

Environmental Cadmium Exposure Limits and Thresholds for Adverse Effects on Kidneys

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Abstract

Kidney and bone destruction in patients with itai-itai disease is caused by consuming rice contaminated with the heavy metal cadmium (Cd). Using a cumulative lifetime exposure of 2 g of Cd and excretion of β_2 -microglobulin (β_2 M) at a rate above 300 $\mu\text{g/g}$ creatinine in risk computation, an identified “tolerable” Cd exposure level was 0.83 $\mu\text{g/kg}$ body weight per day (58 $\mu\text{g/day}$ for a 70 kg person), and a Cd excretion rate of 5.24 $\mu\text{g/g}$ creatinine was a threshold level. However, evidence suggests that these guidelines are inadequate to protect public health. Using experimental dosing and human population data, this review highlights the imprecisions in determining exposure, internal doses, and effects, leading to erroneous conclusions that Cd exposure did not affect the estimated glomerular filtration rate (eGFR) nor it contributed to progressive deterioration of eGFR toward kidney failure among Cd-exposed people. It demonstrates an application of benchmark dose (BMD) modeling to human exposure-effect relationships to identify the Cd burden that produces negligible impacts on eGFR,



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excretion of total protein, albumin and N-acetyl- β -D-glucosaminidase. It offers insights into dose-response models that can be used to define the lower 95% confidence bound of the BMD, termed BMDL value for Cd excretion rate, the equivalent of “no observed adverse effect level” (NOAEL) identified from experimental dosing. A Cd excretion rate of 0.05 $\mu\text{g/g}$ creatinine has emerged as the body burden, below which kidney functional integrity is preserved. This body burden of Cd should form a basis for estimation of a safe dietary Cd exposure level.

Keywords: Benchmark dose limit, cadmium, exposure threshold, glomerular filtration rate, kidneys, urinary β_2 -microglobulin

INTRODUCTION

Consumption of rice contaminated with the toxic metal cadmium (Cd) for 50 years or longer can cause itai-itai disease, marked by severe damage to kidneys and bones^[1-4]. Recently, there has been a significant decrease in the worldwide production and industrial uses of Cd, however, with the continued use of Cd-contaminated phosphate fertilizers in many parts of the world, it is still being added to the food chain^[5-7]. An approximate 15% of world's cropland is found to be contaminated with toxic metals, especially Cd which is widespread in south and east Asia, parts of the Middle East and Africa^[8]. Our reliance on phosphate fertilizers for production of foods and feeds^[9-11] means that Cd is being mobilized from biological inaccessibility to accessible situations within food chains. Inevitably normal diets have become a common route of exposure to the metal^[12-14]. Airborne particle pollution is an additional Cd exposure route, especially among urban populations, and tobacco smoke is a further source of environmental Cd^[15-18].

As a measure against population exposure to excessive Cd, food safety monitoring programs, known as Total Diet Studies have been established, and permissible levels of Cd in human foodstuffs have been determined along with exposure guidelines and corresponding exposure threshold levels^[19]. By definition, a threshold level for any adverse effect is referred to as an exposure level of any health hazardous substance that may adversely affect 5% of the population^[20-23]. This implies that any exposure guideline is aimed to protect 95% of the population at the most. Based on a cumulative

lifetime exposure of 2 g of Cd and β_2 -microglobulin (β_2 M) excretion rates ≥ 300 $\mu\text{g/g}$ creatinine as a sign of the nephrotoxicity of Cd, the Joint Food and Agriculture Organization and World Health Organization (FAO/WHO) Expert Committee on Food Additives and Contaminants (JECFA) defined a Cd exposure level of 0.83 $\mu\text{g/kg}$ body weight per day (58 $\mu\text{g/day}$ for a 70 kg person), as an exposure level that carries an unappreciable health risk^[24]. For this β_2 M endpoint, excretion rate of Cd at 5.24 $\mu\text{g/g}$ creatinine was identified as a threshold level, where $\leq 5\%$ of the population is presumably affected by exposure to excessive Cd.

Also, there is compelling evidence that the above exposure guidelines are not protective of population health. Kidney and bone destructions like those in patients with itai-itai disease have been linked to consumption of rice containing Cd at 0.27 mg/kg dry grain weight^[25]. This rice Cd level does not exceed the Codex standard at 0.4 mg/kg for the staple^[26]. In another study, a 49% increase in mortality from kidney failure has been linked to a lifetime Cd exposure ≥ 1 g, only a half of an intake level that JECFA viewed as a “tolerable” lifetime dietary exposure^[27]. A recent analysis of β_2 M homeostasis has unveiled that an excretion of β_2 M did not reliably inform kidney tubular dysfunction^[28]. Importantly, an abnormally high β_2 M excretion rate in Cd-exposed subjects was found to be a consequence of Cd-induced nephron destruction, which caused the estimated glomerular filtration rate (eGFR) to fall to one third of the normal range (60 mL/min/1.73 m², termed low eGFR)^[29]. Such Cd-induced eGFR reduction was accompanied by rising blood pressure, which consequentially increased risk of having hypertension and albuminuria^[30-32]. A dietary Cd exposure of ≥ 16.7 $\mu\text{g/day}$ has been associated with an increased risk of having low eGFR in Chinese population study^[33].

The present review focuses on toxicological risk assessment applied to environmental Cd exposure and the kidney as a principal toxicity target. The risk of having chronic kidney disease (CKD), signified by a fall of the estimated to one third of a normal range (60 mL/min/1.73 m²) and/or the presence of albuminuria for at least 3 months^[34-36], have been associated with urinary Cd excretion rates of 0.27-0.37 $\mu\text{g/g}$ creatinine^[37-39]. These Cd excretion levels are attained after 50 years of dietary Cd intake levels between 10 and 15 $\mu\text{g/day}$, assuming the intestinal absorption rates of 3-7%^[40]. A prospective cohort study from Switzerland reported that a rapid fall of eGFR was causally

associated with Cd exposure^[41]. Another prospective cohort study of Japanese population observed a fall of eGFR at high a rate (10 mL/min/1.73m² over five years) in those who had β_2 M excretion rate of 300 μ g/g creatinine^[42]. These findings suggest that a high β_2 M excretion rate is indicative of severe kidney pathology and that exposure to a low Cd level could contribute to CKD onset and progression toward end-stage kidney disease. Alarming, the global prevalence of CKD has now reached epidemic proportions, and it is projected to become the 5th leading cause of years of life lost by 2040^[43,44]. Now is the time to identify a Cd exposure level that does not pose an excessive risk.

As its first objective, this review highlights the terminology used in toxicological risk assessment and the benchmark dose (BMD) methodology to define a critical exposure level for any health hazardous substance. The second objective is to provide the Cd exposure limits, and thresholds determined from experimental dosing and human population data based on adverse effects on kidneys, bones, and lungs. The third objective is to demonstrate an application of the BMD modeling to Cd exposure, kidney effects and the prevalence of such effects in human populations to identify the toxic endpoint most sensitive to Cd. In theory, an exposure limit derived from the most sensitive endpoint would be protective against all other adverse effects^[19-21].

Permissible Exposure Levels for Environmental Cadmium

Herin, Cd exposure limits, determined from experimental dosing and human population data, using kidneys, bones, and lungs as targets are highlighted (Tables 1 and 2). These exposure limits rely on the premise that there is a critical exposure level below which an adverse effect is insignificant^[20-22]. This method is applicable to non-carcinogenic substances only. However, it should be noted that Cd is classified as a cancer-causing agent in humans, and a standard two-year rodent/murine bioassay demonstrated unambiguously that Cd is a multi-tissue carcinogen^[45-48]. By systematic reviews and meta-analyses of epidemiological data, increased risks of having tumors in the lung, kidney, pancreas, breast, and liver have independently been linked with chronic exposure to environmental Cd^[49,50]. With respect to tumorigenic effects, maintaining the lowest achievable exposure level of Cd is essential preventive measure.

Exposure Limits Computed from Experimental Dosing

Typically, an exposure limit for a health concern substance is based on a dose-response curve, constructed from experimental dosing, which often involves daily administration of 4-5 different doses for 90 days or longer^[19-21]. From a dose-response curve, a point of departure (POD) is established from the lower bound “no observed adverse effect level” (NOAEL) and the upper bound “lowest observed adverse effect level” (LOAEL)^[19-21]. The NOAEL value is referred to the highest dose tested that produces a statistically insignificant effect, compared to controls. This NOAEL is translated to the benchmark dose (BMD) lower limit (BMDL) by an uncertainty factor, which accounts for species differences and human variability^[19-21].

The POD-based health guidance exposure limits are reported as minimal risk level (MRL), a toxicological reference value (TRV), tolerable weekly intake (TWI), tolerable monthly intake (TMI) and a reference dose (RfD)^[19-21]. These different terms used to describe exposure limits should be standardized because they create unnecessary confusions and barriers.

Table 1. Exposure limits based on dosing experiments.

| Target Organ/Effect Measured | Animal species /Dosing regimes | BMDL/Exposure limits | Reference |
|--|---|---|--|
| Kidneys Tubular malfunction/ Urinary NAG, CdMT, and β_2 M | Inbred pigs. Does: Cd in the feed at 0, 0.5, 2, 8, and 32 mg Cd/kg for 100 days. Cd in tab water was less than 0.001 μ g/L. | BMDL values of Cd were 0.67, 0.88, 1.00, and 3.08 mg/kg feed for RBP, NAG, CdMT and β_2 M. With an uncertainty factor 100, a tolerable Cd intake level in humans was 0.2 μ g/kg body weight/day. | Wu et al. 2012 ^[51] |
| Bones Decrease in bone | Wistar rats. Doses: CdCl ₂ in for oral Cd in an | Minimal risk level (MRL) | Faroon et al. 2017 ^[52-55] |

mineral density drinking water at 0, intermediate exposure
1, 5, or 50 mg/L for duration (15–365 days):
6, 9, or 12 months. 0.5 µg/kg body weight per
day

Lungs Fisher F344 rats MRL for an acute Faroon et al.
Alveolar histiocytic Doses: CdO at 0, 0.1, inhalational exposure to 2017^[55,56]
infiltration and 0.3, 1, 3, or 10 mg Cd for the duration
focal inflammation CdO/m³, for 6.2 between 1 and 14 days:
in alveolar septa. hours/day, 5 0.03 µg/m³
days/week, for 2
weeks.

BMDL, benchmark dose lower limit, RBP, retinol binding protein; NAG, N-acetyl-β-D-glucosaminidase; CdMT, cadmium complexed with metallothionein; β₂M, β₂-microglobulin.

The BMDL values estimated from dosing pigs were 0.67, 0.88, 1.00, and 3.08 mg/kg feed for the RBP, NAG, CdMT and β₂M endpoints, respectively^[51]. The dose of Cd producing abnormal β₂M excretion was the highest and it was lowest for the RBP. Applying an uncertainty factor 100, a tolerable Cd intake level in humans was estimated at 0.2 µg/kg body weight/day. The MRL for oral Cd exposure in an intermediate exposure duration (15–365 days) was be 0.5 µg/kg body weight per day^[52-55], while the MRL for an acute inhalational exposure (1 and 14 days) was 0.03 µg/m³^[56].

Exposure Limits Computed from Human Exposure-Effect Data

Table 2. Exposure limits estimated from human exposure-effect datasets

| Target Measured | Organ/Effect | Permissible Exposure | Exposure Threshold | Reference |
|---|------------------------------|----------------------------|-----------------------|-------------------------|
| Kidneys | | Tolerable Cd intake: | Cd excretion of | JECFA ^[24] |
| Tubular excretion rate ≥ 300 µg/g creatinine. | malfunction/β ₂ M | 0.83 µg/kg body weight/day | 5.24 µg/g creatinine. | |
| Kidneys | | Reference dose (RfD) | Cd excretion of 1 | EFSA ^[57,58] |
| Tubular excretion rate ≥ 300 µg/g | malfunction/β ₂ M | for oral Cd: 0.36 µg/kg | µg /g creatinine | |
| | | body | | |

| | | | |
|--|---------------------------------|----------------------------|-----------------------------|
| creatinine. | weight/day | | |
| Kidneys | Tolerable Cd intake: | Cd excretion of | Qing et al. |
| Tubular injury and | 0.28 $\mu\text{g/kg}$ body | 2.93 and 3.07 | 2021 ^[59] |
| malfunction, $\beta_2\text{M}$ and NAG | weight/day | $\mu\text{g/g}$ creatinine | |
| excretion rates. | | for NAG and | |
| | | $\beta_2\text{M}$ | |
| Bones | Tolerable Cd intake: | Urinary Cd of | Qing et al. |
| Decreased bone mineral | 0.64 $\mu\text{g/kg}$ body | 1.71 $\mu\text{g/g}$ | 2021 ^[60] |
| density | weight/day | creatinine. | |
| Bones | Tolerable Cd intake: | N/A | Leconte et |
| Decreased bone mineral | 0.35 $\mu\text{g/kg}$ body | | al. 2021 ^[61] |
| density | weight/day. | | |
| Kidneys and bones | Toxicological | N/A | Schaefer et |
| Tubular malfunction, | reference value (TRV) | | al. 2023 ^[62,63] |
| decreased bone mineral | for oral Cd: | | |
| density | 0.21–0.36 $\mu\text{g/kg}$ body | | |
| | weight/day | | |

$\beta_2\text{M}$, β_2 -microglobulin; NAG, N-acetyl- β -D-glucosaminidase; CdMT, cadmium complexed with metallothionein; RBP, retinol binding protein.

Using the $\beta_2\text{M}$ endpoint and kidney target, the lowest value of a tolerable dietary Cd exposure was 0.28 $\mu\text{g/kg}$ body weight per day (16.8 $\mu\text{g/day}$ for a 60 kg person)^[59]. This appeared to be close to the exposure limit obtained from experimental dosing in pigs of 0.2 $\mu\text{g/kg}$ body weight per day^[51]. The lowest threshold level for the $\beta_2\text{M}$ endpoint was 1 $\mu\text{g/g}$ creatinine^[57,58]. An exposure limit for a decrease in bone mineral density was 0.64 $\mu\text{g/kg}$ body weight per day with a threshold level of 1.71 $\mu\text{g/g}$ creatinine^[60].

Cadmium Exposure Limits for Workers

The kidney target and abnormal $\beta_2\text{M}$ excretion rates have been applied also in an evaluation of inhalational exposure to Cd in workplace settings^[64,65]. Like the environmental exposure scenarios, there is evidence that workers' exposure limits at blood Cd concentrations of 5 $\mu\text{g/L}$, and Cd excretion rate of 5 $\mu\text{g/g}$ creatinine were not

low enough to protect workers' health. Using data from 326 male and 114 female Japanese workers, Nogawa et al. (2021) estimated the BMDL value for a 40-year cumulative inhalational exposure to Cd to be $17.7 \mu\text{g}/\text{m}^3$ and the BMDL values for blood Cd to be $1.8\text{--}2.0 \mu\text{g}/\text{L}$ ^[66]. Hoshino et al. (2025) analyzed data from 238 workers of two nickel-cadmium battery plants in Japan, they observed risk of having $\beta_2\text{M}$ excretion rate $\geq 300 \mu\text{g}/\text{g}$ creatinine increased 17% even though the geometric mean for blood Cd among workers was $1.97 \mu\text{g}/\text{L}$ ^[67]. The authors suggested Cd exposure monitoring and exposure management remained necessary. Interestingly, this blood Cd level associated with tubular dysfunction in workers was close to the BMDL values $1.8\text{--}2.0 \mu\text{g}/\text{L}$ that Nogawa et al. (2021) estimated^[66]. In a study from Korea^[68], Choi et al. (2020) observed elevated urinary $\beta_2\text{M}$ and protein concentrations plus high Cd excretion rates [mean (range) of $22.15 (3.23\text{--}62.97) \mu\text{g}/\text{g}$ creatinine] in workers of a small-scale silver soldering company who were exposed to air Cd concentrations of $6\text{--}15 \mu\text{g}/\text{m}^3$. The authors suggested that workers' Cd exposure standard should be lowered. Notably, the MRL value, based on lung effects in rats was $0.03 \mu\text{g}/\text{m}^3$ ^[56].

The BMD Modeling to Define a Critical Exposure Level for Kidney Target

This section highlights critical Cd exposure levels, indicated by Cd excretion rates, that have been linked to adverse effects through benchmark dose (BMD) modeling of human exposure-effect data. In this way, a compensation for animal-to-human extrapolation is not required. The BMD definition and terminology are summarized as follows. The BMD is an exposure (dose) level associated with a specified change in response, termed benchmark response (BMR) which can be set at 1%, 5%, and 10%^[23,69-71]. For continuous datasets, the lower 95% confidence bound of BMD, termed BMDL value determined at 5% BMR has been viewed as NOAEL equivalent or the level below which adverse health effect is negligible^[71-73]. The upper 95% confidence bound of BMD, termed BMDU, is also determined to compute the BMDU/BMDL ratio which informs a degree of uncertainty in BMD estimate^[72,73].

For quantal datasets, respective BMDL_5 and BMDL_{10} values of an exposure level are referred to the lower 95% confidence bound of BMD values, determined at 5% and 10% prevalences of any outcome^[74-76]. Similarly, respective BMDU_5 and BMDU_{10} are referred to the upper 95% confidence bound of BMD values, determined at 5% and 10%

prevalences of any outcome. The BMDL5 could be considered as an exposure threshold, where the prevalence rate of an adverse outcome in the population is an acceptable level ($\leq 5\%$).

Table 3. BMDL(BMD) and BMDL₅/BMDL₁₀ values of cadmium excretion rates based on kidney target.

| Data Source | Effect Indicator | BMDL(BMD), values for Cd excretion ($\mu\text{g/g}$ creatinine) | BMDL ₅ /BMDL ₁₀ | Reference |
|--|--|---|---------------------------------------|--------------------------------------|
| China, Jiangshan City, Zhejiang, n = 934 (469 men, 465 women), 10–71+ years. | NAG, $\beta_2\text{M}$, RBP | For males, respective BMDL values at 5% BMR (10% BMR) were 0.49 (1.04), 0.62 (1.30), 0.89 (1.59) $\mu\text{g/g}$ creatinine for NAG, $\beta_2\text{M}$ and RBP. For females, respective BMDL values at 5% BMR (10% BMR) were 0.64 (1.34), 0.65 (1.37), 0.76 (1.53) $\mu\text{g/g}$ creatinine for $\beta_2\text{M}$, NAG and RBP. | | Wang et al. 2016 ^[77] |
| Sweden, n = 790 women, 53–64 years. | NAG, eGFR | Respective BMDL (BMD) values were 0.5 (0.6) and 0.7 (1.1) $\mu\text{g/g}$ creatinine for NAG and eGFR endpoints | | Suwazono et al. 2006 ^[78] |
| Japan, n = 112 (Cd-polluted area, n = 74, non-polluted area, n = 38) | $\beta_2\text{M}$, eGFR, C _{cr} , TR $\beta_2\text{M}$, | For men, respective BMDL values were 1.8, 2.9, 1.8 and 3.6 $\mu\text{g/g}$ creatinine for $\beta_2\text{M}$, eGFR and 5% and 10% decreases in TR $\beta_2\text{M}$. Corresponding BMDL values in women were 2.5, 3.5, 2.6, and 3.9 $\mu\text{g/g}$ creatinine. | | Hayashi et al. 2024 ^[79] |
| Thailand n = 734 (Bangkok, | NAG, $\beta_2\text{M}$, eGFR | For men, respective BMDL and BMDL ₁₀ values were 0.060, 0.469 | | Satarug et al. 2022 ^[80] |

n = 200, Mae Sot,
n = 534), 16–87
years.

and 3.26 $\mu\text{g/g}$ creatinine for NAG,
prevalences of tubular proteinuria ^a
and low eGFR ^b.

Corresponding BMDL and
BMDL₁₀ in women were 0.069,
0.733 and 4.98 $\mu\text{g/g}$ creatinine.

Thailand Total
n = 405 (Bangkok, protein,
n = 100, Mae Sot, n eGFR
= 215), 19–87
years,

For men BMDL and BMDL₅ Satarug et al.
values were 0.021 and 2.07 $\mu\text{g/g}$ 2024^[81]
creatinine for protein excretion and
prevalence of proteinuria ^b.

Corresponding BMDL and
BMDL₅ values of $E_{\text{Cd}}/E_{\text{cr}}$ in
women were 0.023 and 1.80 $\mu\text{g/g}$
creatinine.

For a whole group, respective
BMDL and BMDL₅ values were
0.054, 1.86, and 1.19 $\mu\text{g/g}$
creatinine for protein excretion and
prevalences of proteinuria and low
eGFR.

NAG, N-acetyl- β -D-glucosaminidase; eGFR, estimated glomerular filtration rate; RBP, retinal binding protein; $\beta_2\text{M}$, β_2 -microglobulin; $\text{TR}\beta_2\text{M}$, tubular reabsorption of $\beta_2\text{M}$. ^a Tubular proteinuria $E_{\beta_2\text{M}}/E_{\text{cr}} \geq 300$ $\mu\text{g/g}$ creatinine ^b Low eGFR was defined as $\text{eGFR} \leq 60$ mL/min/1.73 m^2 . ^c Proteinuria was defined as $E_{\text{pro}}/E_{\text{cr}} \geq 100$ mg/g creatinine.

Reported BMDL(BMD) values for Cd excretion rates varied among study populations as well as within the same study populations, depending on authors' choices on the mathematical dose-response models, effects indicators (endpoints), and the cut-off values to define abnormality or deviation from normalcy. Effects of cut-off values are illustrated as follows for urinary $\beta_2\text{M}$ and NAG. Using data from 13 publications, Woo et al. (2015) reported that the BMDL values at 5% BMR for the $\beta_2\text{M}$ endpoint were 4.88, 3.13 and 1.9 $\mu\text{g/g}$ creatinine, depending on the cut-off values to define an abnormal $\beta_2\text{M}$ excretion rate. The BMDL value of 1.9 $\mu\text{g Cd/g}$ creatinine was obtained, when $\beta_2\text{M}$ excretion rates ≤ 400 $\mu\text{g/g}$ creatinine were cut-off values^[82].

Liu et al. (2016), applied the BMD modeling to the excretion rates of Cd and NAG datasets recorded in 30 publications, and they identified BMDL at 5% BMR to be 1.67 $\mu\text{g/g}$ creatinine, when cut-off value of abnormal NAG excretion rate was 8 units/g creatinine^[83]. In a study from the United Kingdom, risks of having NAG excretion rates > 2 units/g of creatinine rose 2.6- and 3.6-fold in those who had Cd excretion of 0.3 and 0.5 $\mu\text{g/g}$ of creatinine, respectively^[84]. Using data from the representative of the Jiangshan City residents (469 men, 465 women, aged 10–71+ years), Wang et al. (2016) reported that abnormal NAG excretion was associated with Cd excretion of 0.49 and 0.65 $\mu\text{g/g}$ creatinine in men and women, respectively^[77]. These Cd excretion rates were lower than those showing associations with abnormal $\beta_2\text{M}$ and RBP excretion rates^[77].

Satarug et al. (2022) found the NOAEL equivalents of Cd excretion to be 0.060 and 0.069 $\mu\text{g/g}$ creatinine in men and women, respectively^[80]. These figures were obtained from four dose–response models, namely inverse exponential, natural logarithmic, exponential, and Hill models, and a 5% increase in the NAG excretion rate as an endpoint. The NOAEL equivalent of Cd excretion rate was 0.054 $\mu\text{g/g}$ creatinine, when a 5% increase in total protein excretion was used as an endpoint^[81].

It is noteworthy that the BMD values of Cd excretion for effects on eGFR, and NAG excretion were marginally different, meaning these two effects are intertwined. The BMDL values of Cd excretion in Swedish women were 0.5 and 0.7 $\mu\text{g/g}$ creatinine for NAG and eGFR endpoints, respectively^[78]. The BMDL values of Cd excretion in Japanese women were found to be 3.9 and 3.5 $\mu\text{g/g}$ creatinine when 10% decrease in tubular reabsorption of $\beta_2\text{M}$ and C_{cr} effect were employed as toxicity endpoints, respectively^[79].

For prevalence (quantal) datasets, the BMDL₅/BMDL₁₀ values of Cd excretion for proteinuria prevalences were 1.86 and 4.47 $\mu\text{g/g}$ creatinine, meaning that the prevalence of Cd-related proteinuria would increase from 5% to 10% when population mean value of Cd excretion increased from 1.86 to 4.47 $\mu\text{g/g}$ creatinine. For the low eGFR endpoint, BMDL₅/BMDL₁₀ values of Cd excretion were 1.19 and 1.35 $\mu\text{g/g}$ creatinine, meaning that the prevalence of Cd-related low eGFR increased from 5% to 10% when population

mean value of Cd excretion increased only slightly (from 1.19 to 1.35 $\mu\text{g/g}$ creatinine). These data suggest that an effect size of Cd on eGFR decline was larger than proteinuria.

In theory, an exposure level (Cd excretion rate) derived from the most sensitive end-point or the one with the lowest BMDL value would be protective against all other adverse effects^[23,55]. However, like the different terms used to describe a critical exposure, the BMD modeling needs to be standardized to be meaningful. Experimental dose-response data in pigs identified oral Cd exposure limit at 0.2 $\mu\text{g/kg}$ body weight per day (Table 1) while the Cd exposure guidelines estimated from human data ranged between from 0.21 and 0.83 $\mu\text{g/kg}$ body weight per day (Table 2). However, most countries employ the JECFA “tolerable” exposure level of Cd at 0.83 $\mu\text{g/kg}$ body weight per day and BMDL₅, a threshold level of 5.24 $\mu\text{g/g}$ creatinine.

The estimated Cd exposure limits for bone effects ranged between 0.21 and 0.64 $\mu\text{g/kg}$ body weight/day^[60-63]. Like kidney effects, these permissible exposure levels did not appear to be low enough to be without an appreciable health risk. A systematic review and meta-analysis of an association between Cd exposure and osteoporosis risk in postmenopausal women found a nearly two-fold increase in risk of having osteoporosis in both groups of low and high exposure to Cd^[85]. In the low-exposure group, risk of osteoporosis rose 1.95-fold, comparing Cd excretion rates ≥ 0.5 versus < 0.5 $\mu\text{g/g}$ creatinine. In the high-exposure group, risk of osteoporosis rose 1.99-fold, comparing Cd excretion rates ≥ 5 versus < 5 $\mu\text{g/g}$ creatinine.

Kidney as the Principal Site of Cadmium Accumulation and Toxicity

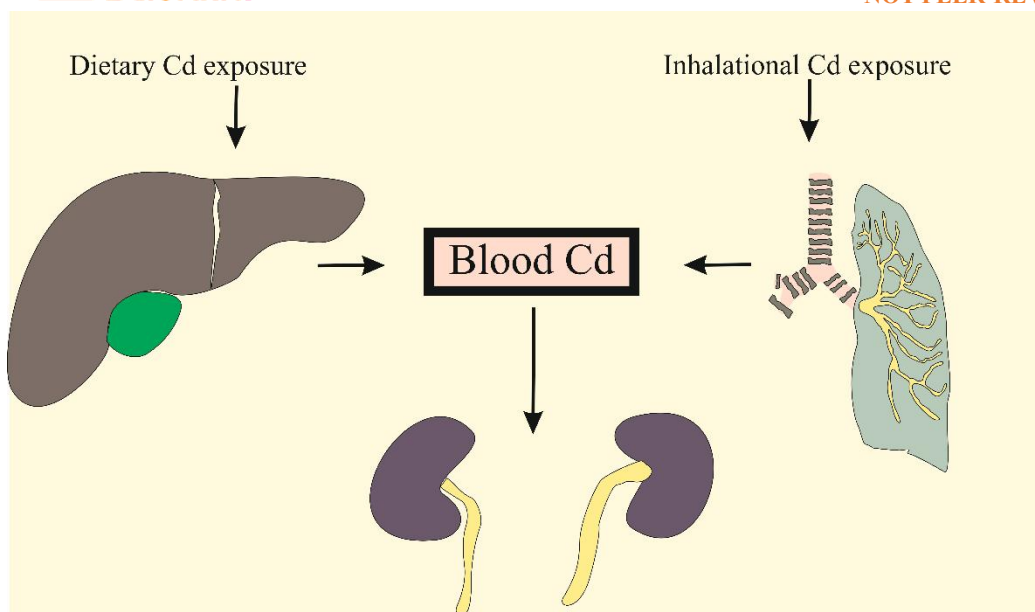


Figure 1. Oral and inhalational routes of exposure to environmental cadmium. Cd from foods enters the portal blood system before reaching liver, while inhaled metallic and oxide forms of Cd reach the lungs. Eventually, nearly all acquired Cd accumulate within proximal tubular epithelial cells (PTCs) of kidneys. Due to a lack of elimination mechanism, Cd is retained within the PTCs cells and appears in urine after these cells are injured or die. Cd-induced tubulointerstitial inflammation can cause a decrease in the glomerular filtration rate.

As Figures 1 and 2 depicts, from the gut, Cd is absorbed by the enterocytes before reaching the portal blood system and then the liver. Cd can be absorbed via specialized transport proteins for essential metals, namely iron (Fe), zinc (Zn), and calcium (Ca)^[86-89]. In addition, Cd ions complexed with metallothionine (CdMT) and phytochelatin (CdPC) can be absorbed through transcytosis and receptor-mediated endocytosis^[90-92]. Therefore, the intestinal absorption rate of Cd can be higher than the absorption rate for Fe, Zn and Ca. Studies of Cd uptake from foods in Japanese women estimated the absorption rates of Cd to be as high as 24 to 45%^[93,94]. The presumed Cd absorption rate of 3-7% in the calculation of a “tolerable” intake level for Cd is one of the errors in toxicological risk assessment of dietary Cd exposure.

In general, the body burden of any contaminant is a balance between absorption and elimination rates. However, because only 0.001–0.005% of the total amount of Cd in the

body was excreted each day^[95,96], the intestinal absorption rate of Cd essentially determines the body burden.

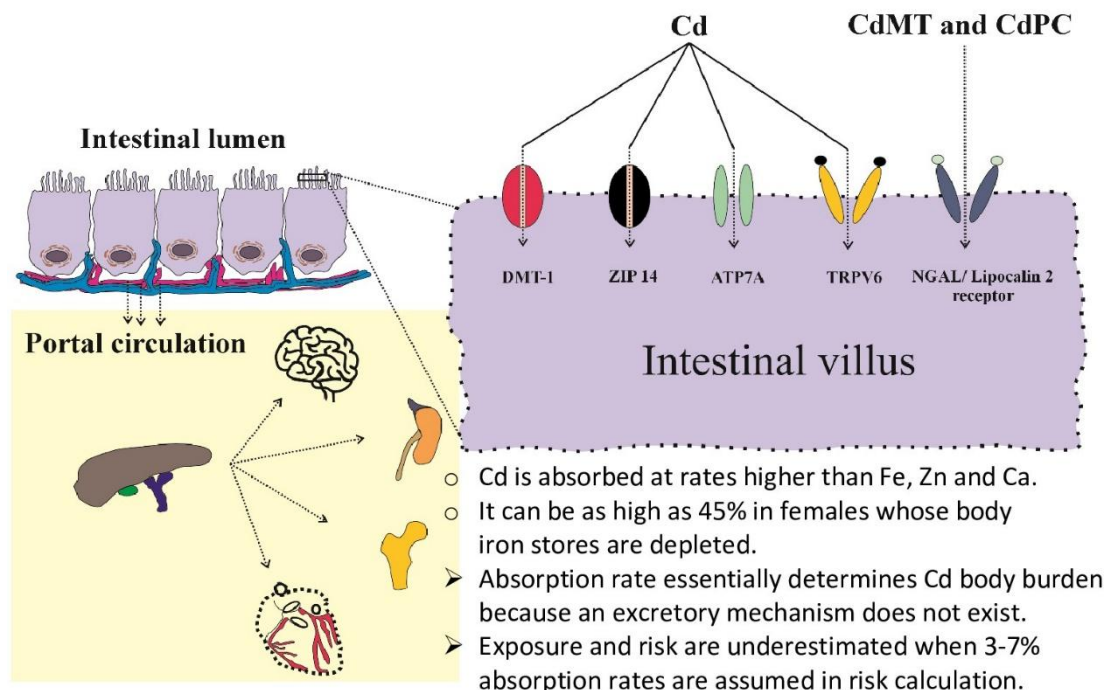


Figure 2. Specialized transport proteins and receptors involved in the absorption of cadmium. Cd from foods is absorbed via transport proteins for iron, zinc, copper, and calcium (Fe, Zn, Cu, and Ca). Abbreviations: DMT1, divalent metal transporter1; ZIP14, Zrt- and Irt-related protein 10; ATP7A, ATPases (Cu-ATPases) ATP7A; TRPV6, transient receptor potential vanilloid6; NGAL, neutrophil-gelatinase associated lipocalin.

An estimated Cd exposure for Portuguese population, aged 18-74 years, was 0.19 µg/kg body weight per day^[11]. Bread was the main source of Cd, and 5.4% of the study population had dietary Cd exposure levels exceeding the JECFA's guideline. An average dietary Cd exposure in China was 34.3 µg/day, varying between 22.6 and 54.5 µg/day across regions, and 15.4% of study population had dietary Cd exposure levels exceeding the JECFA's guidelines^[97]. Fungi and algae had the highest Cd concentration, followed by aquatic foods, nuts, cereals, beans, vegetables, meats, eggs, milk, and fruits. Dietary Cd exposure in Australia was between 9 and 15 µg/day, potatoes, wheat, cocoa, and meat contributed 46, 16, 12, and 7% of total dietary Cd exposure, respectively, while crustaceans, liver, peanuts, and vegetables each contributed 2–3%, adding a further 11% to total dietary Cd exposure^[98]. Data on kidney and urine Cd concentrations in 42 Australians can be found in Figure 3. The strong correlation between kidney Cd

and urine Cd forms a basis for the utility of Cd excretion as an indicator of long-term exposure or kidney burden^[99-101].

Accumulation of Cadmium in Kidneys and Its Excretion in Urine

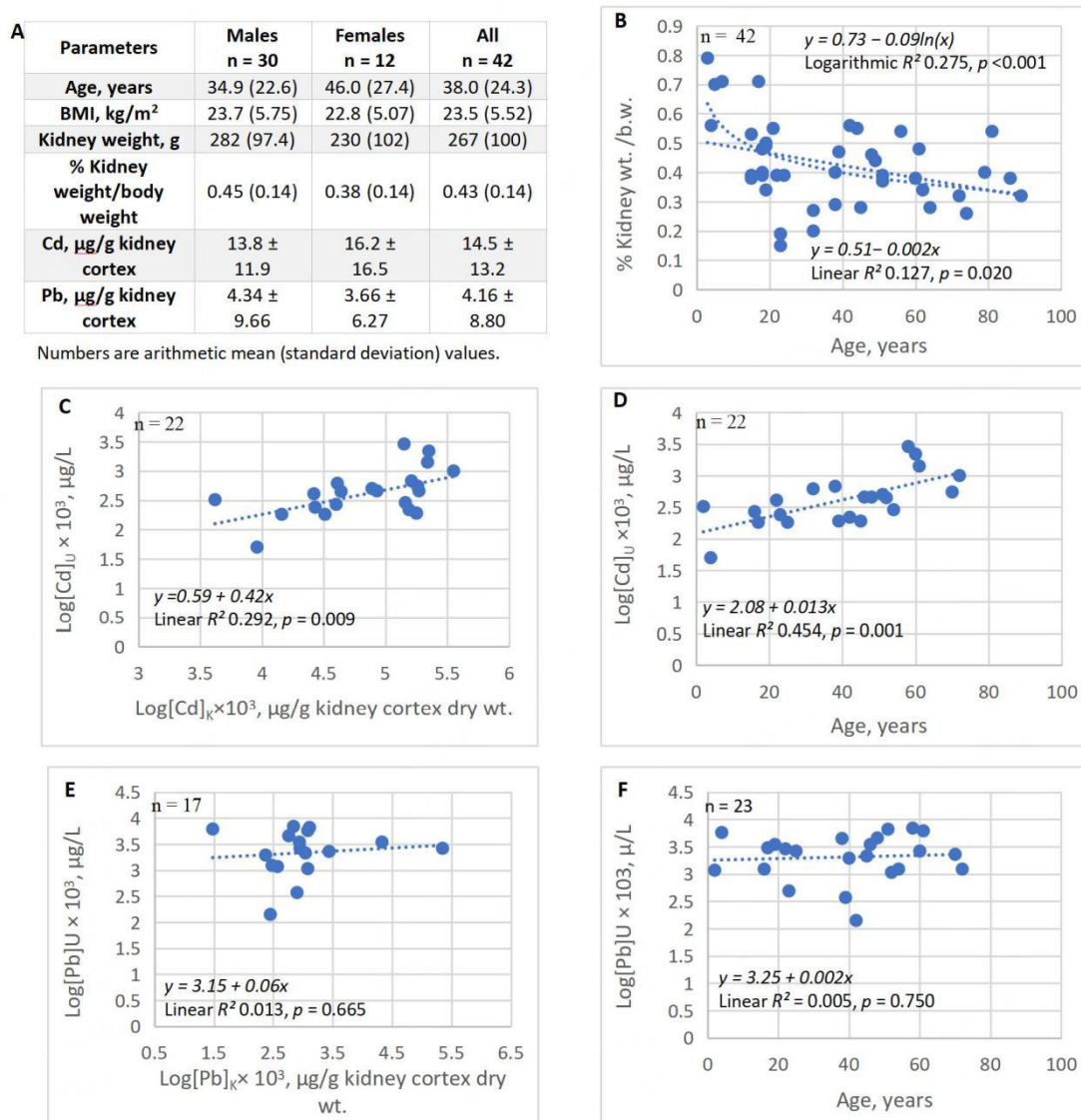


Figure 3. Kidney burden of cadmium as a determinant of urinary cadmium concentration. Weight, Cd and Pb content of kidneys from 42 Australians (A). Scatterplot shows decrease in kidney weight with increasing age (B). Scatterplots show urinary Cd concentrations increase with kidney Cd burden (C) and age (D). Scatterplots show miniscule correlations between urinary Cd concentrations and kidney Pb burden (E) and age (F). These data are from Satarug et al. 2002^[99].

It is notable that the mean Australian kidney Cd content of 14.5 $\mu\text{g/g}$ wet weight was close to the mean kidney content of 12.9 $\mu\text{g/g}$ wet weight found in kidneys from Swedish kidney transplant donors ($n = 109$, 24–70 years, median 51)^[102]. However, the mean Australian kidney Pb content of 4.16 $\mu\text{g/g}$ wet weight was much higher than the median Swedish kidney Pb content of 0.08 $\mu\text{g/g}$ wet weight.

The rate of Australian kidney Cd accumulation was 3–5 $\mu\text{g/g}$ wet tissue weight for each 10-year increase in age, and kidney cortical Cd content peaked at 25.9 $\mu\text{g/g}$ wet tissue by 50 years of age. In comparison, the rate of kidney Cd accumulation among Swedish kidney transplant donors who did not smoke was 3.9 $\mu\text{g/g}$ kidney wet weight for every 10-year increase in age; this rate of kidney Cd accumulation rose to 4.5 $\mu\text{g/g}$ kidney wet weight per 10 years in non-smoking women with low body iron stores^[102]. In line with estimated Cd exposure in Australia of 9–15 $\mu\text{g/day}$, the average dietary Cd exposure in Sweden was 10.6 $\mu\text{g/day}$ with potatoes and wheat contributing to 40–50% of total intake, while consuming seafood and spinach increased the mean dietary Cd exposure to 23 $\mu\text{g/day}$ ^[103]

It is noteworthy that the kidney cortical Cd contents in environmentally exposed Australian and Swedish subjects were well below 180–200 $\mu\text{g/g}$ wet kidney weight, presumed to be the critical kidney concentration range in workplace exposure scenarios^[64,65]. However, even at these low kidney burden, histopathological lesions notably, tubular atrophy, interstitial fibrosis, and arteriolohyalinosis have been observed, and tubular atrophy showed a significant association with kidney Cd content after adjustment for age, gender, and smoking.^[104] These findings are as expected because PTCs are enriched with mitochondria, and their homeostasis and survival depend heavily on autophagy^[105]. Consequently, they are highly susceptible to Cd-induced apoptosis^[106,107], and Cd induced acute kidney injury through inhibiting autophagy and affecting lysosomal function have been demonstrated using rats^[108]. There are many other mechanisms that explain how Cd causes injury to the PTCs and cell death^[109–112], leading to interstitial inflammation and fibrosis.

A decrease in eGFR is a common sequela of ischemic acute tubular necrosis and acute and chronic tubulointerstitial fibrosis because they create impediments to filtration that

include the destruction of post-glomerular peritubular capillaries, amputation of glomeruli from tubules, and obstruction of nephrons with cellular debris^[113].

Environmental Cadmium Exposure and Chronic Kidney Disease

Approximately 8–13% of the world's population is living with CKD, signified by a fall of the eGFR to below 60 mL/min/1.73 m² and/or the presence of albuminuria for 3 months or longer^[34-36]. Albuminuria is indicated by urinary albumin-to-creatinine ratio (ACR) ≥ 20 and ≥ 30 mg/g creatinine in men and women, respectively. The higher cut-off value for ACR in women is to compensate for higher male creatinine excretion (E_{cr}), due to universally higher muscle mass in men compared to women of similar age.

In the China Health and Nutrition Survey (n = 8429), risk of having CKD, based on low eGFR criterion, rose 1.73-fold, 2.93-fold, and 4.05-fold, comparing respective dietary Cd exposure of 23.2, 29.6, and 36.9 $\mu\text{g/day}$ to an exposure to 16.7 $\mu\text{g Cd/day}$ ^[33]. A dietary Cd exposure level associated with a 73 % increase in the risk of CKD was less than half (40%) of the JECFA's tolerable exposure guideline. Interestingly, however, Ginsberg (2012)^[22] proposed that effects of Cd on the kidney represent a useful case study of the unified approach to toxicity assessment that can provide additional perspective to the traditional risk/no risk approaches such as MRL^[55] and RfD^[62]. Ginsberg argued that the implications of current dietary Cd exposure and regulatory limits can be understood in terms of risk for CKD since both Cd adverse effects and CKD are defined by the same continuous parameter (GFR loss).

The traditional toxicological risk assessment requires that a significant relationship between exposure and an outcome be established first. However, non-differential errors in quantifying either exposure or outcome or both can result in a failure to establish a dose-response relationship^[114]. The evidence that those errors have indeed occurred can be found in two meta-analyses of toxicological risk of Cd exposure, published in 2016 and 2021, which led to erroneous conclusion that there was no evidence for an effect of Cd on eGFR nor the progressive eGFR reduction among Cd-exposed individuals^[115,116]. However, data from Swiss prospective cohort study is consistent with the premise that exposure to Cd accelerates the progression of CKD toward kidney failure^[41]. In the latest meta-analysis published in 2024, an effect of Cd on risk of eGFR loss has been

noted, but there was still insufficient data to connect risk of albuminuria to Cd exposure^[117,118]. The reasons for erroneous conclusions on effects of Cd on prevalence of CKD are provided below.

Failure to Demonstrate Dose-Response Relationship

Because urine Cd correlated closely with kidney Cd (Figure 3), urine Cd concentration has been used as an indicator of long-term exposure to the metal^[99,100]. In most studies, urine samples are collected at a single time point, which requires adjusting of the concentrations of Cd and all other urinary biomarkers in urine samples to creatinine excretion (E_{cr}). The purpose of this adjustment is to correct for differences in urine volume (dilution) among people. This E_{cr} -normalization appear to add variance to datasets, leading to underestimating an effect size of Cd and even a miss as shown in Table 4 for risk of low eGFR.

Normalization of Cd and other substances in urine to creatinine clearance (C_{cr}) has been applied instead of E_{cr} adjustment. C_{cr} -normalization corrects for both interindividual differences in urine dilution, and the number of surviving nephrons^[119]. This C_{cr} -normalization does not require timed urine collection, but simultaneous blood and urine sampling is necessary to obtain data on plasma/serum and urine creatinine concentrations. Excretion of x (E_x) normalized to creatinine clearance (C_{cr}) is denoted as E_x/C_{cr} which can be computed with the equation below.

$E_x/C_{cr} = [Cd]_u[cr]_p/[cr]_u$, where x = Cd, albumin, 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} is expressed as an amount of x excreted per volume of the glomerular filtrate^[119].

Effects of Cadmium Exposure on eGFR and Albumin Excretion Rate

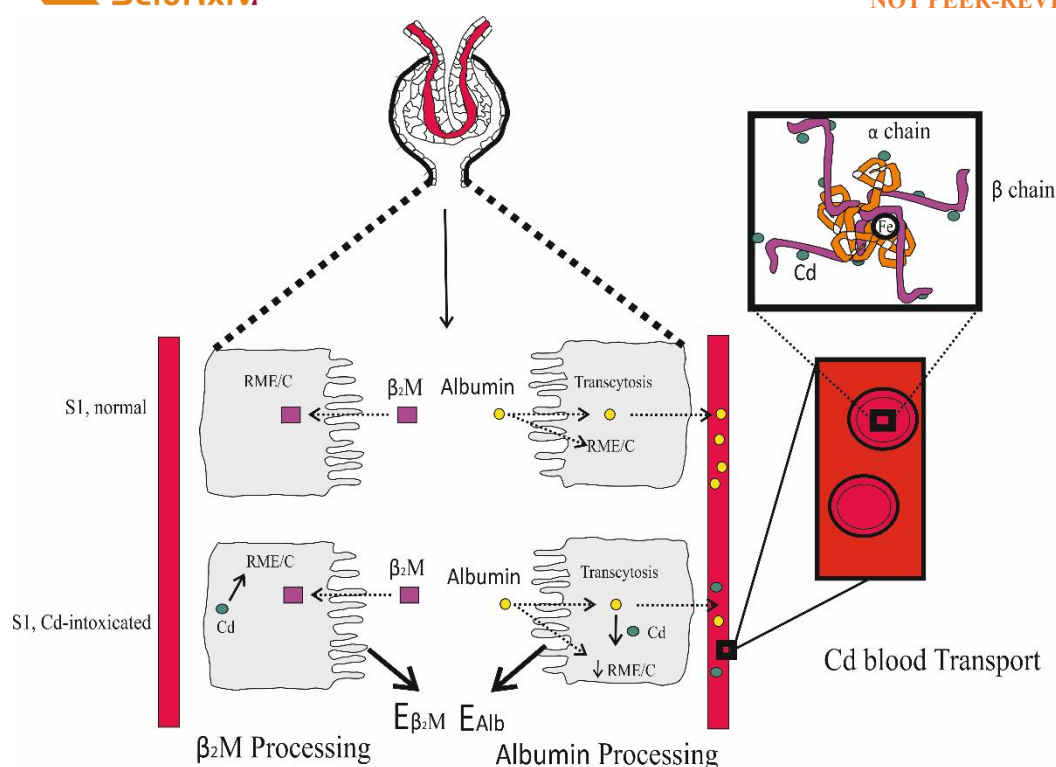


Figure 4. Reabsorption β_2 M and albumin by the proximal tubular epithelial cells (PTCs). In normal kidney health, nearly all β_2 M is reabsorbed via the receptor mediated endocytosis (RME) and is degraded in PTCs^[120,121]. Albumin is reabsorbed through RME, fluid-phase endocytosis and returned to blood stream via transcytosis^[122-124]. Cd intoxication impairs RME, thereby increasing the excretion of both β_2 M and albumin^[125].

Increased β_2 M and NAG excretion rates are indicators of Cd effects most frequently used in toxicological risk assessment. Excretion albumin and eGFR have rarely been studied, especially in high-exposure situations. With the molecular weight of 12,000 Daltons, β_2 M passes through the glomerular membrane to lumen, where it is internalized and degraded by proximal tubular cells^[120,121]. Unlike β_2 M, albumin is not normally filtered by glomeruli due to its large molecular weight and its negative charge^[122-124]. By means of transcytosis through endothelial cells and podocyte foot processes, albumin reaches the proximal tubular lumen^[124] and is reabsorbed and returned to circulation by three major mechanisms: fluid-phase endocytosis, megalin/cubillin receptor-mediated endocytosis, and transcytosis^[122-124].

Using C_{cr} -normalization, an effect of Cd on albumin reabsorption was apparent in a study of Thai subjects ($n = 519$), who were exposed to a high-dose Cd, producing overt tubular malfunction; it was estimated that Cd reduced the fractional reabsorption of albumin by 20%, if a glomerular sieving coefficient for albumin (GSCalb) of 10–4 was assumed^[125].

Similarly, the effects of Cd exposure on CKD prevalence (both low eGFR and albuminuria criteria) were demonstratable when urine Cd concentrations were normalized to C_{cr} as E_{Cd}/C_{cr} (Table 4). Furthermore, from C_{cr} -normalized datasets, it was possible to gain insights into critical Cd exposure levels (BMDL/BMDU) for eGFR effect in high-dose exposure situations (Figure 5) and the impacts of Cd exposure on population prevalence of low eGFR (Figure 6) and albuminuria (Figure 7). As suggested by Ginsberg (2012) that effects of dietary Cd exposure on the kidney represent a useful case study that can provide additional perspective to the POD-based exposure guidelines^[22].

Table 4. Cadmium exposure dose levels associated with increased risk of having low eGFR

| Independent Variables | eGFR ≤ 60 mL/min/1.73 m ² | | | | |
|--|---|---------------------|--------|--------|-----------------|
| | β (SE) | Coefficients POR | 95% CI | | <i>p</i> -value |
| | | | Lower | Upper | |
| Model A, E_{Cd}/E_{cr} , $\mu\text{g/g}$ creatinine | | | | | |
| Quartile 1: 0.03–2.41 | Referent | | | | |
| Quartile 2: 2.42–4.64 | 0.651 (0.377) | 1.917 | 0.915 | 4.015 | 0.085 |
| Quartile 3: 4.65–8.36 | 1.470 (0.482) | 4.349 | 1.692 | 11.183 | 0.002 |
| Quartile 4: ≥ 8.37 | 1.446 (0.440) | 4.245 | 1.792 | 10.055 | 0.001 |
| Model B, $(E_{Cd}/C_{cr}) \times 100$, $\mu\text{g/L}$ filtrate | | | | | |
| | β (SE) | Coefficients POR | Lower | Upper | <i>p</i> -value |
| Quartile 1: 0.03–1.95 | Referent | | | | |
| Quartile 2: 1.96–3.88 | 1.683 (0.432) | 5.382 | 2.310 | 12.543 | <0.001 |
| Quartile 3: 3.89–7.68 | 1.573 (0.426) | 4.820 | 2.090 | 11.115 | <0.001 |

Quartile 4: ≥ 7.69 3.154 (0.603) 23.429 7.179 76.464 <0.001

POR, prevalence odds ratio; S.E., standard error of mean; CI, confidence interval. Urine Cd concentrations were normalized to creatinine excretion (E_{cr}) and creatinine clearance (C_{cr}) in models A and B, respectively. Data were from 603 subjects (400 females, 203males), mean age 52.4 years^[126]. Both models were adjusted for age, BMI, diabetes, hypertension, gender, and smoking.

In model A (Table 4), a dose-response between Cd exposure and risk of having low eGFR was not demonstrable when urine Cd concentrations were adjusted to E_{cr} . Respective risk of having low eGFR increased 4.4- fold and 4.2-fold, comparing E_{Cd}/E_{cr} quartile 3 ($p = 0.002$) and quartile 4 ($p = 0.001$) with the bottom quartile. An association of E_{Cd}/E_{cr} quartile 2 with risk of low eGFR was statistically insignificant ($p = 0.085$).

In model B (Table 4), a dose-response relationship was observed between risk of having low eGFR and E_{Cd}/C_{cr} quartiles; eGFR, where respective risk of low eGFR rose 5.4-, 4.8-, and 23.4-fold in E_{Cd}/C_{cr} quartile 2 ($p < 0.002$), quartile 3 ($p < 0.001$), and the top quartile ($p < 0.001$), compared with the bottom quartile.

Cadmium Exposure Levels Associated with eGFR Loss

The BMD modeling was accomplished with the PROAST software (<https://proastweb.rivm.nl>), To determine Cd exposure levels associated with a 5% eGFR loss, the BMD modeling was applied to data from 603 Thai subjects (400 females, 203males), mean age 52.4 years (Table 4) using inverse exponential, natural logarithmic, exponential, and Hill dose-response models.

For the E_{cr} -normalized dataset, Cd exposure levels associated with 5% loss of eGFR were 6.82 and 2.07 $\mu\text{g/g}$ of creatinine in women and men, respectively. For the C_{cr} -normalized dataset, the Cd exposure levels associated with 5% loss of eGFR in women and men were identical (2.15 $\mu\text{g/L}$ of filtrate).

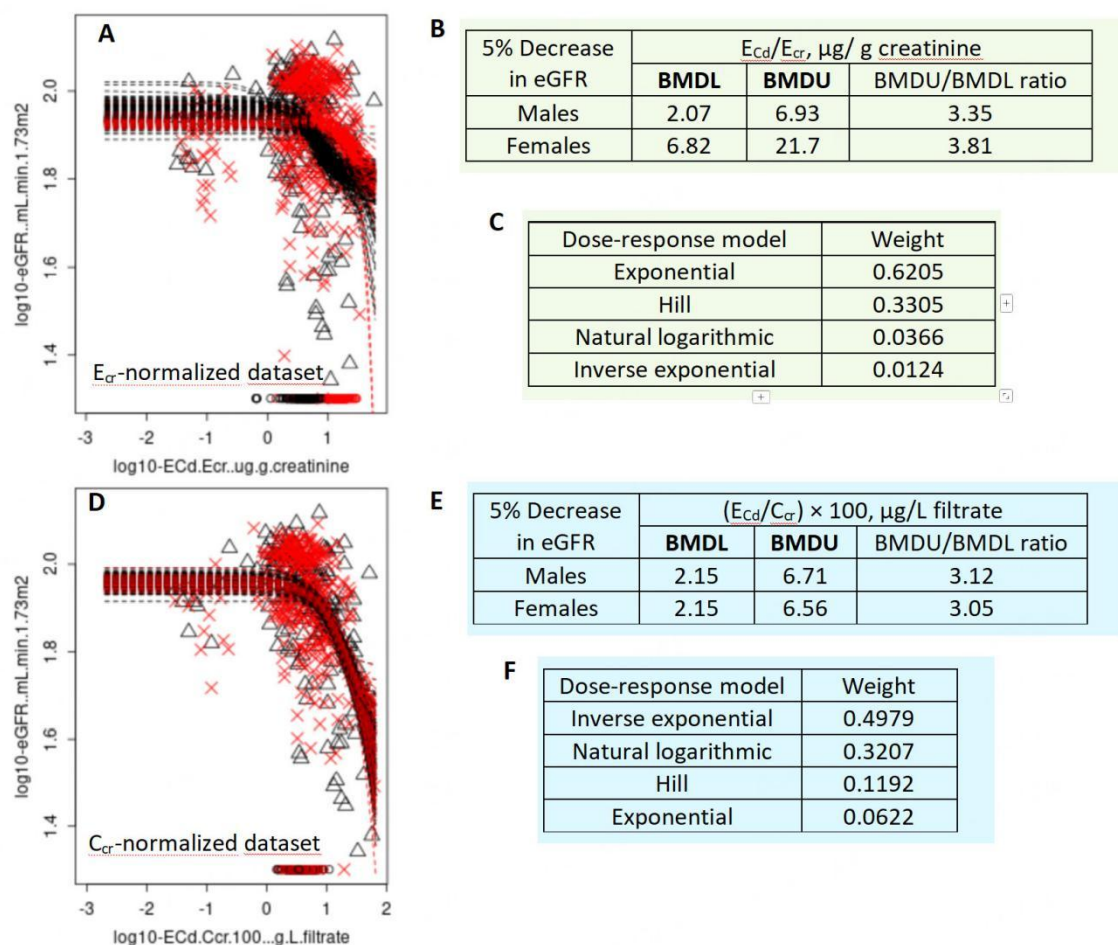


Figure 5. BMDL/BMDU values of cadmium exposure associated with a 5% eGFR loss. Bootstrap dose-response model averaging with 200 repeats for eGFR- E_{Cd}/E_{Cr} (A) eGFR- E_{Cd}/C_{Cr} datasets (C). BMDL/BMDU values of E_{Cd}/E_{Cr} and E_{Cd}/C_{Cr} (B, E). The dose-response models employed to compute BMDL/BMDU values of E_{Cd}/E_{Cr} and E_{Cd}/E_{Cr} (C, F). This figure is adapted from Satarug et al. 2022^[126].

Cadmium Exposure Levels Associated with Prevalence of Low eGFR and Albuminuria

The BMD modeling of quantal data was also undertaken to determine Cd exposure levels associated with 5% and 10% prevalence of low eGFR (Figure 6) plus 5% and 10% prevalence of albuminuria (Figure 7). The mathematical dose-response models applied to prevalence datasets were two-stage, logarithmic logistic, Weibull, logarithmic probability, gamma, exponential, and Hill.

For the E_{cr} -normalized datasets (Figure 6), respective Cd exposure levels associated with 5% and 10% prevalence of low eGFR were 1.93, and 5.31 $\mu\text{g/g}$ creatinine of creatinine in women and corresponding figures in men were 1.47, and 3.92 $\mu\text{g/g}$ of creatinine. However, Cd exposure levels as E_{Cd}/E_{cr} associated with 5% and 10% prevalence of albuminuria could not be reliably determined for any gender (Figure 7).

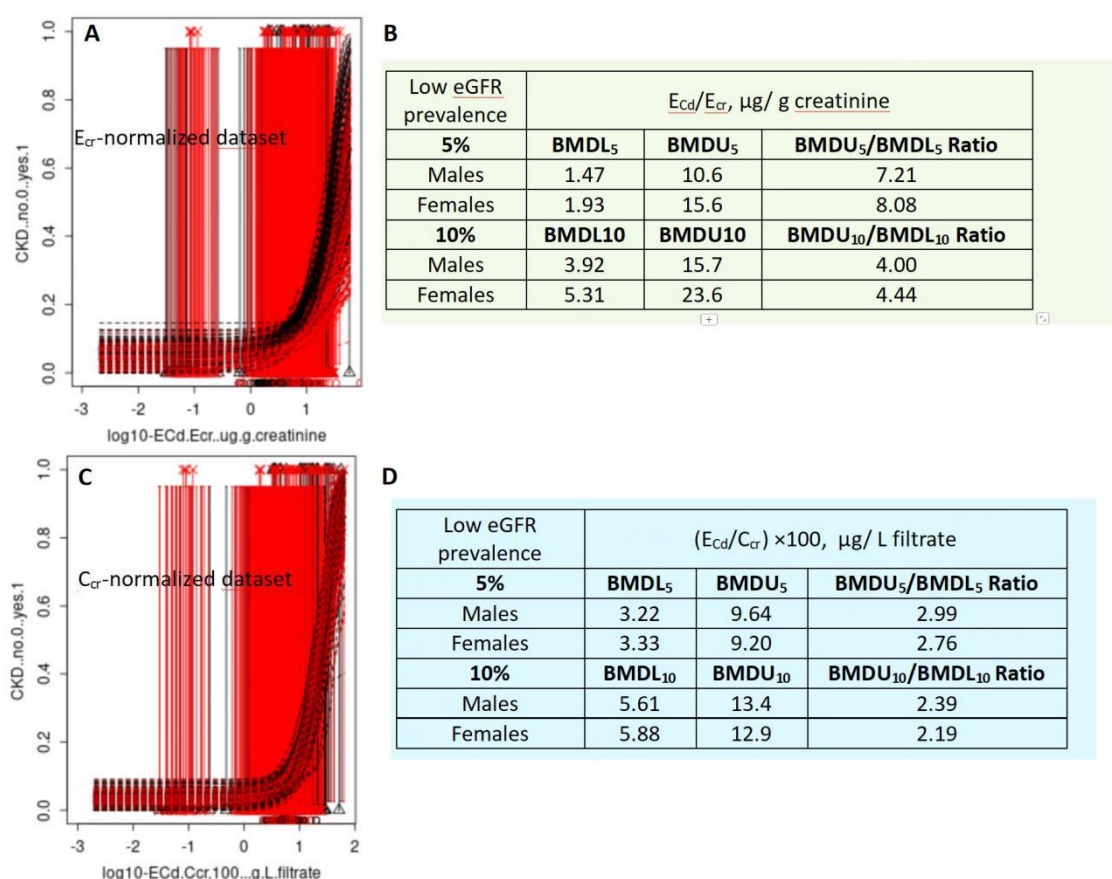


Figure 6. BMDL₅ and BMDL₁₀ values of cadmium exposure levels associated with a 5% and 10% prevalence rate of low eGFR.

For the C_{cr} -normalized dataset (Figure 6), respective Cd exposure levels associated with 5% and 10% prevalence of low eGFR were 3.33, and 5.88 $\mu\text{g/L}$ of filtrate in women, and corresponding figures in men were 3.22, and 5.61 $\mu\text{g/L}$ of filtrate. Respective Cd exposure levels Cd exposure levels associated with 5% and 10% prevalence of albuminuria were 0.718, and 3.55 $\mu\text{g/L}$ in women, and corresponding figures in men were 0.163, and 1.65 $\mu\text{g/L}$ of filtrate.

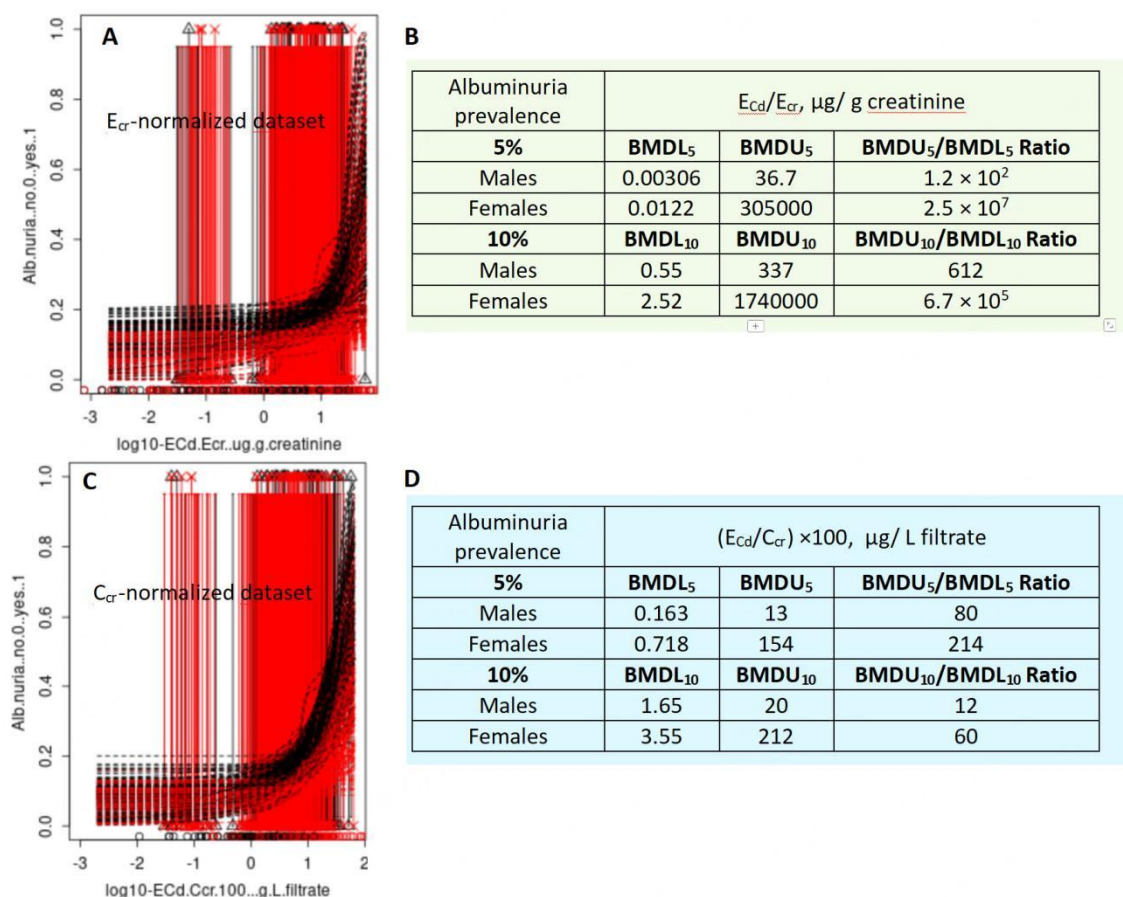


Figure 7. BMDL₅ and BMDL₁₀ values of cadmium exposure levels associated with a 5% and 10% prevalence rate of albuminuria.

Summary of Findings from the BMD Modeling of Cadmium Excretion and Adverse Kidney Outcomes

For E_{cr} -normalized data, loss of eGFR by 5% in females was associated with a Cd excretion 3.3-fold higher than males (Fig. 5B). The higher female Cd excretion rate was a result of their universally small muscle mass, and hence lower creatinine excretion levels, compared to male gender. In females and males, respective prevalence of low eGFR rose from 5 to 10% as Cd excretion rates rose 2.8-fold, and 2.7-fold (Fig. 6B). In comparison, however, Cd excretion rates associated with 5 and 10% prevalences of albuminuria could not be reliably determined, reflected by BMDU₅/BMDL₅ and BMDU₁₀/BMDL₁₀ ratios > 200 (Fig. 7B).

For C_{cr} -normalized data, loss of eGFR by 5% was associated with Cd excretion rate of 2.15 $\mu\text{g/L}$ of filtrate in both females and males (Fig. 5E). The identical exposure level of Cd in both genders can be expected because underlying mechanisms of the cytotoxicity of Cd in any PTCs should be the same. The prevalence of low eGFR rose from 5 to 10% as Cd excretion rate rose 1.7-fold in both men and women (Fig. 6D). In comparison, the prevalence of albuminuria rose from 5 to 10% as Cd excretion rate rose 4.9-fold and 10-fold in women and men, respectively (Fig. 7D). Of interest, the increases in albuminuria prevalence by 5 and 10% in men and women (Fig. 7D) were associated with Cd excretion rates much lower than those associated with increases in prevalence of low eGFR by 5 and 10% (Fig. 6D). These data can be interpreted to suggest that albuminuria occurred in advance of a fall in eGFR to 60 mL/min/1.73 m². Hence, albumin excretion rate could reflect a sensitive adverse Cd effect on kidneys. A study from Spain reported that risk of having albuminuria rose 58% at Cd excretion rates $\geq 0.27 \mu\text{g/g creatinine}$ [39].

Like albuminuria, type 2 diabetes could represent another sensitive adverse effect of Cd exposure. This was evident from a study by Shi et al. (2021) who applied BMDL modeling to Cd excretion and prevalence of type 2 diabetes in the representative U.S. general population [127]. They reported BMD₅ (BMDL₅) value of Cd excretion to be 0.190 (0.178) $\mu\text{g/g creatinine}$ at a 5% prevalence of diabetes. The BMDL₅ value of Cd excretion rate associated with a 5% prevalence of diabetes in the U.S. was only 3.4% of the JECFA's Cd exposure threshold level, estimated from the $\beta_2\text{M}$ endpoint [24].

Low environmental Cd exposure has been implicated in both onset and progression of diabetic kidney disease, evident from the U.S. [128-130] and Dutch [131,132] population studies after adjustment for covariates, which included adiposity and smoking effects [128,129]. An increased risk of prediabetes among U.S. adults was linked with Cd excretion rates $\geq 0.7 \mu\text{g/g creatinine}$ [130]. Globally, diabetic kidney disease is the principal cause of kidney failure, which will only be accelerated further as dietary Cd exposure continues.

CONCLUSIONS

The present review discusses toxicological risk assessment and the benchmark dose (BMD) methodology to define a critical exposure level for a toxic metal cadmium (Cd), which is found in virtually all food types. It addresses dietary exposure limits and workplace exposure limits that were derived from using excretion of β_2 -microglobulin (β_2 M) above 300 $\mu\text{g/g}$ creatinine as an indicator of Cd effect on kidneys. Evidence that these exposure guidelines are not protective of the health of the general population and workers are presented.

Because the 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. This implies that an exposure level derived from the most sensitive endpoint will be protective against all other adverse effects. To this end, results of studies using BMD modeling to identify other sensitive indicators of Cd effects on kidneys are summarized. Loss of eGFR, increased excretion of NAG, total protein and albumin have the potential to serve as a basis for derivation of a new health-protective exposure for Cd. These kidney effects indicators have been underestimated or not demonstrable because of a conventional method of normalization of urine concentrations of Cd, total protein, albumin, and NAG to creatinine excretion. A dose-response relationship between Cd exposure and prevalence of low eGFR is demonstrable only when urine Cd concentrations are normalized to creatinine clearance. Thus, it can be argued that the implications of current dietary Cd exposure and exposure limits can be understood in terms of risk for CKD since both Cd adverse effects and CKD are defined by the same continuous parameter (GFR loss).

DECLARATIONS

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Availability of data and materials

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

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Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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