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Toxic environmental exposures and kidney health in children

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Abstract

High-level exposures to a number of agents are known to have direct nephrotoxic effects in children. A growing body of literature supports the hypothesis that chronic, relatively low-level exposure to various nephrotoxicants may also increase the risk for chronic kidney disease (CKD) or accelerate its progression. In this review we highlight several environmental nephrotoxicants and their association with CKD in children and adolescents. We also discuss unique epidemiological challenges in the use of kidney biomarkers in environmental nephrotoxicology.

Keywords

Aristolochic acid; Arsenic; Cadmium; Chronic kidney disease; Environmental nephrotoxicants; Lead; Melamine

Introduction

More than 84,000 new synthetic chemicals have been registered with the U.S. Environmental Protection Agency (EPA) over the past 40 years, almost 3000 of which are classified as high production volume (HPV) chemicals, with ≥1 million pounds produced per year [1]. These chemicals are widely dispersed in the environment, and children may be exposed via air, drinking water, and food. Measurable quantities of 200 HPV chemicals are routinely detected in the blood and urine of virtually all Americans, as well as in breast milk and cord blood [2]. A large proportion of these chemicals remain untested for their potential toxic effects in children.

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A number of environmental agents have been shown to demonstrate acute and/or chronic nephrotoxicity (Table 1). Limited data exist for children; much of the research has been performed in adults or animal studies. However, children experience unique patterns of environmental exposures and exhibit biological susceptibilities that may affect their risk for toxicity following exposure. In this review we highlight several environmental nephrotoxicants and their association with kidney disease in children.

Children: a vulnerable population

Fetal determinants

Nephrogenesis occurs from the 6th to the 36th weeks of gestation; after 36 weeks nephrogenesis is generally complete, and each kidney has a full complement of nephrons (on average approximately 1 million nephrons per kidney). Factors affecting nephron endowment include genetics and environmental exposures, such as maternal malnutrition, gestational diabetes, uteroplacental insufficiency, maternal or fetal drug exposure, and premature birth [3]. Following birth, there is a rapid increase in glomerular filtration rate (GFR) and a decrease in renal vascular resistance in response to an increase in mean arterial pressure. The GFR averages about 55 mL/ min/1.73 m^2 by 2 weeks of age and reaches adult capacity of 100–125 mL/min/1.73 m^2 around 2 years of age [4]. Exposure to nephrotoxic agents during kidney development can result in a reduction in nephron number, as well as disruption of nephron structure and/or function [5]. The kidney does not have the ability to regenerate nephrons. Although the GFR in single nephrons can increase in response to damage to other nephrons, this adaptive capacity is not unlimited. Therefore, once a critical mass of nephrons has been damaged, the kidney's ability to compensate is overwhelmed, resulting in a decrease in kidney function. In this context it is not surprising that any insult to the developing kidney that impacts nephron development can subsequently increase risk for chronic kidney disease (CKD).

Postnatal determinants

In environmental and occupational medicine, children are often considered to be a particularly vulnerable population. Children experience proportionally greater exposures on a body-weight basis. For example, infants inhale twice as much air and a 6-month-old infant drinks sevenfold more water and consumes three- to fourfold more calories per body surface area than adults [6]. Additionally, children may experience more exposure due to the consumption of to certain "favored foods" (e.g., milk, formula, or fruit juice) which may contain pesticides and age-related behaviors, such as increased hand-to-mouth activity and more time spent on the floor. The fetus and infant may also be especially vulnerable to substances that disrupt developmental processes during sensitive time windows of target organ development [7]. The ability of children to respond to environmental toxicants also differs from that of adults due to relatively immature metabolic pathways, especially in the first few months after birth. Age-dependent differences exist between children and adults which can affect the absorption, distribution, metabolism, and excretion of potential toxicants [8]. The kidney is one of the main excretory organs of the body; however, many renal excretory pathways are not fully mature in the first year of life [9]. The kidneys are susceptible to toxic injury, in part because although they have a relatively low proportion of

body mass, they receive 20–25 % of cardiac output. Due to the high metabolic activity and active uptake by tubular cells, the proximal tubular epithelium is particularly susceptible to toxic injury, although vulnerabilities to various nephrotoxic agents have been described in all parts of the nephron (Fig. 1). Therefore, the kidney may be a vulnerable target of toxicants, particularly in children.

Heavy metal nephrotoxicants

High-level exposure to many of the heavy metals discussed below increases risk for acute kidney injury. Although exposure at high levels is increasingly uncommon in the industrially developed countries, there is increasing recognition that chronic exposures to lower levels of environmental nephrotoxicants may also contribute to kidney injury and increased risk for CKD. Low-level or “environmental” exposures to these chemicals are widespread in the modern world. The proximal tubular cell is the presumed target of action for the majority of heavy metals. The cellular mechanisms underlying nephrotoxicity remain incompletely described, and a review of this literature is beyond the scope of this review. Common mechanisms described or postulated include oxidative stress with associated lipid peroxidation, apoptosis, and cellular necrosis [10].

Arsenic

High-dose intoxication by inorganic arsenic is known to cause acute kidney injury [11], including tubulointerstitial nephritis and acute tubular necrosis [12]. Chronic environmental exposure occurs via contaminated drinking water and food. Contaminated sources can be traced to the past use of copper chromated arsenate as a wood preservative in pressure-treated lumber, occupational sources in mining and smelting, industrial applications, and the agricultural use of pesticides, fertilizers, and antimicrobial additives for animal and poultry feed [11]. In the USA, the EPA has established the standard arsenic limit in water at 10 μg/L, although millions of individuals are estimated to live in an area that exceeds this standard [13].

Several recent studies, primarily done in adults, suggest that chronic low-level exposure to arsenic may be associated with CKD [14]. A cross-sectional analysis of 3851 adults participating in the Strong Heart Study in the USA reported an adjusted odds ratio of prevalent CKD comparing the 75th to 25th percentile of arsenic exposure (defined as the sum of inorganic and methylated arsenic) to be 0.7 [95 % confidence interval (CI) 0.6–0.8]. In contrast, prospective analysis of 3119 of these participants demonstrated a positive relationship between urinary arsenic and incident CKD, with an adjusted hazard ratio of 1.2 (95 % CI 1.03–1.41) [15]. The discrepancy between the cross-sectional and prospective findings was attributed to reverse causation, in that reduced GFR leads to impaired inorganic arsenic excretion at baseline. A community-based survey of 1043 Taiwanese adults found a graded, dose-related increase in the odds of elevated β2-microglobulin and an estimated GFR (eGFR) value of≤ 90 mL/min/1.73 m^2 as urinary total arsenic levels increased above the reference group (≤35 μg/g creatinine) [16]. A case–control study of 125 patients with CKD (mean eGFR 28 mL/ min/1.73 m^2) and 229 age-matched controls (mean eGFR 80 mL/min/1.73 m^2) showed that total urinary arsenic level was significantly associated with

CKD in a dose–response relationship, with those in the highest tertile of total arsenic having 4.3 (95 % CI 1.9–9.7) higher odds of CKD versus controls [17]. Estimated GFR was also significantly negatively associated with total urinary arsenic concentrations in another case–control study of 132 patients with renal cell carcinoma, as compared to age- and sex-matched controls [18]. In Antofagasta, Chile, arsenic exposure from the public water supply occurred from 1958 up to 1970, after which time arsenic mitigation efforts began. This presented a unique scenario, rare in environmental epidemiology, with a known exposure time period and large study population (125,000 in 1970). Increased mortality from bladder cancer [standardized mortality rate (SMR) 18.1; 95 % CI 11.3–27.4] and chronic kidney disease (SMR 2.0; 95 % CI 1.5–2.8) was observed in young adults aged 30–49 years in who were exposed to high arsenic levels (mean 870 μg/L) in utero and/or≤18 years of age during the high exposure time period of 1958–1970 [19].

Studies of the impact of arsenic on kidney function in children are relatively rare. A 2006 cross-sectional study of more than 800 European children found no relation between inorganic arsenic and various serum markers of GFR (creatinine, cystatin C, or β2 microglobulin) [20]. A follow-up of 1887 children enrolled in the MINIMat study in Bangladesh (a country with endemic high arsenic exposure) who were exposed to arsenic and cadmium in utero found modest increases in blood pressure (3.7 mmHg systolic and 2.9 mmHg diastolic) per 1 mg/L increase in maternal urinary arsenic during pregnancy [21]. However, a recent follow-up of this cohort found a negative association between urine cadmium and eGFR, but no relationship with arsenic [22]. A recent cross-sectional examination of 1253 participants in the National Health and Nutrition Examination Survey (NHANES) aged 12–30 years found a *positive* relationship between arsenic and eGFR, but only when results were corrected for urinary concentration by urinary creatinine, not by urine osmolality [23].

Cadmium

Cadmium is another well-known nephrotoxicant that targets the proximal tubule in the kidney. Exposure occurs through fossil fuel combustion, agricultural use of phosphate fertilizers, tobacco smoking, and various occupational exposures, including battery manufacture, copper and zinc smelting, and welding [24]. In the USA, the largest source of cadmium exposure for nonsmoking adults and children is through dietary intake of contaminated food and water. In contrast to lead, exposure to secondhand smoke has not been associated with elevated urinary cadmium levels in children [25]. Cadmium bioaccumulates in the liver and kidney, and therefore cadmium levels in urine are thought to be a good biomarker of the cumulative internal dose and kidney and body burden of cadmium, whereas blood levels are thought to be more indicative of recent exposure. Longitudinal studies in occupationally exposed workers and people with high environmental exposures to cadmium have reported these populations to have an increased risk for CKD [26, 27]. Cross-sectional studies have also reported nephrotoxicity at lower levels of exposure to cadmium [28-30], and, with co-exposure to lead, an increased risk for albuminuria and CKD [30].

Results have been mixed among studies that have examined GFR measures and/or albuminuria in children. A study of 200 Belgian adolescents living near a lead smelter showed no association between blood or urine cadmium levels and serum cystatin C levels [31]. In the European cohort study of 804 children mentioned in the preceding section, higher urine cadmium levels were associated with lower serum creatinine, which is a finding opposite from that expected in nephrotoxicity [20]. There was no association between urine cadmium levels and serum β2-microglobulin or cystatin C levels, although higher levels of blood and urine cadmium were associated with higher levels of retinol-binding protein and *N*-acetyl-β-D-glucosaminidase (NAG). A study of adults and children residing near a zinc smelter and a control group reported no associations between urine cadmium levels and NAG or albuminuria in 159 children aged 6–17 years, although a positive association between these was observed in 150 adults [32]. Finally, the MINIMat study of 1,06 rural Bangladesh preschool children found that, at levels>0.12 μg/L, a 0.5 μg/L increase in urinary cadmium was associated with a decrease in eGFR of 2.6 mL/min/ 1.73 m^2 in girls [22].

Lead

Lead is the most notable and best studied environmental nephrotoxicant. Environmental levels of lead have increased more than 1000-fold over the past three centuries as a result of human activities, including the Industrial Revolution, leaded gasoline, lead-based paint, mining operations, plumbing, and other industrial applications [33]. Acute lead poisoning (blood lead levels>80–100 μg/dL) disrupts both proximal tubular structure and function. Histologically, acute lead poisoning leads to the development of intranuclear inclusion bodies containing lead–protein complexes and mitochondrial swelling in proximal tubular cells [34]. The molecular mechanism of toxicity is thought to involve the effects of lead on mitochondrial respiration and phosphorylation [35]. Clinically, acute lead poisoning is characterized by the development of glucosuria, aminoaciduria, phosphaturia, or Fanconi's syndrome. Lead is bioaccumulative, with detectable lead levels in the bones of chronically exposed children and adults which can be mobilized by the body and contribute to ongoing endogenous exposure [36]. Lead poisoning is also known to reduce 1,25-dihydroxyvitamin D synthesis [37] and has been associated with bone demineralization and rickets in children [38]. The kidney manifestations of acute lead poisoning are usually reversible after cessation of lead exposure and, if indicated, chelation therapy [35, 39].

Chronic lead poisoning (blood lead levels>60 μg/dL) has been reported in children and adults and may result in lead nephropathy [40], which is characterized by tubulointerstitial fibrosis, tubular atrophy, glomerular sclerosis, and ultimately diminished GFR (Fig. 2) [41, 42]. Inflammatory cells are typically absent, and intranuclear inclusion bodies are also often absent [42]. Chronic lead exposure has also been shown to cause hypertension in animal models [43] and humans [44].

Chronic lead nephropathy in young adults was first described in 1929 after an outbreak of lead poisoning in children in Queensland, Australia due to the ingestion of lead-based paint [45]. A follow-up study in 1954 of 401 young adults diagnosed with lead poisoning in childhood between 1915 and 1935 revealed that 165 individuals had died in young adulthood, of whom 108 deaths were due to nephritis or hypertension, an incidence which

far exceeded that in the rest of Australia [46]. The kidneys of these individuals were found to be contracted and small, with histologic changes of interstitial fibrosis, hypertensive vascular changes, and “alterative glomerulitis” [47, 48], which is a term coined by Kimmelstiel and Wilson in 1936 to describe histological findings of nuclear proliferation and irregular pyknotic nuclei in the glomerular tuft adjacent to the vascular pole seen in hypertension-induced glomerulosclerosis [49]. Although subsequent studies of adults who suffered childhood lead poisoning have reported hypertension [50, 51], persistent partial Fanconi’s syndrome [52], and individual cases consistent with lead nephropathy [50], they have not demonstrated overall increased mortality or statistically significant decreased kidney function [53]. A possible explanation for this discrepancy may be that the children in the Queensland epidemic were untreated, whereas children in subsequent studies were treated with chelation therapy. Hyperfiltration may also be a factor in these disparate findings. Hyperfiltration is a complex phenomenon described in multiple pathophysiological states (including diabetes, sickle cell disease, and obesity) characterized by maladaptive alterations in glomerular hemodynamics and structural changes within the glomerulus; it is often associated with albuminuria and a transient *increase* in GFR [54]. Lead has also been implicated as a cause of hyperfiltration in both animal models [55] and human studies [40, 56]. The substantial nephron reserve and lack of sensitive outcome measures may be additional factors that contribute to the challenges of linking lower level toxicant exposures to kidney disease.

More recent investigations of childhood effects of lead on kidney outcomes have focused on participants living in close proximity to industrial pollution sources. Contradictory results have been reported. In a study of 200 Belgian adolescents, classified into a rural control group and two exposed groups from industrialized suburbs, blood lead level was positively associated with serum cystatin C level, with mean blood lead levels of 1.5, 1.8, and 2.7 μg/dL, respectively [31]. In contrast, negative associations with serum creatinine and cystatin C were reported in a cross-sectional survey of 804 European children, with mean blood lead levels ranging from 2.8 to 6.5 μg/dL [20]. The authors of the latter study implicated hyperfiltration as potential explanation for these contradictory findings. In unadjusted analyses in other populations of exposed children, blood lead levels were positively associated with a variety of urinary biomarkers, including retinol-binding protein [57], beta2-microglobin and Clara cell protein [58], and NAG [59]. A prospective Yugoslavian birth-cohort study identified significant increases in blood pressure and proteinuria with higher blood lead levels in 577 children born to women living near a lead smelter, refinery, and battery plant [60].

Fortunately, mitigation efforts in the USA and worldwide have significantly reduced childhood exposure to lead over the past 50 years [61]. Although stringent control measures have been enacted in the last few decades, lead still persists in the soil and to a lesser extent in the air and water (and consequently in the food chain), with potential consequences of chronic, low-level environmental exposure. Thus, research efforts have more recently focused on populations with lower levels of environmental exposure to lead. Multiple cross-sectional studies in adults have demonstrated a significant positive association between blood lead level and serum creatinine [62-64], as well as increased all-cause and cardiovascular mortality [65]. An analysis of 769 adolescents participating in the 1988–1994

NHANES with median blood lead and cystatin C-based eGFR levels of 1.5 μg/dL and 112.9 mL/ min/1.73 m^2, respectively, identified a statistically significant, negative association between blood lead level and kidney function [66]. In fully adjusted models, cystatin C-based eGFR was lower (−6.6 mL/min/1.73 m^2; 95 % CI −0.7 to −12.6) in children with lead levels in the highest quartile (≥3.0 μg/dL) compared with those in the lowest quartile (<1 μg/dL). A doubling of blood lead level was associated with a lower cystatin C-based eGFR (−2.9 mL/min/1.73 m^2; 95 % CI −0.7 to −5.0). The association with serum creatinine-based eGFR was also negative but did not reach statistical significance.

The association between lead exposure and GFR was evaluated in a potentially more vulnerable population of North American children with CKD in the Chronic Kidney Disease in Children (CKiD) study. Median blood lead level and measured GFR were 1.2 μg/dL and 44 mL/min/1.73 m^2, respectively. The average percentage change in GFR for each 1 μg/dL increase in blood lead level was −2.1 (95 % CI −6.0 to 1.8). In analyses stratified by CKD diagnosis, the association between lead level and GFR was stronger among children with glomerular disease underlying CKD; in this group, each 1 μg/dL increase in lead level was associated with a −12.1 (95 % CI −22.2 to −1.9) percentage change in GFR [67]. Significantly elevated lead levels have also been reported in other pediatric CKD populations. Filler et al. reported a significantly higher mean blood lead level in 16 patients (9 on hemodialysis, 1 on peritoneal dialysis, and 6 at CKD stage 3 or 4)compared to 647 healthy controls without kidney disease (21.1±15.8 vs. 6.35 μg/L, respectively) and correlated these with calcium carbonate dose and GFR [68].

The hypothesis of reverse causality attributes higher lead levels to reduced lead excretion as a consequence—rather than cause—of decreased kidney function and is raised as an explanatory factor for negative associations between higher blood lead and kidney function in cross-sectional studies. Longitudinal studies are useful to address the potential impact of this mechanism on associations between lead and kidney function. In a prospective study of 121 patients with CKD, a 1 μg/dL increase in blood lead level was associated with a 4.0 mL/min/1.73 m^2 decline in GFR over 48 months of observation [69]. Longitudinal data on children are scarce. A study in which lead exposure was assessed by lead content in deciduous teeth observed higher levels in 22 German children with CKD compared to a control group of 20 siblings or neighbors and another group of 16 healthy children without known lead exposure (2.8, 1.7, and 1.4 μg/g, respectively [70]. Importantly, lead level in teeth was not correlated with duration of kidney function impairment, providing evidence against reverse causality.

In a series of randomized experimental trials, a research group in Taiwan observed that chelation with EDTA slows CKD progression in adults, even at lead levels considered to be normal [71]. The same group reported an *increase* in GFR of 6 mL/min/1.73 m^2 in a group of diabetic CKD patients treated over 2 years with chelation therapy (average of 7.0 g $CaNa_2EDTA$) compared to a GFR decline of 1.4 mL/min/ 1.73 m^2 in the untreated group [72]. However, this research is preliminary and requires replication in other populations, including children, before chelation at lower lead levels can be recommended [73].

Mercury

Mercury exposure occurs through the oral, inhalation, and dermal routes, with distinct clinical toxidromes related to the three forms of mercury: elemental, inorganic, and organic. Exposure to elemental mercury by inhalation can occur from breathing mercury vapor emitted from coal-fired power plants, cinnabar ore smelting and gold extraction/processing plants, dental amalgams, thermometers, and caustic soda production. Acute exposure to mercury vapor may result in chemical pneumonitis; chronic exposure may cause excessive salivation, intention tremor, and myriad psychiatric symptoms. Inorganic mercury exposure occurs via mercury mining (cinnabar ore) and from a variety of medicinal uses; for example, skin lightening creams and, historically, calomel powder used for teething in small children. Exposure in children may result in acrodynia (Pink disease), characterized by red discoloration of the skin of the hands and feet, fever, profuse sweating, photophobia, and psychiatric manifestations [74]. Dietary sources of seafood are a major source of organic mercury compounds, notably methyl mercury, which is a particular health hazard to infants and the developing fetus.

Mercury exposure has two distinct nephrotoxic effects: (1) acute kidney injury and proximal tubule damage; (2) rarely, an immune-complex-mediated nephrotic syndrome which has been described in animal models [75] and humans [76]. Age-related differences in kidney function may influence mercury toxicity. Animal data suggest that immature kidneys may have decreased tubular transport, and therefore less mercury excretion, which may increase toxicity [5].

Amalgam dental fillings contain elemental mercury and are a common source of environmental exposure in the general population. Several recent studies have examined the impact of these fillings on kidney function in children. The New England Children's Amalgam Trial enrolled 534 children, 6–10 years of age, who had at least two cavities but no prior amalgam fillings, and randomized them to receive either amalgam or resin composite fillings [77]. Follow-up over 5 years showed no significant differences between treatment groups in average levels of urine biomarkers (α1-microglobulin, gamma-glutamyl transpeptidase, and NAG), although a significantly increased prevalence of microalbuminuria in the amalgam group in years 3–5 (adjusted odds ratio 1.8; 95 % CI 1.1–2.9) was observed. The authors noted that microalbuminuria was present in years 3 and 5 in ten children in the amalgam group compared to only two children in the composite group (p value0.04). The Casa Pia trial, in which 507 children, randomized to amalgam or composite resin fillings, were enrolled, revealed no significant differences in albuminuria and other markers by treatment group over the 7-year follow-up period [78]. However, a subsequent posthoc analysis of the same dataset using an alternative statistical approach demonstrated statistically significant dose-dependent correlations between cumulative mercury exposure and urinary glutathione-S-transferase-alpha, a urinary biomarker of proximal tubule injury [79]. This posthoc analysis has been criticized by the authors of the parent study as employing a flawed statistical approach [80]. Continued longitudinal follow-up of children in the experimental studies would be of interest, as would an examination of GFR measures.

Uranium

Renal toxicity is considered to be a hallmark of uranium poisoning and is well-established in multiple experimental animal studies [81, 82]. Exposure occurs via groundwater contamination from natural uranium deposits, as well as from uranium mining, milling, and processing. Uranium bioaccumulates in bone, although to a lesser extent than lead. The S3 segment of the renal proximal tubule is a target site of involvement, resulting in tubular dysfunction. Epidemiological data are scarce and have not shown consistent findings with GFR, although there is some limited evidence of urinary biomarkers indicating proximal tubular damage [83]. A follow-up of 35 Gulf War veterans exposed to depleted uranium showed a trend towards increased levels of β2-microglobulin and retinal binding protein levels in the highest uranium exposure group, although there was no association with GFR [84]. A case study of a family exposed to naturally uranium-contaminated well-water also demonstrated elevated β2-microglobulin in the youngest child, suggesting that young children may be particularly vulnerable [85]. The child's β2-microglobulin level subsequently declined after cessation of exposure. Age-related differences in kidney toxicity have also been reported in animal models [5].

Naturally occurring chemical nephrotoxicants

Aristolochic acid nephropathy

Aristolochic acid is a naturally occurring toxic compound found in plants of the Birthwort (Aristolochiaceae) family that includes the *Asarum* (wild ginger) genus and *Aristolochia* genus. Herbal drugs derived from plants belonging to genus *Aristolochia* have been used since antiquity for treating snake bites, obstetrics, arthritis, gout, and rheumatism, and in some parts of the world *Aristolochia* plants and their extracts are used in traditional Chinese herbal medications [86]. Aristolochic acid has been implicated as the cause of end-stage renal disease (ESRD) in a 10-year-old child [87], as well as the causative agent in Balkan endemic nephropathy and Chinese herb nephropathy [88]. Balkan endemic nephropathy was described in the 1950s among several communities near tributaries of the Danube River in the Balkan Peninsula and is characterized by a chronic tubulointerstitial renal disease with increased risk for urothelial carcinoma. Heavy metals, viruses, trace-metal deficiencies, and mycotoxins (especially ochratoxin A) were considered as possible etiologies, but most experts now agree that chronic exposure to dietary aristolochic acid was the likely cause [88]. In 2001 the U.S. Food and Drug Administration advised consumers of the risks of botanical products containing aristolochic acid due to the risk of permanent kidney damage (including ESRD) and certain types of cancers occurring in the urinary tract [89]. The exact mechanism of action of nephropathy remains unknown, although formation of unique aristolochic acid–DNA adducts in human kidney cells as well as mutation of the tumor suppressor gene TP53 have been implicated in carcinogenesis [90].

Mycotoxins

Mycotoxins are secondary metabolites produced by several species of fungi which are capable of causing disease in human or animal species. Ochratoxin A and citrinin are two such mycotoxins isolated from *Penicillium*, *Aspergillus*, and *Monascus* species with known nephrotoxicity in multiple animal models, although the significance for the human

population remains unknown [91]. They have been found in many human foods, including wheat, oats, rye, barley, and rice. Citrinin and ochratoxin A have also been implicated as a cause of Balkan nephropathy and yellow rice fever [91]. Animal studies have demonstrated citrinin transport via the organic anion transporter in the proximal tubule cell [92], as well as synergistic disruption of RNA synthesis in murine kidneys by citrinin and ochratoxin A [91].

Synthetic nephrotoxicants

Melamine nephropathy

Melamine is a synthetic chemical with multiple commercial applications, including manufacture of colorants, glues, laminates, adhesives, production of dinnerware, dry-erase boards, cleaning products (such as Magic Eraser), and flame retardants [93]. Although not intended for human consumption and banned by the World Health Organization, melamine has a high nitrogen content and is known to falsely inflate the protein content in foodstuffs. It has been used to deliberately adulterate animal and human foods in an effort to lower production costs. Several well-publicized outbreaks of kidney failure and kidney stones in animals and humans have been reported in the last decade, with one such outbreak in 2007 resulting in a widespread pet food recall and the Chinese epidemic of 2008, involving the consumption of melamine-tainted infant formula, affecting over 294,000 infants and children, 51,900 of whom required hospitalization and at least six of whom died [94].

The mechanism of melamine nephrotoxicity in pet and livestock outbreaks is related to its ability to react with cyanuric acid in the bloodstream and form large round melamine–cyanuric acid crystals which lead to urinary obstruction and acute kidney injury [93]. The formation of these crystals has been associated with extremely high mortality in animal outbreaks. In the tainted Chinese infant formula outbreak, the kidney stones were composed primarily of melamine and uric acid and, consequently, they were radiolucent and not visible on plain X-ray films [95]. Symptoms included irritability, dysuria, renal colic, hematuria, stone passage, and, rarely, symptoms of acute kidney injury related to urinary obstruction, including elevated creatinine, hypertension, edema, and/or oliguria. Acute kidney injury occurred in 2.5 % of cases [95].

Other

CKD of unknown etiology

An epidemic of CKD of unknown etiology, termed “Mesoamerican nephropathy”, has recently been described to disproportionately affect young to middle-aged Central American agricultural workers without traditional risk factors for kidney disease, such as diabetes or hypertension [96]. Symptoms are suggestive of nonglomerular disease, as patients present without significant proteinuria or hypertension, small echogenic kidneys are seen on ultrasound imaging, and biopsy findings indicate the presence of chronic tubulointerstitial disease [97]. A frequent symptom complex identified among individuals is *chistata* which is a colloquial term in Central America for dysuria. Similar patterns of kidney disease in adults without traditional risk factors have been reported in Sri Lanka, the state of Andhra Prakesh in India, and the El-Minia Governorate in Egypt. Given that the cause(s) remains

uncharacterized, it has been labeled CKD of unknown etiology (CKDu). Tragically, as the disease occurs in communities in which dialysis and transplantation are not routinely available, CKDu is often considered to be a terminal diagnosis. Although the etiology remains unknown, multiple hypotheses have been proposed, including chronic dehydration from hard labor, agrochemicals (such as pesticides), heavy metals, aristolochic acid, medications [nonsteroidal anti-inflammatory drugs (NSAIDs), and/or infections, such as leptospirosis [98]. Although this disease typically affects adults in their third to fifth decade of life, pediatric cases have been reported [99]. A preliminary study in which four urinary biomarkers of early-stage kidney damage [neutrophil gelatinase-associated lipocalin (NGAL), NAG, interleukin-18 (IL-18), and albumin/creatinine ratio] were assessed in 245 Nicaraguan adolescents found evidence of elevated IL-18 levels relative to those in healthy participants in other countries [100]. The prevalence in children may be underestimated given the challenges in characterizing and detecting the disease, especially in early stages.

Although it remains unknown whether the cause(s) of CKDu are related to environmental and/or occupational exposures, there is similarity (clinically and histologically) to prior outbreaks of environmental toxin-mediated nephropathy. The causes implicated in previous outbreaks of nephropathy have not yet been established as risk factors for CKDu, and further research into novel risk factors and multifactorial etiologies is being pursued.

Challenges in exposure assessment

Many recent epidemiological studies examining low-level chronic nephrotoxicants have observed unexpected positive associations with eGFR, a direction opposite to that expected with exposure to a nephrotoxicant [23, 83, 101, 102]. This association is more often observed with serum creatinine-based eGFR and when urinary levels of a nephrotoxicant (exposure) are adjusted for urine concentration using creati-nine, and it has been highlighted in a recent review [103]. The mechanism or mechanisms for this unexpected association remain unclear. Hypotheses include the possibility of reverse causality, as discussed earlier in this review. It is also possible that biomarker concentrations could be impacted by any level of GFR, even when in the normal physiologic range. If this were to be true, it could have important implications on any research which utilizes urinary biomarkers and may indicate a need to adjust for GFR, even in healthy populations. Other hypotheses to account for these unexpected positive associations could be a statistical interaction using correlated bio-markers, such as serum and urine creatinine in exposure and outcome variables, or potentially the impact of kidney tubule processing of urinary creatinine, which may be differentially affected by metal exposure.

Because kidney function is affected by multiple exposures and host characteristics, the causal contribution of a single putative environmental nephrotoxicant can be difficult to isolate, particularly when the exposures are chronic and low-level. Large population studies are necessary to achieve the statistical power needed to overcome imprecise outcome measures and the possibility of simultaneous exposure to multiple nephrotoxic exposures. Inconsistent results and/or weak correlations are to be expected, particularly as smaller and smaller outcome effects are evaluated. Consequently, the findings of statistical significance for some but not all biomarkers do not necessarily invalidate the importance of positive

associations observed. There remains an obligation to recognize the potential importance of statistically significant findings in environmental epidemiological research and acknowledge that many exposures have been understudied. It is imperative to be vigilant with preventative strategies, the cornerstone of risk mitigation and public health.

Conclusions

There is a growing awareness of the adverse effects of a multitude of potential nephrotoxicants, including heavy metals and other chemicals or substances found in the environment, on kidney health in children. Several key challenges remain in this area of research. There continues to be a paucity of high-quality epidemiological studies designed to assess environmental exposures in children with multiple health outcomes, kidney and otherwise. Barriers include lack of statistical power due to small sample sizes, quality of exposure assessment, adequate control of potential confounders, and freedom from bias. Further work into the unexpected positive associations between urinary biomarkers and kidney outcomes is necessary. As environmental exposures are modifiable, in contrast to most causes of acute and CKD, well-designed epidemio-logical studies should be prioritized in order to further our understanding of and to characterize relationships between potential nephrotoxic exposures and health outcomes in children. Clinicians should be cognizant that environmental exposures are relatively common and be vigilant in screening. A targeted history based on the exposure sources for the potential toxicants in Table 1 should be performed for each patient, and if there is concern for exposure, a more detailed exposure assessment can be considered.

Multiple choice questions (answers are provided following the references)

1. Which of the following is TRUE regarding the epidemiology of kidney disease due to environmental exposures?

- **a.** Cadmium and lead co-exposure is associated with a significantly higher risk of albuminuria and CKD than either exposure alone.
- **b.** Aristolochic acid nephropathy is associated with acute tubular injury but has not been associated with ESRD.
- **c.** Chelation studies in patients with lead nephropathy have been overall disappointing, with no evidence of improvement in GFR with chelation therapy.
- **d.** Most of the known environmental toxins primarily affect the glomerulus.

2. Which of the following have been proposed as possible etiologies of CKDu?

- **a.** Infections.
- **b.** Recurrent dehydration.

c. Pesticides.

d. Chronic NSAID exposure.

e. All of the above.

3. What is the proposed mechanism of acute kidney injury and nephrotoxicity of melamine?

a. Proximal tubulopathy.

b. Immune-complex-mediated glomerulonephritis.

c. Urinary obstruction from melamine-induced urinary stones.

d. Chronic tubulointerstitial nephritis.

4. Which of the following heavy metals are not known to accumulate in the body (bioaccumulative) after exposure?

a. Lead.

b. Cadmium.

c. Arsenic.

d. Uranium.

5. Which of the following is NOT a known exposure to lead in the modern world?

a. Residential paint.

b. Gasoline.

c. Dental amalgams.

d. Mining operations.

e. Plumbing.

Answers

1: a

2: e

3: c

4: c

5: c

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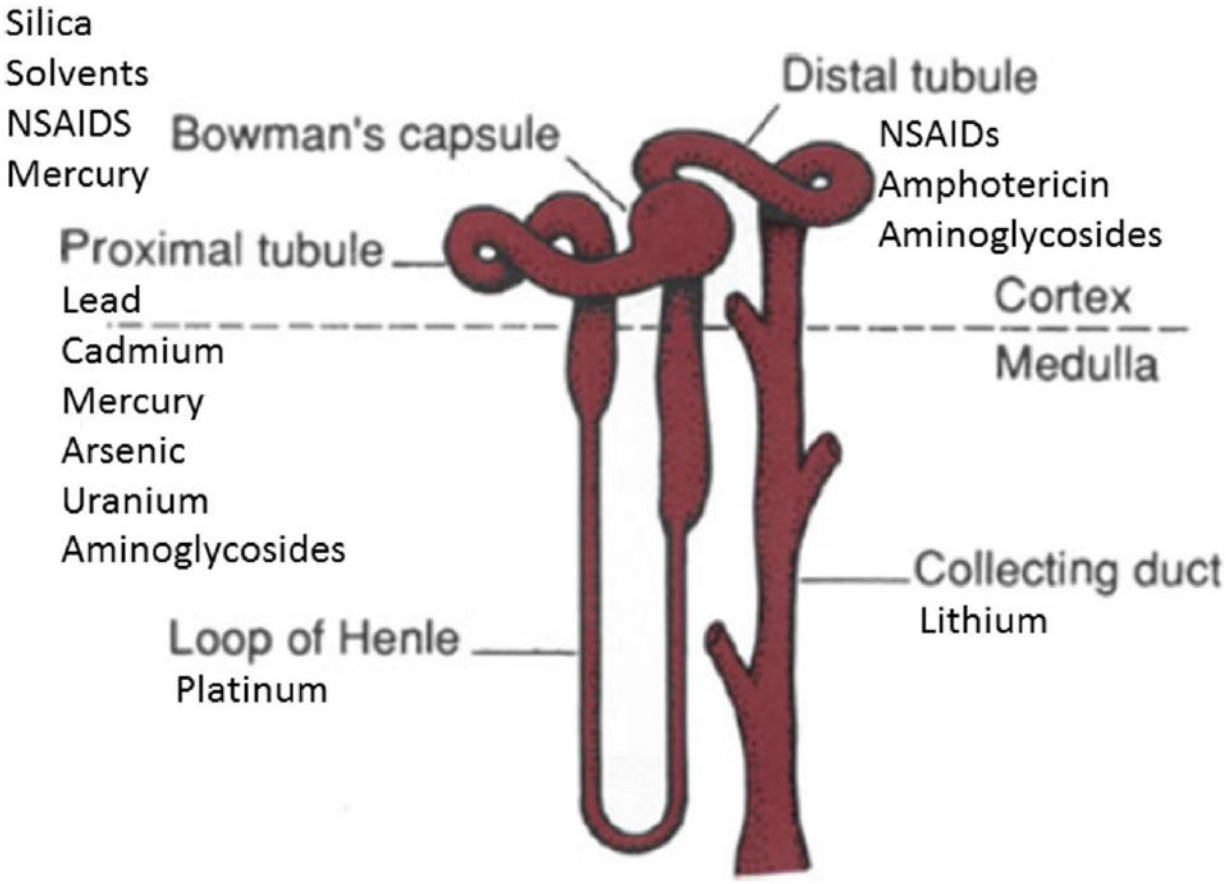

Fig. 1.

The nephron and associated sites of action of various nephrotoxicants. *NSAIDs* Nonsteroidal anti-inflammatory drugs. Adapted from: Lote C (2012) Principles of renal physiology, 5th edn, Springer, New York, p 23, with permission

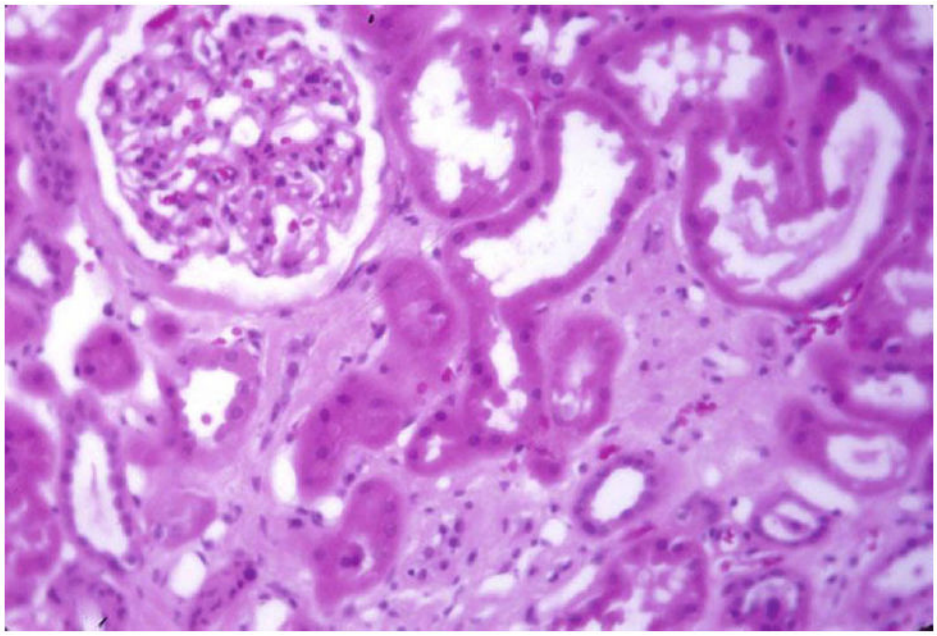

Fig. 2.

Histopathology of a patient with chronic lead nephropathy, characterized by a normal glomerulus, nonspecific tubular atrophy, and interstitial fibrosis. (Image courtesy of Vecihi Batuman)

Table 1

Environmental exposure to nephrotoxicants and associated kidney disease manifestations

Agent	Source of exposure	Short-term (acute toxicity)	Long-term (chronic exposure)
Lead	Lead-based paint; soil and dust (paint, gasoline, industrial sources); drinking water (lead pipes), cigarette smoke	Fanconi's syndrome	Lead nephropathy, CKD
Arsenic	Groundwater contamination; food contamination (apple juice, rice, wine)	Acute tubular necrosis	CKD; kidney cancer
Cadmium	Fossil fuel combustion; phosphate fertilizers; iron and steel production; batteries; municipal solid waste incineration; food contamination (rice, root crops)	Acute tubular necrosis	CKD
Mercury	Coal-fired power plants; smelters, gold production; municipal waste incineration; natural sources (volcanoes)	Acute tubular necrosis; immune-complex mediated nephritic syndrome	Limited evidence; possibly microalbuminuria
Uranium	Groundwater contamination of natural uranium deposits; uranium mining, milling, and processing	Acute tubular necrosis	Limited evidence; proximal tubular injury (^{2}-2 microgobulin)
Aristolochic acid	*Aristolochiaceae* family of plants (used in Chinese herbs)	Interstitial nephritis	Interstitial nephritis; urothelial carcinoma
Melamine	Food adulterant; manufacture of colorants, glues, laminates, adhesives, dinnerware, dry-erase boards, cleaning products, and flame retardants	Urinary stones, acute kidney injury	No long-term known outcomes described

CKD, Chronic kidney disease