An Acceptable Kidney Burden of Cadmium?

The kidney burden of Cd that was unlikely to reduce eGFR more than 5% has been determined, for the first time [149] using data from 1189 Thai subjects (493 males and 696 females) mean age of 43.2 years (Figure 3).

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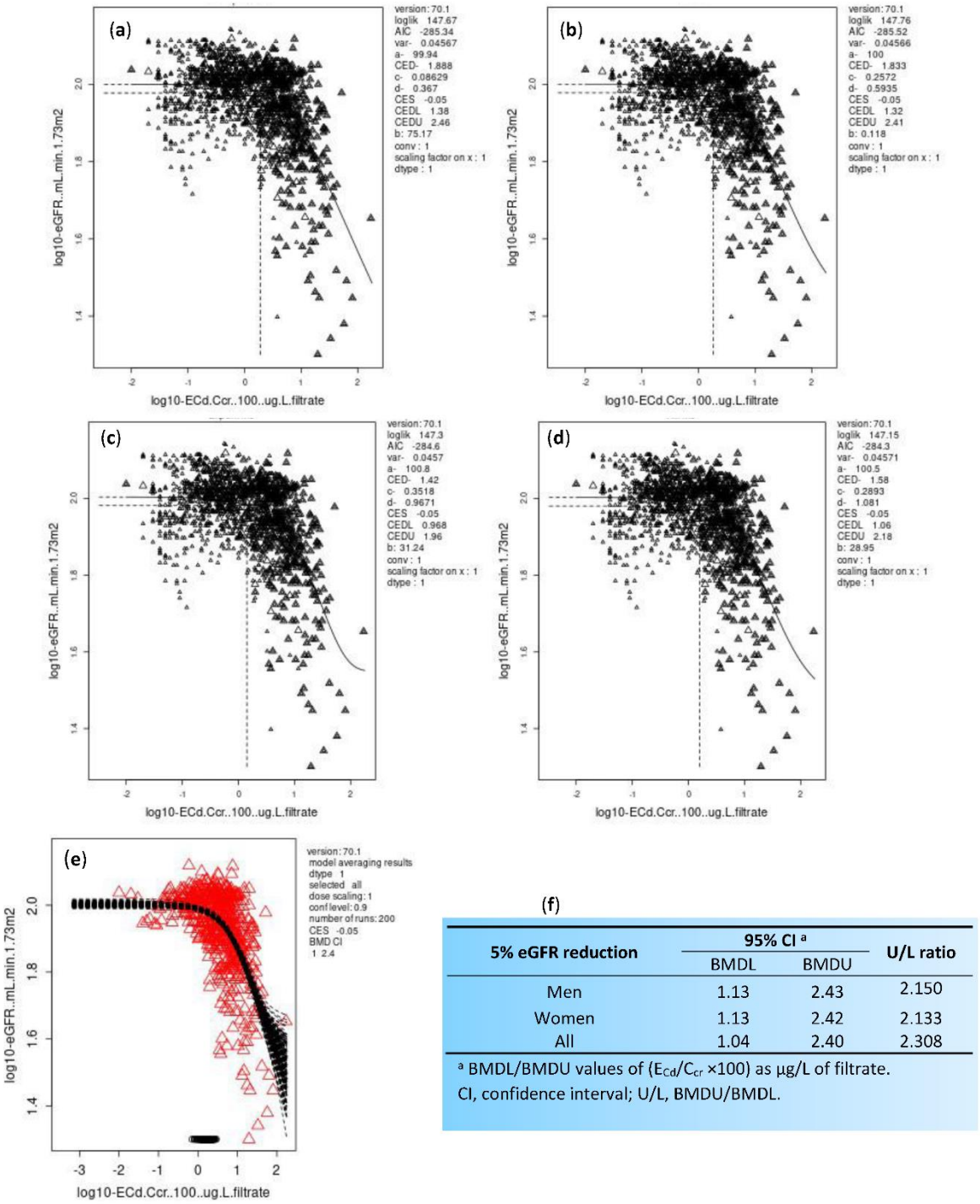

(f)

5% eGFR reduction	95% CI [a]		U/L ratio
	BMDL	BMDU	
Men	1.13	2.43	2.150
Women	1.13	2.42	2.133
All	1.04	2.40	2.308

[a] BMDL/BMDU values of (E_{Cd}/C_{cr} ×100) as µg/L of filtrate.
CI, confidence interval; U/L, BMDU/BMDL.

Figure 3. Determination of the burden of Cd producing 5% reduction in eGFR. E_{Cd}/C_{cr} and eGFR data were fitted to (**a**) an inverse exponential model; (**b**) a natural logarithmic model; (**c**) an exponential model; and (**d**) Hill model. Bootstrap curves for model averaging of E_{Cd}/C_{cr} BMD estimates for all subjects (**e**). BMDL/BMDU values of E_{Cd}/C_{cr} producing 5% reduction in eGFR (**f**). Data are from Satarug et al. 2022 [149].

The overall percentages of smokers, subjects with hypertension and low eGFR in this group of subjects were 33.6%, 29.4% and 6.2%, respectively. In a conventional dose-response evaluation, low eGFR was associated with higher E_{Cd}/C_{cr}, older age and higher BMI, but not with gender, smoking, or hypertension.

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In benchmark dose estimation (Figure 3), the BMDL value of ECd/Ccr × 100 producing a 5% reduction in eGFR was 1.13 μg/L of filtrate in both men and women. These BMDL values can be translatable to Cd excretion rate between 0.01 and 0.02 μg/g creatinine. Because the basic (fundamental) mechanism of Cd toxicity should be the same, the BMDL value for any effect of Cd. In comparison, however, a previous risk analysis conducted on Mae Sot residents, the BMDL values of E_{Cd}/E_{cr} for the β_2M endpoint were 6.9 and 8.1 μg/g creatinine in men and women, respectively [108].

Another conventional dose–response analysis of data from 482 non-occupationally exposed persons with a 1250-fold difference in Cd burden and a 667-fold difference in levels of blood Cd, environmental exposure to Cd was confirmed to be closely associated with a declining GFR and albuminuria [150]. When a declining GFR is considered along with albuminuria, the NOAEL equivalent of Cd excretion ranged is 0.01–0.02 μg/g creatinine. Now is the time to acknowledge there is no safe level of Cd exposure.

4.4. Past and Present Health Threat of Environemnatl Cadmium

An outbreak of human cases with severe Cd poisoning, referred to as "itai-itai" disease [151,152], has brought into focus health threat from consumption of rice heavily contaminated with Cd. To safeguard against excessive dietary exposure, a tolerable intake level of Cd, a reference dose (RfD), toxicological reference value, and permissible levels of Cd in foods were determined [121,131,153,154].

Cd is now detectable in virtually all food types, and is becoming a toxic metal pollutant of global public health significance because lifelong Cd exposure has now been identified as one of the contributing factors to the rising prevalence of CKD, diabetes type 2 and many types of cancer worldwide [155,156]. New health guidance values are needed and this Section is aimed to address the practice of health risk estimation of non-occupational exposure situations.

In theory, for a toxicant that affects many organs and tissue, a threshold level of its toxicity and exposure guidelines should be based on the most sensitive endpoint with consideration given to susceptible subpopulations [56]. For any risk assessment practice, the critical elements are accurate measurements of both exposure and adverse effects. The impact of these key elements has revealed by systematic reviews and meta-analyses reporting discrepancies [34–36] (Sections 2.2 and 2.3).

4.4.1. The WHO Exposure Guidelines and the Nephrotoxicity Threshold Level

The Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) suggested a tolerable monthly intake (TMI) of Cd to be 25 μg per kg body weight per month, equivalent to 0.83 μg per kg body weight per day (58 μg/day for a 70 kg person), and E_{Cd}/E_{cr} of 5.24 μg/g creatinine was adopted as a nephrotoxicity threshold value [153]. Both figures were based on a risk assessment model based solely on $E_{\beta 2M}/E_{cr} \geq 300$ μg/g creatinine, as a toxic endpoint or an effect of health concern. Consequently, an increased β_2M excretion became the most frequently reported adverse effect of oral Cd exposure.

A rice Cd content of 0.27 mg/kg was associated with kidney and bone damage like those found in itai-itai disease patients [157]. This rice Cd content is below the Codex standard for rice of 0.4 mg/kg [154]. Also, a lifetime Cd intake ≥ 1 g, which is half of the JECFA exposure guideline [253], yielded a 49% increase in mortality from kidney failure, especially among women [158]. These findings cast considerable doubt on the Codex maximally permissible Cd level in rice of 0.4 mg/kg, and the lifetime tolerable Cd intake of 2 g, as suggested by JECFA [153].

Studies from China suggested an upper limit of permissible level of Cd in rice to be 0.2 mg/kg, one half of the Codex standard [159–161]. All these estimations relied on E_{Cd}/E_{cr} of 5.24 μg/g creatinine to indicate a toxic Cd accumulation level. Of note, prevalence odds for low eGFR and albuminuria rose at E_{Cd}/E_{cr} values ≥ 0.27-0.32 μg/g creatinine (Table 1). Thus, these indicators of Cd toxicity occurred long before E_{Cd}/E_{cr} reached 5.24 μg/g creatinine level, at which $E_{\beta 2M}/E_{cr}$ rises to ≥ 300 μg/g creatinine. Furthermore, the likelihood of eGFR to fall below 60 mL/min/1.73 m^2 rose 4.7-fold, 6.2-fold and 10.5-fold in those who had $E_{\beta 2M}/E_{cr}$ values of 100–299, 300–999, and ≥ 1000 μg/g creatinine, respectively [162]. Because eGFR values ≤ 60 mL/min/1.73 m^2 are indicative of destruction and loss of

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nephrons [162]. A rise of $E_{\beta 2M}/E_{cr} \geq 300$ μg/g creatinine is a manifestation of severe toxicity of Cd; as such its use in health risk estimation is inappropriate. Reasons for a rise of β2M excretion in those with low eGFR can be found below.

4.4.2. β2-Microglobulinuria as an Indicator of Toxicity?

The protein β2M with a molecular weight of 11.8 kDa is a component of class I major histocompatibility complexes, found on the surface of most nucleated cells [83]. The plasma β2M concentration is relatively constant, but it may rise in patients with chronic inflammatory conditions or hematologic malignancies [163].

By β2M is eliminated exclusively by the kidneys. A modest fraction of the amount removed is taken up from peritubular capillaries [164], but most elimination results from glomerular filtration, proximal tubular reabsorption, and intracellular degradation. When the GFR is normal, the equilibrium between plasma influx and renal processing establishes a plasma concentration between 1.2 and 2.7 mg/L [163]. As GFR falls, the filtrate is presented to proximal tubules at a rate that is absolutely reduced but normal or increased per surviving nephron. Plasma β2M concentration rise secondarily, and equilibrium between the influx and the degradation of the protein is maintained [164–169].

In Cd research, it has been customary to declare that proximal tubular toxicity is present at $E_{\beta 2M}/E_{cr} > 300$ μg/g creatinine [153]. At an arbitrary Eβ2M of 300 μg/d, E_{cr} of 1 g/d, GFR of 144 L/d (100 mL/min), and filterable $[\beta 2M]_p$ of 2.0 mg/L, fractional excretion of β2M (FEβ2M) is 0.1% and fractional reabsorption (FRβ2M) is 99.9%. Doubling of Eβ2M to 600 μg/g creatinine, a clearly elevated value, entails an increase in FEβ2M from 0.1% to 0.2% and a reduction in FRβ2M to 99.8%. Miniscule Cd-induced reductions in FRβ2M, therefore, lead to substantial increments in Eβ2M [170].

The sensitivity of Eβ2M to slight reductions of FRβ2M should not be interpreted as evidence that the underlying cellular injury is trivial. Values of ECd at which Eβ2M exceeds 300 μg/g creatinine are at least 10 times higher than in normal populations [171,172]. If ECd itself is a marker of toxicity, then the customary cutoff value of Eβ2M is not a sensitive metric for detecting tubular injury. For pathophysiologic insight, Eβ2M is most logically related to the normal maximal reabsorptive capacity for the protein—i.e., the tubular maximum (Tmβ2M)—if such a Tm exists. Hall could not demonstrate one in dogs with an infusion of human β2M [164], but in rats, Gauthier documented a Tmβ2MG when [β2M]p was approximately four times the norm [67].

In theory, if a Tmβ2M existed in humans, a decline in GFR might expose it. In this circumstance, surviving nephrons would be presented with a higher concentration of β2M in less total filtrate volume, and a normal rate of presentation to a reduced nephron mass could exceed a putative Tmβ2M. Multiple investigators have argued that this scenario occurs, but it is often possible that the disease lowering GFR has also lowered Tmβ2M [166,169]. In patients with hepatorenal syndrome, in which the perfusion of normal kidneys is severely limited, a Tmβ2M was not demonstrable despite extreme reductions in GFR and elevations in $[\beta 2M]_p$ [168]. Similarly, in children with glomerular disease exclusively, on biopsy, FEβ2M did not correlate with GFR [169].

If some humans can reabsorb all filtered β2M despite a low GFR and high $[\beta 2M]_p$, then nephron loss is insufficient to explain excessive Eβ2M in patients with Cd nephropathy. It appears that Cd imposes a Tmβ2M or reduces one that already exists, and increased Eβ2M indicates reduced β2M reabsorption per nephron at any GFR [173]. Once Cd has established a Tmβ2M, we expect Eβ2M to rise substantially as GFR falls. Multiple investigators have documented this phenomenon [162,174,175], but none have quantified the individual contributions of GFR and Tmβ2M to excessive Eβ2M.

5. Conclusions

As the result of cadmium accumulation in renal proximal tubular cells, the fractional reabsorption rates for albumin and β2-microglobulin are reduced simultaneously, leading to an increased excretion of both proteins. It appears that cadmium adversely affects a single phenomenon

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involved in reabsorption of both albumin and β_2-mcroglobulin. The affected phenomenon is probably receptor-mediated endocytosis involving megalin.

The conventional method for adjusting the excretion rates of cadmium and albumin to the excretion of creatinine incorporates a conceptual flaw that can be eliminated if the rates are normalized to creatinine clearance. The NOAEL equivalent of Cd accumulation levels corresponding to a discernable GFR reduction are is extremely low. Now is the time to acknowledge there is no safe level of Cd exposure.

At present, no treatments exist for mitigation of Cd nephropathy or effective chelation therapy for removal of Cd from tubular cells. Commonsense therapeutic measures include cessation of environmental exposure.

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