Supplementary Material: Use of Urinary β2-Microglobulin in the Assessment of the Health Risk from Environmental Cadmium Exposure

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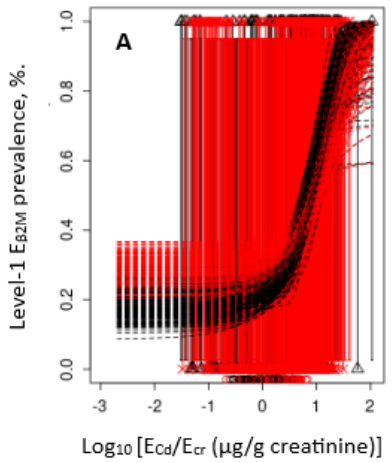
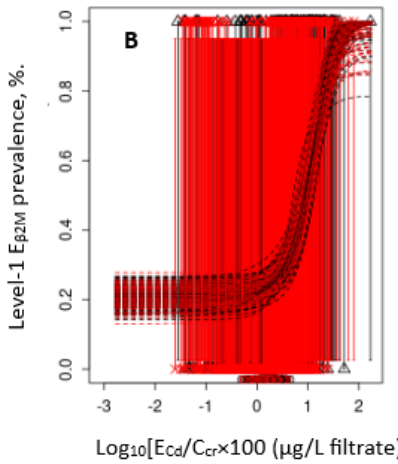
I. Demonstration that Ex/Ccr = [x]u[cr]p/[cr]u.

Let p = plasma and u = urine; E_x = urinary excretion rate of substance x; Vu = urine flow rate; cr = creatinine; and C_{cr} = creatinine clearance ($E_{cr}/[cr]_p$), an approximation of glomerular filtration rate (GFR). It follows that $E_x/C_{cr} = [x]_u(Vu)/[cr]u(Vu)/[cr]_p$. After simplification, $E_x/C_{cr} = [x]_u[cr]_p/[cr]_u$.

II. Comparison of results of normalization of excretion rates to E_{cr} or C_{cr}.





C

Dose-response model	Weight
Logarithmic probability	0.3220
Logarithmic logistic	0.2508
Exponential	0.1750
Hill	0.1715
Weibull	0.0313
Two-stage	0.0289
Gamma	0.0204

D

Dose-response model	Weight
Logarithmic probability	0.4425
Logarithmic logistic	0.3087
Exponential	0.1038
Weibull	0.0655
Gamma	0.0531
Two-stage	0.0179
Hill	0.0085

E

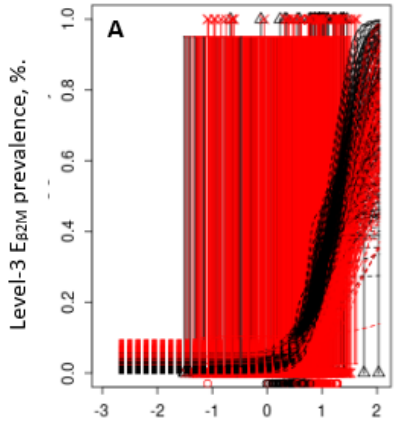
5% Prevalence of β2M excretion level 1 [a]	ECd/Ecr, µg/ g creatinine		
	BMDL5	BMDU5	BMDU5/BMD 5 ratio
Men	0.451	2.65	5.88
Women	0.668	4.49	5.72
All	0.640	3.68	5.75

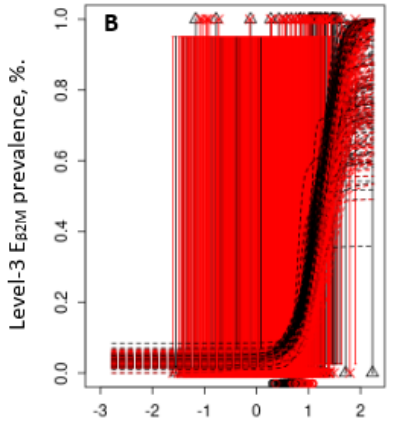
F

5% Prevalence of β2M excretion level 1 [b]	(ECd/Ccr) × 100, µg/L filtrate		
	BMDL5	BMDU5	BMDU5/BMDL5 ratio
Men	0.907	3.58	3.95
Women	0.909	3.18	3.50
All	0.930	3.30	3.55

Figure S1. Cadmium excretion rates associated with 5% prevalence of β2M excretion level 1. Bootstrap dose-effect model averaging for $E_{β2M}/E_{cr}$ (**A**) $E_{β2M}/C_{cr}$ (**B**). Model weights for $E_{β2M}/E_{cr}$ (C) and $E_{β2M}/C_{cr}$ (D).

$BMDL_5/BMDU_5$ values of E_{Cd}/E_{cr} (**E**) and E_{Cd}/C_{cr} (**F**). [a] $E_{\beta 2M}/E_{cr}$ level 2 was defined as $E_{\beta 2M}/E_{cr} \geq 100$ μg/g creatinine. [b] $E_{\beta 2M}/C_{cr}$ level 2 was defined as $(E_{\beta 2M}/C_{cr}) \times 100 \geq 100$ μg/L filtrate. β_2M: β_2-microglobulin; $E_{\beta 2M}$: urinary β_2M; Cd: cadmium; E_{Cd}: urinary Cd; E_{cr}: creatinine excretion; BMDL: benchmark dose limit; BMDU: upper 95% confidence bound of BMD.





C

Dose-response model	Weight
Exponential	0.7252
Hill	0.1152
Logarithmic probability	0.0915
Logarithmic logistic	0.0523
Weibull	0.0053
Gamma	0.0053
Two-stage	0.0052

D

Dose-response model	Weight
Exponential	0.5344
Hill	0.4080
Logarithmic logistic	0.0303
Logarithmic probability	0.0271
Gamma	0.0001
Two-stage	0
Weibull	0

E

5% Prevalence of β_2M excretion level 3 [b]	E_{Cd}/E_{cr}, μg/ g creatinine		
	$BMDL_5$	$BMDU_5$	$BMDU_5/BMDL_5$ ratio
Men	1.52	4.96	3.26
Women	3.11	13.8	4.44
All	2.35	6.76	2.88

F

5% Prevalence of β_2M excretion level 3 [b]	$(E_{Cd}/C_{cr}) \times 100$, μg/L filtrate		
	$BMDL_5$	$BMDU_5$	$BMDU_5/BMDL_5$ ratio
Men	2.93	7.41	2.53
Women	4.50	9.74	2.16
All	3.62	7.80	2.15

Figure S2. Cadmium excretion rates associated with 5% prevalence of β_2M excretion level 3. Bootstrap dose-effect model averaging for $E_{\beta 2M}/E_{cr}$ (**A**) $E_{\beta 2M}/C_{cr}$ (**B**). Model weights for $E_{\beta 2M}/E_{cr}$ (C) and $E_{\beta 2M}/C_{cr}$ (D). $BMDL_5/BMDU_5$ values of E_{Cd}/E_{cr} (**E**) and E_{Cd}/C_{cr} (**F**). [a] $E_{\beta 2M}/E_{cr}$ level 3 was defined as $E_{\beta 2M}/E_{cr} \geq 1000$ μg/g creatinine. [b] $E_{\beta 2M}/C_{cr}$ level 2 was defined as $(E_{\beta 2M}/C_{cr}) \times 100 \geq 1000$ μg/L filtrate. β_2M: β_2-microglobulin; $E_{\beta 2M}$: urinary β_2M; Cd: cadmium; E_{Cd}: urinary Cd; E_{cr}: creatinine excretion; BMDL: benchmark dose limit; BMDU: upper 95% confidence bound of BMD.

III. Assessment of a Threshold at E_{Cd}/E_{cr} 0.2 μg/g cr.

Table S1. Logistic regression analysis for an association between the prevalence odds for CKD and a newly identified threshold

Independent Variables/Factors	CKD [a]				
	β Coefficients (SE)	POR	95% CI		*p*
			Lower	Upper	
Age, years	0.143 (0.016)	1.153	1.118	1.189	<0.001
BMI, kg/m^2	0.060 (0.038)	1.062	0.987	1.143	0.109
Gender	0.170 (0.347)	1.185	0.600	2.341	0.624
Hypertension	0.120 (0.306)	1.128	0.619	2.055	0.695
Smoking	0.245 (0.351)	1.278	0.642	2.546	0.485
$E_{Cd}/E_{cr} \geq 0.2$ μg/g cr.	1.464 (0.631)	4.323	1.255	14.89	0.020

CKD, chronic kidney disease; POR, prevalence odds ratios; CI, confidence interval; BMI, body mass index; Cd, cadmium; cr, creatinine; Ccr, creatinine clearance. [a] CKD was defined as eGFR ≤ 60 mL/min/1.73 m^2.