



Supplementary Materials

Current Levels of Environmental Exposure to Cadmium in Industrialized Countries as a Risk Factor for Kidney Damage in the General Population: A Comprehensive Review of Available Data

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Table S1. Etiological factors for kidney damage.

Etiological Factors of Kidney Damage			
Illnesses	Medicines		Other factors
· hypertension	· polymixin A	· tobramycin	· xenobiotics other than medicines: heavy metals (cadmium, lead, mercury, arsenic, chromium, bismuth, nickel), alcohols and glycols (ethyl alcohol, methyl alcohol, ethylene glycol) · toxins (amanitin) · components of tobacco smoke
· diabetes	· bacitracin	· colistin	
· sepsis	· phenacetin	· amphotericin B	
· liver failure	· acetaminophen	· foscarnet	
· obesity	(paracetamol)	· adefovir	
· glomerular	· cisplatin	· cidofovir	
disease	· cyclosporine	· tenofovir	
· polycystic kidney	· ifosfamide	· iopromide	
disease	· pemetrexed	· tacrolimus	
	· gentamycin	· pamidronate	
	· kanamycin	· zoledronic acid	
	· streptomycin		

Table S2. The accumulation of cadmium (Cd) in the kidney in an experimental rat model of human environmental exposure to this heavy metal^a.

Cd Content (µg) or Concentration (µg/g w.w.)	Exposure Duration				Time-related Changes
	3 Months	10 Months	17 Months	24 Months	
Control					
Content	0.0682 ± 0.0060	0.0912 ± 0.0056	0.1078 ± 0.0059	0.2271 ± 0.0297	3–10*, 3–17‡, 3–24‡ 10–24‡, 17–24*
Concentration	0.0375 ± 0.0102	0.0497 ± 0.0079	0.0467 ± 0.0085	0.0844 ± 0.0357	3–24‡, 10–24‡, 17–24‡
1 mg Cd/kg of feed (daily Cd intake: 37.50–84.88 µg/kg b.w.)					
Content	0.6340± 0.0369***	2.1794± 0.1202***	2.8677± 0.3347***	5.247± 0.4784***	3–10‡, 3–17‡, 3–24‡ 10–24‡, 17–24‡
Concentration	0.3495± 0.0601***	1.103± 0.1968***	1.213± 0.3763***	1.981± 0.5089***	3–17‡, 3–24‡, 10–24‡
5 mg Cd/kg of feed (daily Cd intake: 196.69–404.76 µg/kg b.w.)					
Content	2.562± 0.1454***	10.16 ± 0.427***	25.23 ± 1.678***	22.18 ± 0.971***	3–10‡, 3–17‡, 3–24‡ 10–17‡, 10–24‡
Concentration	1.362± 0.2254***	4.788± 0.5586***	10.77± 1.9360***	8.009± 0.8918***	3–10‡, 3–17‡, 3–24‡ 10–17‡, 10–24‡

Data is mean ± standard error (SE) for 8 rats, except for 7 animals in the group maintained on the diet containing 1 mg Cd/kg for 24 months. *** $p < 0.001$ compared to the control group at the same time point; time-related changes: * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$; w.w., wet weight, b.w., body weight.

^a prepared based on Brzóska et al. [1].

Table S3. The effect of oral exposure to cadmium (Cd) on the kidneys of experimental animals^b.

Dosage, Form, and Time of Exposure to Cd	Experimental Model	Changes in the Morphological Structure of the Renal Tissue	Changes in Various Parameters in the Renal Tissue or Serum	Reference
100 mg Cd/L of drinking water, 2 weeks	Male Wistar rats	– intertubular congestion – loss of the brush border – dilatation of convoluted tubules		[2]
200 mg CdCl ₂ /kg b.w./day in drinking water, 12 weeks	Male rabbits		– ↑ renal expression of the apoptotic (Caspase3), proliferation (MKI67), proto-oncogene (C-fos), and antioxidant (GST) genes – ↓ renal expression of anti-apoptotic (Bcl2) genes	[3]
5 mg CdCl ₂ /kg of feed, 30 days	Male Wistar rats	– congestion of the cortical blood vessels – focal replacement of the renal parenchyma with numerous lymphocytes infiltrates – dilation of glomeruli		[4]
15 mg CdCl ₂ /kg b.w./day, 5 weeks	Male Wistar rats	– disruption in the organization of the renal glomeruli and tubules	– ↑ DNA damage in the kidney	[5]
6.3 mg Cd(NO ₃) ₂ /kg b.w./day, single dose	Male Wistar rats	– swelling with thickened blood vessel – fatty vacuole – fatty infiltrate – lymphocyte aggregate and infiltration	– ↓ SOD, ↓ CAT, and ↓ GPx activities in the kidney	[6]
5 mg CdCl ₂ /kg b.w./day, 5 weeks	Male Sprague–Dawley rats	– tubular necrosis	– ↓ SOD, ↓ CAT, and ↓ GPx activities in the kidney – ↑ creatinine and ↑ LDH concentrations in the serum – ↓ total thiol concentration in the kidney	[7]
8.8 mg CdCl ₂ /kg b.w./day, 20 days	Pregnant female Sprague–Dawley rats	– hydropic degeneration of the cytoplasm – deterioration of the nuclei of the lining cells of PT and DT in both maternal and fetal kidney		[8]
0.685 mg CdCl ₂ /L of drinking water, 90 days	8 weeks old C57BL mice	– severe vascular degeneration and necrosis of renal tubules with glomerular deterioration		[9]

CAT, catalase; CdCl₂, cadmium chloride; Cd(NO₃)₂, cadmium nitrate(V); DT, distant tubule; GPx, glutathione peroxidase; GSH, reduced glutathione; GST, glutathione S-transferase; LDH, lactate dehydrogenase; MKI67, a marker of proliferation KI67; PT, proximal tubule; SOD, superoxide dismutase. ^b based on the studies published within the last 10 years.

Table S4. The effect of exposure to cadmium (Cd) via routes other than oral on the kidneys of experimental animals^b.

Dosage, Form, Route, and Time of Exposure to Cd	Experimental Model	Changes in the Morphological Structure of the Renal Tissue	Changes in the Various Parameters in the Renal Tissue, Blood/serum, or Urine	Reference
10 mg CdCl ₂ /kg b.w./day, s.c., 15 and 30 days	Male Wistar rats	mononuclear cell infiltration, interstitial congestion around the glomeruli with wide lumen, pyknotic nuclei, high dilatation in intertubular blood vessels impacted with hemolysed blood and cellular infiltration, congestion and inflammation around glomeruli, degenerated glomeruli with wide space and detached basement membrane, DT with wide lumen, deformed PT with detached brush border, degeneration and hyalinization of glomerular tuft, tubular degeneration, tubular and tubulointerstitial necrosis	<ul style="list-style-type: none"> – ↑ LOOH, ↑ MDA, and ↑ PC concentrations in the kidney, ↑ TOS, ↑ OSI – ↑ expression of inflammatory markers: Hsp70, COX2, and TNFα in the kidney – ↓ TAS, ↓ activities of SOD and CAT, ↓ GSH concentration in the kidney 	[10]
0.6 mg CdCl ₂ /kg b.w., s.c., 5 days/week, 12 weeks	Male Sprague–Dawley rats	fibrosis of the tubules	<ul style="list-style-type: none"> – ↑ KIM-1 and ↑ β₂-MG concentrations and ↑ NAG activity in the urine 	[11]
6.5 mg CdCl ₂ /kg b.w./day, i.p., 5 days	Male Wistar rats	moderate to severe inflammation and widespread degeneration of cells, cytoplasmic vacuolization, congested glomeruli, severe apoptosis, karyomegaly, and hyperchromatic nuclei in the tubular epithelial cells	<ul style="list-style-type: none"> – ↑ MDA concentration in the kidney – ↓ SOD, ↓ CAT, and ↓ GPx, activities in the kidney 	[12]
2 mg CdCl ₂ /kg b.w./day, i.p., 4 weeks	Male Wistar rats	severe tubular necrosis and apoptosis, vacuolization, degeneration	<ul style="list-style-type: none"> – ↑ urea nitrogen concentration in the blood – ↑ creatinine concentration in the serum – ↓ creatinine clearance – ↓ NO, ↓ protein thiols, ↓ free thiols, and ↓ total thiols concentrations and ↓ CAT and ↓ SOD activities in the kidney 	[13]
3 mg CdCl ₂ /kg b.w./day, i.p., 7 days	BALB/c mice	cloudy swelling of tubular cells, narrow renal tubules, and fibrosis	<ul style="list-style-type: none"> – ↓ SOD activity and ↓ GSH concentration in the kidney – ↑ ROS generation and ↑ MDA concentration in the kidney 	[14]
1 mg CdCl ₂ /kg b.w./day, i.p., 2 weeks	Male Sprague–Dawley rats		<ul style="list-style-type: none"> – ↑ creatinine concentration in the urine – ↑ ADA, ↑ TNFα, ↑ IL-6, and ↑ IL-10 concentrations in the kidney 	[15]
1 mg CdCl ₂ /kg b.w./day, i.p., 5 weeks	Wistar rats	vacuolization of epithelial lining renal tubules, congestion and atrophy of glomerular tufts, and distension of Bowman's space	<ul style="list-style-type: none"> – ↓ SOD, ↓ CAT, and ↓ GPx, activities in the kidney 	[16]
4 mg CdCl ₂ /kg b.w./day, i.v., 2 weeks	Male Wistar rats	tubular degeneration, necrosis and severe renal cortical congestion	<ul style="list-style-type: none"> – ↑ lipid peroxidation in the kidney – ↓ GSH concentration, ↓ AST, ↓ ALT, ↓ SOD, ↓ CAT and ↓ GPx activities in the kidney 	[17]

ADA, renal adenosine deaminase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; β₂-MG, β₂-macroglobulin; CAT, catalase; CdCl₂, cadmium chloride; COX2, cyclooxygenase 2; DT, distant tubule; GPx, glutathione peroxidase; GSH, reduced glutathione; GST, glutathione S-transferase; Hsp70, heat shock protein 70; IL-6, interleukin 6; IL-10, interleukin 10; i.p., intraperitoneally; i.v., intravenously; KIM-1, kidney

injury molecule-1; LOOH, lipid peroxides; MDA, malondialdehyde; NAG, N-acetyl- β -D-glucosaminidase; NO, nitrogen(II) oxide; OSI, oxidative stress index; PC, protein carbonyls; PT, proximal tubule; ROS, reactive oxygen species; s.c., subcutaneously; SOD, superoxide dismutase; TAS, total antioxidative status; TNF α , tumor necrosis factor α ; TOS, total oxidative status. ^b based on the studies published within the last 10 years.

Table S5. The odds risk (OR) of decreased estimated glomerular filtration rate (eGFR) and albuminuria due to low-level environmental exposure to cadmium (Cd).

Country	n	Cd in the Blood (µg/L)	OR ^c		Cd in the Urine (µg/L or µg/g Creatinine)	OR		Reference
			(95% Confidence Interval)			(95% Confidence Interval)		
			Decrease in eGFR	Albuminuria		Decrease in eGFR	Albuminuria	
China S and NS	884	Men: < 0.5 0.5–2.3 > 2.3 Women: < 0.35 0.35–0.69 > 0.69	1.00 1.88 (1.10–3.21) 1.17 (0.67–2.05) 1.00 1.38 (0.82–2.32) 0.97 (0.56–1.66)	1.00 <				

Albuminuria, the albumin/creatinine ratio in the urine > 30; decrease in eGFR, eGFR < 60 mL/min/1.73 m². NS, non-smokers; S, smokers; OR, odds risk. ^c The OR represents the odds of an outcome during a particular level of exposure, compared to the odds of the outcome occurring in the absence of this exposure. The OR > 1 indicates an increased risk of the appearance of an effect.

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