

# The effects of environmental chemicals on renal function

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**Abstract** | The global incidence of chronic kidney disease (CKD) is increasing among individuals of all ages. Despite advances in proteomics, genomics and metabolomics, there remains a lack of safe and effective drugs to reverse or stabilize renal function in patients with glomerular or tubulointerstitial causes of CKD. Consequently, modifiable risk factors that are associated with a progressive decline in kidney function need to be identified. Numerous reports have documented the adverse effects that occur in response to graded exposure to a wide range of environmental chemicals. This Review summarizes the effects of such chemicals on four aspects of cardiorenal function: albuminuria, glomerular filtration rate, blood pressure and serum uric acid concentration. We focus on compounds that individuals are likely to be exposed to as a consequence of normal consumer activities or medical treatment, namely phthalates, bisphenol A, polyfluorinated alkyl acids, dioxins and furans, polycyclic aromatic hydrocarbons and polychlorinated biphenyls. Environmental exposure to these chemicals during everyday life could have adverse consequences on renal function and might contribute to progressive cumulative renal injury over a lifetime. Regulatory efforts should be made to limit individual exposure to environmental chemicals in an attempt to reduce the incidence of cardiorenal disease.

Kataria, A. *et al.* *Nat. Rev. Nephrol.* advance online publication XX Month 2015; doi:10.1038/nrneph.2015.94

## Introduction

The impact of environmental chemicals on public health and clinical well-being has long been recognized, with a historical focus on heavy metals and molecules that are produced in the work place.<sup>1</sup> Increasing data have, however, indicated that the general public is unknowingly exposed to a wide range of chemicals as a consequence of normal consumer activities. These activities include dietary intake of food, domestic and commercial food preparation, household maintenance procedures, and routine medical and dental care.<sup>2–5</sup>

A major food safety incident in 2009 exemplified the potential scope of the adverse renal consequences that can occur following population-wide exposure to organic contaminants.<sup>6</sup> Melamine is an organic nitrogenous compound used in the industrial production of plastics, dyes, fertilizers and fabrics that was considered safe on the basis of standard animal studies. This molecule was deliberately added to diluted raw milk at milk-collecting stations in China, with the presumed aim of falsely elevating assay results for protein content.<sup>7,8</sup> Melamine was later detected in numerous food and milk-containing products that were exported from China to many countries worldwide.<sup>7,8</sup> More than 300,000 infants and children exposed to milk-based formulas contaminated with melamine developed radiolucent stones, as well as impaired renal function and renal growth.<sup>6,9</sup> The long-term consequences of melamine exposure in infancy and early childhood remain unknown,<sup>10</sup> but exposure to

melamine during adulthood might increase the risk of urolithiasis.<sup>11</sup> The melamine story, therefore, provides a striking cautionary note regarding the potential serious adverse consequences of exposure to environmental organic chemicals during normal consumer activity.

The liver has long been considered the major target organ for most of the chemicals implicated in eliciting toxic effects following environmental exposure. Nevertheless, emerging data suggest that the kidney is also an important site of injury after chemical exposure, although substantial gaps remain regarding the effects of environmental chemicals on specific aspects of kidney function (Table 1).

In this Review, we analyse the clinical effects of a select list of organic compounds on measures of cardiorenal function, including changes in blood pressure, albuminuria, glomerular filtration rate (GFR), and uric acid concentration. These parameters should not be considered an all-inclusive definition of cardiorenal function, and other clinical indicators, including vascular stiffness and left ventricular mass, could play a part. In addition, we distinguish the cardiorenal effects from cardiometabolic effects, such as insulin resistance and obesity. The toxicokinetic and toxicodynamic characteristics of environmental chemicals, and inter-species differences in susceptibility to injury, are beyond the scope of this Review. Furthermore, the ethical constraints imposed on clinical investigations in this field limit our capacity to discuss the underlying mechanisms of kidney injury in full. Here, we highlight both the scope of potential adverse renal effects and gaps in our knowledge for individual chemicals.

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## Competing interests

The authors declare no competing interests.

**Key points**

- Exposure to organic contaminants occurs through normal daily and routine medical procedures, and is ubiquitous among healthy children and adults
- Exposure to environmental chemicals that can damage the kidney can occur via dietary intake or as a consequence of medical interventions, such as haemodialysis or parenteral nutrition
- The full impact of persistent exposure to environmental chemicals on renal function has not been addressed in great detail
- Cross-sectional data from numerous studies worldwide indicate that exposure to organic chemicals can have adverse effects on glomerular filtration rate, albuminuria, blood pressure and serum uric acid concentration
- Oxidative stress is a contributing factor to the adverse effects of environmental chemicals on cardiorenal function; additional studies are required to clarify the mechanism and long-term effects of environmental chemicals

[Au:table title ok?]

**Table 1** | Associations between environmental toxins and cardiorenal disease

Chemical class	Albuminuria	eGFR	Blood pressure	Serum uric acid concentration
Phthalates	↑	No studies	↑	No studies
Bisphenol A (BPA)	↑	↑	↑	No studies
Perfluoroalkyl acids (PFAAs)	No studies	↓	↑	↑
Dioxins	↑	↓	↑	↑
Polycyclic aromatic hydrocarbons (PAHs)	No studies	Unknown	No studies	No studies
Polychlorinated biphenyls (PCBs)	↑	↓	↑	↑

Abbreviation: eGFR, estimated glomerular filtration rate.

**Phthalates**

**Sources of contamination**

Phthalates are esters of phthalic acid that can be either low-molecular weight (LMW) or high-molecular weight (HMW) (Table 2, [Supplementary Figure 1a and b](#)). Phthalates of LMW are frequently added to shampoos, cosmetics, lotions and other personal hygiene products to preserve scent.<sup>6</sup> Phthalates of HMW are typically used in the production of vinyl plastics used in flooring, food packaging and intravenous tubing.<sup>12</sup> Within the HMW category, di-2-ethylhexylphthalate (DEHP) is commonly found in plastic products used during industrial food production,<sup>13,14</sup> and its metabolites are often considered a subcategory of phthalates.<sup>3</sup>

Cross-sectional and interventional studies have identified strong associations between diet and urinary levels of DEHP metabolites.<sup>4,5</sup> A trial that intended to reduce the consumption of food contaminated with DEHP through dietary replacement led to unexpected increases of DEHP metabolites in the urine of individuals administered a controlled diet.<sup>15</sup> These findings occurred as a result of unwitting [Au:OK?] contamination of food products included in the controlled diet with DEHP, and thus suggest that DEHP contamination is wider than expected. Substituting packaged and/or canned foods with fresh food products can reduce the presence of DEHP metabolites in the urine by 53–56%.<sup>16</sup>

DEHP can leach into solutions that are administered to patients through polyvinyl chloride medical devices, including endotracheal, orogastric and nasogastric

tubes.<sup>17</sup> Infants maintained on parenteral nutrition exhibit variable increases in serum concentrations of DEHP at the end of the treatment period.<sup>18</sup> Given these findings, use of polyvinyl chloride-free medical devices is recommended in neonatal intensive care units.<sup>17</sup> Leaching of DEHP from intravenous blood lines might be especially severe among patients undergoing dialysis. In a study of 21 patients with end-stage renal disease undergoing chronic haemodialysis, the plasma level of DEHP rose during a 4 h dialysis session and an estimated 75 mg DEHP was extracted from the dialyzer.<sup>19</sup> *In vitro* studies confirmed that ~7.7 µg/ml DEHP migrates each hour from haemodialysis tubing into the blood without modifying the plasma concentration.<sup>20</sup> Another study of adult patients on haemodialysis found that urinary excretion of 4-heptanone, a metabolite of DEHP, was increased more than ninefold after a standard treatment session.<sup>21</sup> The amount of DEHP transferred during one haemodialysis session can be as much as the total annual exposure for patients receiving chronic ambulatory peritoneal dialysis.<sup>22</sup>

**Metabolism**

Pharmacokinetic studies of DEHP have not been performed in children and/or adolescents. Studies in animals suggest that DEHP is rapidly metabolized into three primary products: mono-2-ethylhexylphthalate; mono-2-ethyl-5-carboxypentylphthalate; and mono-2-ethyl-5-hydroxyhexylphthalate. These three metabolites have been identified as excretory products in human urine.<sup>23</sup> Evidence obtained from animal studies suggests that some phthalates might be secreted by organic anion transporters,<sup>24</sup> but comparable data are not available for humans.

Metabolites of phthalates undergo modest enterohepatic recirculation and intestinal excretion.<sup>25</sup> Monoesters of phthalates have a biological half-life of 12–48 h, which can be lengthened owing to phthalate deposition in adipose tissue. The presence of phthalates in the urine probably represents short-term, current exposure rather than chronic exposure, although a single sample of urine can provide moderate sensitivity (54–69%) and high specificity (76–84%) for DEHP metabolites to estimate the level of phthalate exposure over a 3-month period.<sup>26–28</sup>

**Albuminuria**

Low-grade albuminuria might be a marker of endothelial dysfunction and is a risk factor for the development of cardiovascular disease (Table 3). A study of 667 children, aged 6–19 years, who participated in the National Health and Nutrition Examination Survey between 2009 and 2010 (NHANES 2009–2010), found that for each approximate threefold increase in DEHP metabolites detected in the urine, a 0.55 mg/g increase [Au:OK?] in the albumin-to-creatinine ratio was identified.<sup>29</sup> Phthalates of LMW had no effect on albuminuria.<sup>29</sup> Short-term exposure to DEHP during neonatal extracorporeal membrane oxygenation therapy was not associated with any abnormalities in kidney function, including albuminuria.<sup>30</sup>

**Table 2** | Molecular structure, common derivatives, and source of contamination of environmental chemicals

Environmental toxin	Common derivatives	Molecular structure	Source
Phthalates	DEHP	Esters of phthalic acid	Shampoos, cosmetics, personal hygiene products, vinyl plastics, food packaging, intravenous tubing
Bisphenol A	NA	Synthetic compound with two phenol rings connected by a methyl bridge, with two methyl groups attached to the bridge	Polycarbonate plastics, epoxy resins, intravenous tubing
Perfluoroalkyl acids	PFOS, PFOA, PFHxA, PFNA, PFHxS, PFHS	Synthetic organic chlorinated compounds, in which all hydrogen atoms of the hydrocarbon backbone are substituted with fluorine	Electrochemical fluorination, telomerization, surface protection agents, sealants, surfactants, food packaging, non-stick cooking surfaces, stain-resistant sprays, fire-retarding foams
Dioxins	PCDD	Synthetic halogenated aromatic hydrocarbon	Pesticides, bleaching of wood pulp, waste incineration
Flurans	PCDF	Synthetic halogenated aromatic hydrocarbon	Pesticides, bleaching of wood pulp, waste incineration
Polycyclic aromatic hydrocarbons	Benzo[a]pyrene	Composed purely of carbon and hydrogen atoms in multiple aromatic rings	Incomplete combustion of coal, oil, and gas; tobacco smoke, charbroiled meat
Polychlorinated biphenyls	NA	Two benzene rings with varying degrees of saturation with chlorine moieties on the ringed backbone	Capacitants and coolants in electrical equipment

Abbreviations: DEHP, di-2-ethylhexylphthalate; NA, not applicable; PCDD, polychlorinated dibenzo-p-dioxins; PCDF, polychlorinated dibenzo-p-furans; PFHS, perfluorohexane sulfonate; PFHxA, perfluorohexanoic acid; PFNA, perfluorononanoic acid; PFOA, perfluoro-octanoic acid; PFOS, perfluoro-octane sulfonic acid.

### Blood pressure

A cross-sectional analysis of children aged 6–19 years who participated in NHANES 2003–2008 found an increase in the systolic blood pressure z-score of 0.041 standard deviation units for each approximate threefold increase in DEHP metabolite excretion [Au:OK?] (Table 4) [Au: Order of tables swapped to match text OK?].<sup>31</sup> For school age children and adolescents, this change in z-score translates into a 0.4–0.6 mmHg increase in systolic blood pressure. In contrast, exposure to LMW forms of phthalates had no effect on blood pressure.<sup>31</sup> In line with the effect of HMW phthalates on blood pressure, the degree of exposure to these contaminants has been linked to the severity of cardiovascular disease. In 1,016 individuals aged  $\geq 70$  years, phthalate exposure correlated with the size of overt coronary artery atherosclerotic plaques.<sup>32</sup> Interestingly, evidence from animal studies also suggests that DEHP might induce arrhythmia,<sup>33</sup> alter metabolic profiles and elicit cardiomyocyte dysfunction.<sup>34</sup> Other studies using the same population, however, failed to demonstrate any association between four phthalate derivatives and coronary risk, assessed using the Framingham Risk Score.<sup>35,36</sup>

### Bisphenol A

#### Sources of contamination

Bisphenol A (BPA) is a synthetic chemical comprised of two phenol rings connected by a methyl bridge, with two methyl groups attached to the bridge (Table 2, [Supplementary Figure 1c](#)). BPA was initially designed as a synthetic oestrogen, but is now widely used for its cross-linking properties in the manufacture of polycarbonate plastics and epoxy resins, and is present in intravenous tubing, including dialysis circuits.<sup>37</sup> Incomplete polymerization and polymer degradation of BPA causes

it to leach out of food and beverage containers and dental sealants.

Ubiquitous environmental exposure to nano-concentrations of BPA can occur through various routes, including ingestion, respiration, and absorption through the skin, and consequently detectable levels of BPA are found in the urine of >93% of adults.<sup>38</sup> Serum BPA levels are high among males and smokers,<sup>39</sup> and are inversely associated with socioeconomic status.<sup>40</sup> A study of 22 patients with predialysis chronic kidney disease (CKD) of [Au:OK?] found that serum BPA levels were inversely associated with renal function [Au:OK?].<sup>41</sup> Patients receiving dialysis have increased exposure to BPA owing to their near daily use of dialysis tubing. BPA levels are higher in patients undergoing haemodialysis ( $5.3 \pm 0.3$  ng/ml) and peritoneal dialysis ( $3.8 \pm 0.2$  ng/ml), than in healthy controls ( $2.6 \pm 0.1$  ng/ml).<sup>37</sup> Elution of BPA might be enhanced from polysulfone and polyester-polymer alloy hollow fibres.<sup>41</sup>

#### Metabolism

Studies in animals have shown that BPA is rapidly and efficiently absorbed across the oral mucosa, especially after sublingual exposure.<sup>42</sup> This efficient systemic route of entry via saliva, which bypasses first-pass hepatic clearance, might lead to greater BPA exposure than can be accounted for solely on the basis of absorption from the gastrointestinal tract.<sup>42</sup> This observation, however, has not been confirmed in humans and requires further study.<sup>43</sup> In humans, free BPA is metabolized by rapid glucuronidation or sulfo-conjugation and is eliminated by the kidneys.<sup>44</sup> Physiologically based pharmacokinetic modelling suggests that renal tubular reabsorption of BPA conjugates contribute to serum levels of BPA detected in humans,<sup>45</sup> but the contribution of this pathway to renal

**Table 3** | Effects of environmental chemicals on albuminuria

Chemical class	Reference	Country (study)	Participants	Main findings
Phthalates	Trasande <i>et al.</i> (2014) <sup>29</sup>	USA (NHANES 2009–2010)	667 children	A three-fold increase in DHEP metabolites caused a 0.55 mg/g creatinine increment in albuminuria
BPA	Li <i>et al.</i> (2012) <sup>50</sup>	China	3,055 adults	Graded increase in BPA exposure caused an increase in low-grade albuminuria
	Trasande <i>et al.</i> (2013) <sup>51</sup>	USA (NHANES 2009–2010)	710 children	Graded increase in BPA exposure caused an increase in low-grade albuminuria
	Trachtenberg <i>et al.</i> (2014) <sup>53</sup>	USA	434 children	No effect of BPA associated with dental use on albuminuria
PCDDs and PCDFs	Everett <i>et al.</i> (2014) <sup>93</sup>	USA (NHANES 1999–2004)	2,588 adults with diabetes mellitus	Increased risk of nephropathy in association with select PCDDs and PCDFs
PCB	Everett <i>et al.</i> (2014) <sup>93</sup>	USA (NHANES 1999–2004)	2,588 adults with diabetes mellitus	Increased risk of nephropathy in association with select PCBs

Abbreviations: BPA, bisphenol A; DEHP, di-2-ethylhexylphthalate; NHANES, National Health and Nutrition Examination Survey; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-p-dioxins; PCDF, polychlorinated dibenzo-p-furans. [Au: Table OK? Please check refs carefully.]

injury has not been studied. Enterohepatic recirculation and lipid storage can also influence the rate of BPA elimination by the kidney,<sup>46,47</sup> and might explain the differences between measured serum BPA levels in humans and those predicted from pharmacokinetic data.<sup>48</sup> A minor pathway of BPA metabolism involves oxidation by hydroxylation to a catechol followed by transformation to an o-quinolone,<sup>44,49</sup> which might elicit oxidative stress and augment BPA toxicity.<sup>49</sup>

#### Albuminuria

The first study to document albuminuria in healthy individuals exposed to BPA involved 3,055 adults living in Shanghai, China.<sup>50</sup> Participants with the highest level of BPA exposure based on urinary excretion were at greater risk of [Au: “increased” deleted OK?] low-grade albuminuria (<30 mg/g creatinine), regardless of whether BPA excretion was evaluated as a continuous or categorical variable. This association was confirmed in a study of 710 children enrolled in NHANES 2009–2010.<sup>51</sup> Children in the highest quartile of urinary BPA levels had a statistically significant 0.91 mg/g higher albumin-to-creatinine ratio compared to those in the lowest quartile. The effect of BPA on albuminuria was similar to that noted for phthalates (Table 3). No association between BPA exposure and microalbuminuria or macroalbuminuria was observed in either of these studies in children or adults.<sup>50,51</sup> Nevertheless, a study of 534 children aged 6–10 years found no difference in the urinary excretion of albumin or N-acetyl-β-D-glucosaminidase (both measures of renal damage) in those who were randomly assigned to dental restoration using BPA-free amalgam or BPA-containing resin.<sup>52,53</sup> BPA exposure associated with dental restoration materials or preventive dental sealants might not be as important as dietary intake in determining the renal consequences of this molecule.

Injection of mice with 50 mg/kg BPA per day for 5 weeks causes albuminuria and podocytopaenia.<sup>54</sup> Although the exact cause of BPA-induced albuminuria is unclear and could arise from oxidative stress-induced endothelial dysfunction, these data suggest that BPA has adverse effects on the glomerulus. *In vitro* exposure of

podocytes to low (10 nM) or high (100 nM) concentrations of BPA promotes cellular hypertrophy, reduces cellular viability, induces apoptosis and diminishes expression of podocin and nephrin.<sup>54</sup>

#### Estimated GFR

One study has evaluated the effect of BPA exposure on kidney function.<sup>55</sup> A reduction in urinary excretion of BPA and triclosan (a synthetic antibacterial agent found in many household products, including antimicrobial hand soaps) with declining GFR was identified in 2,573 adults without known kidney disease who were enrolled in NHANES 2003–2006.<sup>55</sup> Use of the CKD-EPI formula to estimate GFR demonstrated no association between BPA excretion and GFR (Table 5) [Au: Table 5 OK?].<sup>55</sup>

#### Blood pressure

A study of 239 adults (mean age 52 years), found that participants with urinary excretion of BPA >0.85 μg/l had an increased risk of hypertension and diabetes mellitus, compared to those with urinary excretion of BPA <0.85 μg/l.<sup>56</sup> A study of 560 non-institutionalized adults aged ≥60 years similarly showed that the odds ratio of having a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg was 1.27 for those in the fourth quartile versus the first quartile of urinary BPA excretion.<sup>57</sup> Similarly, an analysis of 1,380 participants in NHANES 2003–2004 showed that high urinary BPA levels were associated with development of hypertension, defined as blood pressure >140/90 mmHg.<sup>38</sup> The multivariate adjusted odds ratio for hypertension associated with the third tertile (BPA >4.0 ng/ml) was 1.50 versus the first tertile (BPA <1.5 ng/ml).<sup>38</sup> BPA exposure in a small cohort (*n* = 39) of obese children aged 3–8 years was associated with elevated diastolic blood pressure.<sup>58</sup> In a randomized crossover study of 60 Korean adults, drinking soy milk from a can versus a glass container led to a 4–5 mmHg rise in blood pressure and a marked increase in urinary BPA excretion, 2 h after consumption [Au:OK?] (Table 4).<sup>59</sup>

The effect of BPA on blood pressure has encouraged longitudinal studies to investigate cardiovascular

**Table 4** | Effects of environmental chemicals on blood pressure

Chemical class	Reference	Country (study)	Participants	Main findings
Phthalates	Trasande <i>et al.</i> (2013) <sup>31</sup>	USA (NHANES 2003–2008)	2,447 children	Log unit increase in DEHP exposure were associated with a 0.041 unit increase in BP z-score
BPA	Ahmadkhanliha <i>et al.</i> (2014) <sup>56</sup>	Iran	239 adults	Urinary BPA above the mean associated with increased risk of hypertension
	Bae <i>et al.</i> (2012) <sup>57</sup>	Korea	560 adults	Highest quartile BPA excretion associated with 1.27-fold increased risk of hypertension
Perfluoroalkyl acids (PFAAs)	Geiger <i>et al.</i> (2014) <sup>81</sup>	USA (NHANES 1999–2000 and 2003–2008)	1,665 children	No association between serum PFOA or PFOS levels and BP
Dioxins	Chang <i>et al.</i> (2010) <sup>96</sup>	Taiwan	1,490 adults	High dioxin levels associated with increases in BP
	Ha <i>et al.</i> (2009) <sup>95</sup>	USA (NHANES 1999–2002)	524 adults	High dioxin levels associated with increases BP in women
	Lee <i>et al.</i> (2007) <sup>98</sup>	USA	721 adults	High dioxin levels associated with increases in BP
	Nakamoto <i>et al.</i> (2013) <sup>99</sup>	Japan	2,264 adults	High dioxin levels associated with increases in BP
	Uemura <i>et al.</i> (2009) <sup>100</sup>	Japan	1,374 adults	High dioxin levels associated with an increases in BP
PCB	Goncharov <i>et al.</i> (2011) <sup>129</sup>	USA (NHANES 1999–2002)	394 adults	High occupational exposure to PCB associated with elevated BP
	Everett <i>et al.</i> (2008) <sup>130</sup>	USA (NHANES 1999–2002)	2,556 adults	Seven PCBs associated with an increased risk of hypertension (highest risk score = 2.4)
	Ha <i>et al.</i> (2009) <sup>95</sup>	Sweden	524 adults	High PCB exposure associated with an increased risk of incident hypertension
	Lind <i>et al.</i> (2014) <sup>132</sup>	Iceland	Elderly adults	High PCB levels associated with high BP
	Valera <i>et al.</i> (2013) <sup>135,136</sup>	Greenland	Adults	High PCB levels associated with fish consumption associated with increased BP levels

Abbreviations: BPA, bisphenol A; BP, blood pressure; DEHP, di-2-ethylhexylphthalate; NHANES, National Health and Nutrition Examination Survey; PCB, polychlorinated biphenyls; PFOA, perfluoro-octanoic acid; PFOS, perfluoro-octane sulfonic acid. [Au: Table OK? Please check refs carefully]

outcomes. The UK-based European Prospective Investigation of Cancer–Norfolk study, which included 758 individuals aged 40–74 years who were previously free of cardiovascular disease, found that participants with higher levels of BPA at entry had an increased risk of incident coronary artery disease during 10 years of follow-up compared to participants who had low BPA levels at entry. Specifically, each standard deviation (4.56 ng/ml) increment in urinary BPA excretion was associated with an odds ratio of 1.13 for coronary artery disease [Au:OK?].<sup>60</sup> Graded exposure to BPA among a subset of 745 participants in this cohort was associated with an increased likelihood of developing clinically detectable peripheral arterial disease.<sup>61</sup> Coronary risk, based on the Framingham Risk Score, did not correlate with serum BPA levels in 1,016 patients aged 70 years who were included in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study.<sup>35</sup> Moreover, other studies utilizing the NHANES database have failed to confirm associations between exposure to BPA and cardiovascular outcomes.<sup>62</sup> Investigators have, therefore, questioned the validity of cross-sectional analyses of NHANES to derive conclusions about the effects of short-lived environmental chemicals on chronic complex diseases.<sup>62,63</sup>

### Perfluoroalkyl acids [Au: spelling OK?]

#### Sources of contamination

Perfluoroalkyl acids (PFAAs) are synthetic organic fluorinated compounds in which all the hydrogens of the hydrocarbon backbone are substituted with fluorine. This chemical structure imparts high stability and thermal resistance (Table 2, Supplementary Figure 1d). Potential precursor compounds for PFAAs derive from two major technologies: electrochemical fluorination (a method for the preparation of fluorocarbon-based organofluorine compounds) and telomerization (a radical polymerization reaction). These processes are used in the production of various specialized surface protection agents, sealants and surfactants. PFAAs have wide utility in stain-resistant sprays for carpets and upholstery, fire-retarding foams, non-stick cooking surfaces and food packaging.<sup>64,65</sup> National biomonitoring surveys have revealed that >98% of the US population (from age 12 years to ≥60 years) have detectable levels of PFAAs in their blood.<sup>66</sup> Similar to BPA, levels of PFAA are greatest among males, individuals ≥40 years of age, and in those with a high BMI, as shown among the general population of Daegu, Korea.<sup>67</sup> In contrast to BPA exposure, serum PFAA levels are directly associated with socioeconomic status, such that those on high incomes

**Table 5** | Effects of environmental chemicals on eGFR

Chemical class	Reference	Country (study)	Participants	Main findings
BPA	You <i>et al.</i> (2011) <sup>55</sup>	USA (NHANES 2003–2006)	2,573 adults	Low BPA excretion associated with lowered eGFR
Perfluoroalkyl acids (PFAAs)	Shanker <i>et al.</i> (2011) <sup>78</sup>	USA (NHANES 1999–2000)	4,587 adults	Highest quartile of PFOA and PFOS associated with a 1.8-fold increased risk of CKD
	Watkins <i>et al.</i> (2013) <sup>79</sup>	USA	9,600 children	Interquartile rise in PFOA excretion associated with an 0.75 ml/min/1.73 m <sup>2</sup> decline in eGFR
	A. Kataria, <i>et al.</i> unpublished work	USA (NHANES 2003–2010)	1,961 children	Highest quartiles of PFOA and PFOS excretion associated with a 10–13 ml/min/1.73 m <sup>2</sup> decline in eGFR [Au:OK?]
Dioxins	Chang <i>et al.</i> (2013) <sup>94</sup>	Taiwan	1,531 adults	Highest quartile exposure associated with a 15–22 ml/min/1.73 m <sup>2</sup> reduction in eGFR
PAH	Stefanovic <i>et al.</i> (2006) <sup>118</sup>	NA	NA	Possible association of PAH exposure with Balkan endemic nephropathy
PCB	Baker <i>et al.</i> (1980) <sup>127</sup>	USA	148 adults	No association between PCB and eGFR

Abbreviations: BPA, bisphenol A; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; PAH, polycyclic aromatic hydrocarbons; PCB, polychlorinated biphenyls; PFOA, perfluoro-octanoic acid; PFOS, perfluoro-octane sulfonic acid. [Au: Table OK? Please check refs carefully.]

exhibit lower body burdens of PFAA.<sup>40</sup> Differences in food purchasing patterns by income might account for the variable association between socioeconomic status and exposure to environmental chemicals.

Perfluoro-octane sulfonic acid (PFOS) and perfluoro-octanoic acid (PFOA) are 8-carbon perfluoroalkyl chemicals that have been in widespread use for several decades. The utilization of PFOS was phased out of circulation in the USA in 2002 and long-chain PFAAs were [Au:OK?] to be phased out in the USA by 2015.<sup>68</sup> The effects of previous exposure to long-chain PFAAs remain relevant owing to their 7–15 year half-life. Short-chain PFAAs with short half-lives, such as perfluorohexanoic acid (PFHxA) and perfluorononanoic acid (PFNA), have also been in circulation in the environment and might also cause short-term and long-term health problems. Sustained increases in serum PFNA concentrations were detected among participants of NHANES 2003–2004 compared to the levels detected during NHANES 1999–2000.<sup>66</sup> Median serum levels of perfluorohexane sulfonic acid (PFHxS), the primary PFHxA metabolite, remained stable through NHANES 2009–2010 and 2007–2008.<sup>69</sup> A Swedish study of trends in blood serum concentrations of PFAA between 1996 and 2010 found [Au: “found” ok, since these data conflict with the stable levels found in NHANES OK?] a 4.3% increase in PFHxS per year, and an 11% increase per year in perfluoroalkylbutane sulfonate (PFBS)—a short half-life metabolite of a four-carbon PFAA and a substitute for PFOS that is increasingly found in food.<sup>70</sup> These data suggest that the potential adverse cardiorenal effects of PFAAs are likely to be an enduring health problem for several years to come.

### Metabolism

PFAAs have the potential for marked bioaccumulation in the brain, liver, lung, bone and kidney.<sup>71</sup> PFAAs are exceptionally stable to metabolic and environmental degradation, owing to the strength of their carbon–fluorine bond.<sup>72</sup> The persistence of PFAAs in human serum

over time probably reflects a combination of materials released from final products, materials used in the manufacturing process, and environmental and metabolic degradation of precursor compounds.

The persistence of PFAAs with long whole body half-life estimates in humans and animals is well known,<sup>73</sup> but their toxicokinetic profiles and underlying mechanisms for such persistence are not fully understood. Excretion of PFAAs primarily occurs via the kidney and is a slow and concentration-dependent process.<sup>74,75</sup> The carbon chain length of a given PFAA can influence its pharmacokinetic properties, with smaller molecules having a tendency to be eliminated more efficiently by the kidney than larger molecules.<sup>74</sup> Differences in PFAA levels between species and by sex might reflect differences in the expression of organic anion transporters and postulated renal tubular reabsorption.<sup>73</sup>

Low levels of PFAAs can persist in tissues for prolonged periods of time.<sup>76</sup> A study of 26 adults who had retired from employment in fluorochemical production and were free of other occupational PFAA exposures showed that the geometric serum elimination half-lives of the PFAAs were [Au:OK?] 4.8 years for PFOS, 7.3 years for perfluorohexane sulfate (PFHS) and 3.5 years for PFOA.<sup>77</sup> Despite the increasing number of studies on PFAAs, major gaps still exist in our understanding of the pharmacology and toxicity of these compounds, which are important for the assessment of PFAA risk [Au:OK?] (Table 1).

### Estimated GFR

The association between exposure to PFAAs and perturbed kidney function is not as strong as for some of the other organic contaminants covered in this Review. The existing literature does suggest, however, that PFAAs can have adverse renal effects and more research is needed in this area (Table 5).

A study of 4,587 adults included in NHANES 1999–2000 and 2003–2008 identified that those with PFOA or

**Table 6** | Effects of environmental chemicals on uric acid

Chemical class	Reference	Country (study)	Participants	Main findings
Perfluoroalkyl acids	Shankar <i>et al.</i> (2011) <sup>82</sup>	USA (NHANES 1999–2000, 2003–2008)	3,883 adults 1,772 children	Highest quartile of PFOA associated with a 1.97-fold increased risk of hyperuricaemia
	Geiger <i>et al.</i> (2013) <sup>83</sup>	USA (NHANES 1999–2000, 2003–2008)	1,961 children	Highest quartile of PFOA associated with 1.62-fold increased risk of hyperuricaemia
	A. Kataria, <i>et al.</i> unpublished work	USA (NHANES 2003–2010)	1,961 children	Highest quartiles of PFOA associated with a 0.19–12.5 µmol/l (0.21 mg/dl) increase in serum uric acid level [Au:OK?]
Dioxins	Lee <i>et al.</i> (2013) <sup>102</sup>	USA (NHANES 2003–2004)	1,331 adults	Adjusted odds ratio for hyperuricaemia 2.3–3.0 depending on compound
	Chang <i>et al.</i> (2013) <sup>94</sup>	Taiwan	1,531 adults	Men with dioxin levels lower than reference group levels had a 2.2-fold increased risk of hyperuricaemia
PCB	Imamura <i>et al.</i> (2009) <sup>137</sup>	Japan	477 adults	Direct correlation between serum PCB and uric acid concentrations

Abbreviations: NHANES, National Health and Nutrition Examination Survey; PCB, polychlorinated biphenyl; PFOA, perfluorooctanoic acid. [Au: Table OK? Please check refs carefully.]

PFOS levels in the fourth quartile (>5.9 ng/ml) had a 1.73-fold and 1.82-fold higher risk of CKD (defined as GFR <60 ml/min/1.73 m<sup>2</sup>), respectively, than those in the first quartile (<2.8 ng/ml).<sup>78</sup> Studies in children have verified a comparable adverse effect on kidney function. In a cohort of 9,600 children aged 1–18 years, an interquartile range increase in PFOA serum concentration was associated with a 0.75 ml/min/1.73 m<sup>2</sup> decrease in estimated GFR.<sup>79</sup> Cross-sectional analyses have found that measured PFOS, PFNA and PFHxS serum levels are associated with a decrease in GFR, but the predicted serum PFOA concentrations at the time of enrolment were not statistically associated with GFR. These data raise the possibility that cross-sectional associations between PFAA and GFR might be a consequence, rather than a cause, of reduced kidney function.<sup>79</sup> A longitudinal study of PFAA exposure among individuals living near a hazardous waste site failed to show an effect on GFR, based on residential address and distance from the waste site.<sup>79</sup> Finally, a study of 1,961 12–19-year-old adolescents included in NHANES 2003–2010 identified that those in the highest quartile for PFOA and PFOS excretion had a 6.6–9.5 ml/min/1.73 m<sup>2</sup> lower estimated GFR than those in the lowest quartile (A. Kataria *et al.*, unpublished work).

### Blood pressure

Pre-clinical data have linked PFAA exposure to vascular injury and hypertension.<sup>80</sup> An association between serum PFOA and PFOS concentrations and hypertension (systolic and/or diastolic blood pressure >95<sup>th</sup> percentile), however, was not identified in a cohort of 1,665 children from NHANES 1999–2000 and 2003–2008 (Table 4).<sup>81</sup>

### Uric acid concentration

Serum levels of PFOA and PFOS are positively associated with hyperuricaemia in adults (Table 6).<sup>82</sup> Adults included in the NHANES 1999–2000 and 2003–2008 who were in the highest quartile for PFOA and PFOS serum levels had a multivariate-adjusted odds ratio for

hyperuricaemia (uric acid ≥ 357 µmol/l [Au: SI units needed. Conversion correct?] [≥6 mg/dl]) of 1.97.<sup>82</sup> The same association was observed in 1,772 children in NHANES 1999–2000 and 2003–2008, with a multivariate-adjusted odds ratio for hyperuricaemia of 1.62.<sup>83</sup> In the NHANES 2003–2010 study of 1,961 participants aged 12–19 years, those in the highest PFAA quartile had a statistically significant 12 µmol/l [Au: SI units correct?] (0.20 mg/dl) increase in serum uric acid concentration compared to those in the lowest quartile (A. Kataria *et al.*, unpublished work).

### Dioxins and furans

#### Sources of contamination

Dioxins, such as polychlorinated dibenzo-p-dioxins (PCDD), and furans, such as polychlorinated dibenzo-p-furans (PCDFs), are synthetic halogenated aromatic hydrocarbons (Table 2, [Supplementary Figure 1e](#)). PCDDs and PCDFs are ubiquitous environmental contaminants that are formed as waste products from the manufacture of pesticides, bleaching of wood pulp and waste incineration.<sup>84</sup> PCDDs and PCDFs were banned worldwide under the Stockholm Convention in 2001, but still remain in items that were produced before the ban, as well as in the environment and in humans owing to their resistance to degradation by biological processes [Au:OK?].<sup>84</sup> The half-lives of PCDDs and PCDFs range from 2–15 years.<sup>85</sup> The majority of human exposure to dioxins occurs as a result of eating products containing meat, milk, eggs and fish due to accumulation of dioxins in animal fat.<sup>86</sup>

The effects of dioxins are chiefly mediated by the aryl hydrocarbon receptor (AHR)—a ligand-activated transcription factor that regulates gene expression through binding the dioxin response element in DNA sequences together with AHR nuclear translocator (ARNT).<sup>87</sup> The WHO developed the Toxic Equivalency Factor scale for this diverse group of chemicals based on the potency of their [Au:OK?] agonistic effects on the AHR. The

Toxic Equivalency Factor expresses the relative AHR mediated potency of PCDDs and PCDFs compared to 2,3,7,8 tetrachloro-dibenzo-p-dioxin (TCDD), the most potent and well-studied molecule in this class. Induction of PCDD-mediated organ damage and cardiotoxicity correlates with the activation of the AHR.<sup>87,88</sup> [Au: refs OK?] Although these effects were first characterized for dioxins and polychlorinated biphenyls (PCBs), cardiotoxicity has also been demonstrated for polybrominated diphenyl ether (PBDE) through AHR mechanisms in developing zebrafish embryos.<sup>89,90</sup>

### Metabolism

PCDDs and PCDFs are readily absorbed through the digestive tract, which is enhanced through the ingestion of fatty foods. The lipophilic characteristics of PCDDs and PCDFs allows for slow excretion in bile and urine.<sup>91</sup> These compounds become toxic through activity of the CYP1A1 enzyme, a well-characterized target of AHR/ARNT and is often used as a marker of AHR activation.<sup>92</sup> The intra-renal mechanisms involved in the handling of PCDDs and PCDFs have not been fully established.

### Albuminuria

No studies have provided information regarding the effects of PCDDs and PCDFs on albuminuria among healthy individuals (Table 3). A study of 2,588 adults with diabetes mellitus enrolled in NHANES 1999–2004 found that serum levels of three different PCDFs were associated with diabetic nephropathy, as defined by the presence of microalbuminuria (albumin-to-creatinine ratio >30 mg/g) or macroalbuminuria. When levels of at least four of the 23 chemicals analyzed in this study were elevated in the serum, the odds ratio was 7.00 (95% CI, 1.80–27.20) for diabetic nephropathy and 2.13 (95% CI, 0.95–4.78 [Au: 95% CI OK?]) for diabetes mellitus without nephropathy (Table 3).<sup>93</sup>

### Estimated GFR

Moderate-to-high level exposure to dioxins is associated with decreased kidney function (Table 5). A cross-sectional study of 1,531 healthy adults living in close proximity to a pentachlorophenyl factory that was no longer in use found a strong monotonic inverse association between PCDD exposure and estimated GFR.<sup>94</sup> Compared to the lowest quartile, the highest quartile of toxin exposure resulted in a 14.8 ml/min/1.73 m<sup>2</sup> and a 21.5 ml/min/1.73 m<sup>2</sup> reduction in estimated GFR in men and women, respectively.<sup>93</sup> The association between low levels of dioxin exposure on kidney function in otherwise healthy adults or children without occupational exposure is unknown.<sup>95</sup>

### Blood pressure

A study of 1,490 adults without diabetes mellitus living near a dioxin-contaminated area showed that increasing serum dioxin levels are correlated with elevated diastolic blood pressure.<sup>96</sup> Furthermore, the prevalence of hypertension was correlated with serum PCDD and PCDF levels in adults with suspected dioxin exposure due to

proximity to an uncontrolled and abandoned hazardous waste site.<sup>97</sup> A modest association between dioxin exposure and hypertension was also noted in a US study of 721 adults without diabetes mellitus, living far from evident sources of contamination.<sup>98</sup> Follow-up studies in adult populations residing in Japan have confirmed this finding (Table 4).<sup>99,100</sup>

### Uric acid concentration

The study of adults living near a deserted pentachlorophenyl factory previously discussed also found that healthy men, but not women, in the highest quartile for toxin exposure had a 35 μmol/l [Au: SI units correct?] (0.59 mg/dl) increase in serum uric acid concentration. Furthermore, men with serum dioxin concentrations above the reference group had a 2.20-fold higher risk of hyperuricaemia.<sup>93</sup> A similar observation was made among 94 workers at the Nose Bika Center incinerator in Osaka, Japan, which was heavily contaminated with PCDD.<sup>101</sup> Adults with only background exposure to dioxins are also at heightened risk of hyperuricaemia. The adjusted odds ratio for hyperuricaemia in 1,331 adults from NHANES 2003–2004, ranged from 2.3 to 3.0, depending upon the specific dioxin compound exposure (Table 6).<sup>102</sup>

## Polycyclic aromatic hydrocarbons

### Sources of contamination

Polycyclic aromatic hydrocarbons (PAHs) are a group of >100 different chemicals composed purely of carbon and hydrogen atoms that are arranged in multiple aromatic rings (Table 2, Supplementary Figure 1f). The majority of PAHs are formed during the incomplete burning of coal, oil, and gas, and from other organic substances, such as tobacco and meat grilled over charcoal.<sup>103</sup> Although exposure to these compounds predominantly occurs in the work environment, such as in chemical and coke (fuel) factories, the ubiquity of motorized vehicles with internal combustion engines and increased industrial activity has resulted in substantial environmental exposure, especially in urban areas.<sup>104</sup> Incomplete burning of carbon-based fuels produces oxidized PAHs that can be highly mutagenic and carcinogenic.<sup>105</sup> Benzo[a]pyrene is among the most well studied of the PAHs and is a prime carcinogen in tobacco smoke.<sup>106</sup> PAH has been detected in the serum of pregnant non-smokers that reside in the New York City area, and the level of exposure correlated with time spent outdoors, residential heating, and indoor burning of incense.<sup>107</sup> Urinary excretion of PAH among children living in New York declined in response to legislative regulations targeting air pollution derived from traffic.<sup>108</sup>

### Metabolism

PAHs are activated by CYP1A1 and polymorphisms in the gene encoding this enzyme are associated with alterations in PAH metabolism.<sup>109</sup> Glutathione S-transferases are involved in the conjugation of PAHs with glutathione, and genetic variations in these proteins also contribute to the observed differences in PAH metabolism.<sup>110</sup> Benzo[a]pyrene-diol epoxide forms adducts with albumin<sup>111</sup>

and DNA,<sup>112</sup> which have been identified in parallel with PAH exposure. The formation of these chemical adducts might provide a more accurate assessment of PAH exposure and potential nephrotoxicity.

### Estimated GFR

High PAH exposure was associated with a 3.60-fold odds ratio of elevated levels of C-reactive protein in a study of 999 NHANES 2003–2004 participants.<sup>113</sup> In view of the effect of inflammation in the development of atherosclerosis,<sup>114</sup> these results are consistent with a role for PAH in cardiovascular disease. Very few studies, however, have addressed the effect of PAH exposure on either glomerular (estimated GFR and albuminuria) or tubular markers of kidney injury (Table 5).

Balkan endemic nephropathy is a chronic tubulointerstitial disease that is associated with an enhanced risk of urothelial cancer and has been attributed to PAH exposure.<sup>115</sup> Drinking water contaminated with PAHs that have leached from pliocene lignite coal and coke factories into the water supply, has been implicated in renal parenchymal disease and urological malignancies.<sup>116–118</sup> Additional epidemiological studies and pre-clinical investigations are needed to confirm the role of PAH in Balkan endemic nephropathy.

### Blood pressure

A single, small-scale study of 88 adult non-smokers residing in Belgium found that the serum levels of select PAH compounds were linearly associated with systolic and pulse pressure.<sup>119</sup> Further studies with larger diverse cohorts are now needed to verify an association between PAH exposure and risk of hypertension (Table 4).

## Polychlorinated biphenyls

### Sources of contamination

Polychlorinated biphenyls (PCBs) are molecules composed of two benzene rings with varying degrees of saturation with chlorine moieties on the ringed backbone. This variation can result in 209 unique related chemicals (Table 2, [Supplementary Figure 1g](#)). PCBs were widely used in capacitors and coolants in electrical equipment, until the recognition of their persistence in the environment and their bioaccumulation and toxicity in animals and humans.<sup>120</sup> PCB production was subsequently banned in the USA in 1979 and by the Stockholm Convention in 2001, but PCBs remain ubiquitous in human populations as a result of their persistence in the environment, incomplete disposal, and ongoing use of PCB-containing products. The Hudson River is contaminated with PCBs due to intentional disposal of PCB-containing products in the 1970s. This river is, therefore, the largest US Environmental Protection Agency Superfund site—covered by a US federal law that is designed to clean up sites contaminated with hazardous substances [Au:OK?]. Standing advisories consequently caution against fish consumption from this stretch of water. Serum levels of PCBs in those residing in the USA without occupational exposure to PCBs range from 0.6–4.0 ng/g in adolescents (12–19 years old) and 8.9–60.8 ng/g in the elderly

(>60 years old).<sup>121</sup> PCB serum levels in those with high consumption of fish from contaminated waters are several times higher than in those without PCB exposure, and are comparable to workers in PCB plants.<sup>122,123</sup>

### Metabolism

PCB metabolism primarily occurs in the liver, where it must first be hydroxylated to increase the polarity of the molecule, before it is excreted in the bile.<sup>124</sup> The rate of metabolism varies depending on the degree of chlorination of the congener.<sup>125</sup> Metabolism of PCBs can also produce toxicologically active agents, such as arene oxides that can be enzymatically detoxified and excreted, or can form toxic adducts.<sup>126</sup>

### Albuminuria

No data have been reported on the effect of PCBs on proteinuria in individuals with no known kidney disease. In a study of 2,588 patients with diabetes mellitus enrolled in NHANES 1999–2004, higher levels of exposure to PCB congeners were associated with an increased risk of diabetic nephropathy (Table 3).<sup>93</sup>

### Estimated GFR

An event that occurred at an electrical capacitor manufacturing plant in Bloomington, USA, resulted in PCB discharge into the municipal sewage system. PCB compounds were detected in the sewage sludge that was used as fertilizer.<sup>127</sup> In a limited follow-up study, serum PCB levels were elevated only among sewage workers exposed to PCB. No association was found between PCB serum concentration and kidney function,<sup>127</sup> but no large-scale investigations of the effect of PCBs on kidney function or albuminuria have been performed (Table 5).

### Blood pressure

Associations between high serum PCB levels and elevated systolic and diastolic blood pressure have been identified in residents near an agrochemical plant that manufactured PCB (Table 4).<sup>128,129</sup> The association between PCB serum levels and blood pressure has also been confirmed among individuals with no occupational exposure. In a study of 2,556 adults in NHANES 1999–2002 who were assessed for serum levels of 11 different PCBs, the risk of hypertension was increased for seven of the compounds, with the highest odds ratio being 2.45.<sup>130</sup> Elevated levels of one or more PCB in the serum were identified in ~25% of the population, with an odds ratio of 1.84 for elevated blood pressure.<sup>130</sup> A similar study of 524 adults from the same NHANES cohort demonstrated that the extent of PCB exposure was markedly associated with the incidence of new-onset hypertension among men.<sup>95</sup> The association between PCBs and hypertension has been verified in an independent evaluation of the NHANES 1999–2004 participants using clustering analyses.<sup>131</sup> The PIVUS study also verified the association between PCB serum levels and blood pressure in a cohort of Swedish individuals aged 70 years.<sup>132</sup> A follow-up investigation of this cohort noted an association between PCB exposure and disturbances in left ventricular systolic and diastolic function.<sup>133</sup>

Furthermore, a study of US adults in NHANES 1999–2008 aged >20 years found that although exposure to lead was most predictive of diastolic and mean blood pressure, serum levels of PCB were most predictive of systolic blood pressure.<sup>134</sup> An association between high PCB serum levels as a consequence of fish consumption and an increased risk of hypertension has been reported in a study of adult Inuits residing in Greenland and Canada.<sup>135,136</sup>

#### Uric acid concentration

An industrial incident that occurred in Japan in 1968 resulted in large-scale exposure to PCBs. Serum levels of PCBs were directly correlated with uric acid concentration, with higher PCB concentration being associated with increased risk of hyperuricaemia (Table 6).<sup>137</sup>

#### Impact on the developing world

This Review has focused primarily on the effect of environmental chemicals on the residents of affluent, developed countries. Nonetheless, the molecules discussed might also contribute to renal disease in developing regions of the world. Over the past 10 years, there has been growing recognition of the major health impact of an epidemic of CKD in Central America, known as Mesoamerican nephropathy. This condition occurs primarily in hot, tropical, agricultural communities located along the Pacific coast.<sup>138,139</sup> A similar endemic outbreak of CKD has been documented among farmers living in the north central province of Sri Lanka.<sup>140</sup> Conflicting reports have been made regarding the potential role of cadmium, arsenic and pesticide exposure on the occurrence of CKD in farmers in Sri Lanka.<sup>141,142</sup> In both locales, the affected patients are predominantly men who present with minimal symptoms, including marginally elevated blood pressure, low-grade proteinuria, non-inflammatory urinalysis and azotaemia (abnormally high levels of nitrogen-containing compounds in the blood).<sup>138,139</sup> Several hypotheses have been proposed to explain this multifactorial condition, including recurrent dehydration and activation of polyol-fructokinase and vasopressin pathways.<sup>143</sup> No conclusive evidence has linked Mesoamerican nephropathy to pesticides, herbal toxins, heavy metals, or certain medications, such as NSAIDs, but the role of environmental chemicals, including pesticides, has not been systemically addressed. Given the findings in developed countries where exposure is endemic, the environmental chemicals discussed in this Review might be a contributing factor to this emerging epidemic of CKD. This issue is especially pressing in developing countries where regulatory systems to control agrochemical use of hazardous compounds are not routinely implemented and where compliance with existing rules and standards to protect the health of the work force are not aggressively enforced.<sup>144</sup>

#### Limitations of published reports

##### Cross-sectional data

Much of the literature on the cardiorenal effects of environmental chemicals is based on cross-sectional data that associate exposure to chemicals with the development of

the outcome of interest. Most studies rely on single measurements without serial sample collection. Although not a major concern for persistent organic compounds that exhibit stable serum levels over extended periods of time, such as PFAA, single measurements become problematic when considering short-lived molecules, such as BPA and phthalates. Short-term variations in exposure can dramatically influence urinary excretion of these described compounds and can lead to a misclassification of the degree of cumulative long-term exposure.<sup>145</sup>

#### Acute versus chronic exposure

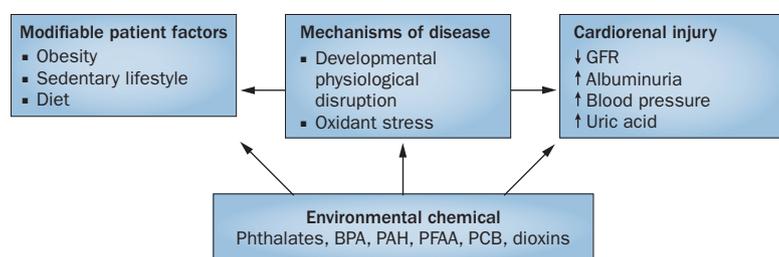
Exposure to environmental chemicals can be acute or chronic in nature. In this Review, we have reported data accumulated following industrial exposure that is presumed to be chronic or after major accidents that presumably reflects acute high-level exposure. The majority of published studies have, however, been cross-sectional in design and cannot discriminate between short-term and long-term exposures to organic contaminants. Prospective cohort studies using serial biosample collection methods are needed to address this important issue. Furthermore, no studies have detailed the consequences of combined exposure to different classes of chemicals, which requires prospective sample collection with simultaneous measurements of numerous analytes.

#### Biomarkers of renal injury

No standardized protocol has been devised to assess the effects of environmental chemicals on renal parameters, including albuminuria, estimated GFR, blood pressure, and serum uric acid concentration. Consequently, the full scope of these effects have not been fully studied for all classes of compounds (Tables 3–6). Specific markers of glomerular injury (for example, urinary excretion of podocytes) and tubular injury (for example, levels of NGAL, KIM-1 and IL-18) could also be studied, but these biomarkers do not identify the cause of renal damage and are not specific for environmental chemical exposure.<sup>146,147</sup> Abnormal serum concentrations and urinary excretion of these biomarkers might, however, precede routine clinical tests, such as measurement of serum creatinine concentration, and be sensitive for the detection of acute kidney injury and CKD.<sup>148,149</sup> Furthermore, these biomarkers could enable precise localization of the site of renal damage as a consequence of environmental toxins. To date, such measurements have not been routinely performed because of the reliance on cross-sectional observational cohort studies. Future work in this area should incorporate these novel biomarkers to clarify the full effect of organic contaminants on kidney injury and dysfunction.

#### Reverse causation

The kidney excretes many of the organic chemicals that have been discussed in this Review. By the concept of reverse causation, serum levels of organic chemicals might be elevated as a consequence of a reduction in GFR that is secondary to other factors. Moreover, a primary decline in GFR should decrease the urinary excretion of



**Figure 1** | The integrated effects of environmental chemicals on cardiorenal function. The schematic summarizes the potential effects of environmental chemicals on renal and/or vascular function and integrates these effects with the known adverse consequences of obesity and the metabolic syndrome. Abbreviations: BPA, bisphenol A; GFR, glomerular filtration rate; PAH, polycyclic aromatic hydrocarbons; PCB, polychlorinated biphenyl; PFAA, perfluoroalkyl acid.

[Au: spelling OK? Figure OK?]

the organic contaminants. For this reason, some investigators devalue the data derived from NHANES and dismiss a causative effect of environmental chemicals on kidney function.<sup>150</sup> Various statistical approaches that incorporate multivariate analyses have been used to address this important point.<sup>151</sup> Prospective longitudinal cohort studies are the next step to corroborate findings from cross-sectional studies, which are supported by clinical data. Such analyses will require serial sampling for environmental chemicals and measurements of kidney function, and will enable precise delineation of the association between environmental toxins and renal function. In this way, the effect of the environmental chemicals as modifiable risk factors for albuminuria, hypertension, hyperuricaemia and CKD can be determined.

### Potential mechanisms of injury

#### Oxidative stress

Prospective or interventional studies have not been performed to confirm the association between environmental chemicals and potential cardiorenal injury. A biological plausibility is required first to link these two phenomena. Oxidative stress is a major pathophysiologic mechanism that underlies cardiometabolic risk and renal injury and can be induced by exposure to environmental chemicals.<sup>152</sup> Peroxidation of lipids induces cellular damage and inflammation, and oxidative stress perturbs the endothelial relaxant nitric oxide, thus promoting vasoconstriction, platelet adhesion and release of inflammatory cytokines.<sup>153,154</sup> Production of free radicals from oxygen is increased in the glomerular podocyte in animal models of CKD.<sup>155</sup> Excessive oxidative stress alters the podocyte cytoskeleton and can lead to albuminuria,<sup>156</sup> podocyte loss and tubular injury, which are prominent pathologies in the progression of primary glomerulopathies.<sup>157</sup> Tubulointerstitial fibrosis, which develops in patients with all forms of CKD secondary to oxidative stress, is a better predictor of prognosis and progressive decline of renal function than are glomerular abnormalities.<sup>158</sup>

Environmental chemicals such as BPA, phthalates and biphenyls have been identified as possible contributors to cardiometabolic risk, independent of an increased risk of obesity.<sup>159</sup> Animal studies indicate that BPA induces

oxidative stress<sup>160–162</sup> and inhibits the release of the adiponectin from human adipose tissue.<sup>163</sup> Laboratory studies have found that metabolites of phthalates can enhance the release of IL-6<sup>164</sup> and elevate the expression of integrin in neutrophils.<sup>165</sup> Biomarkers of phthalate exposure have also been associated with increases in C-reactive protein,  $\gamma$ -glutamyltransferase,<sup>166</sup> and markers of oxidative stress, such as malondialdehyde and 8-hydroxydeoxyguanosine.<sup>31,167</sup> Cell culture studies have shown that exposure of microvascular endothelial cells to PFAA increases the production of reactive oxidative species and induces endothelial permeability,<sup>168</sup> which has a critical function in ischaemic renal injury.<sup>169</sup> Exposure of animals to PBDE can induce oxidative stress-mediated hepatotoxicity and nephrotoxicity.<sup>170</sup> PAHs are potent oxidant stressors<sup>171</sup> that can enhance lipid oxidation and cause subsequent inflammation. PAHs also reduce production of nitric oxide,<sup>172</sup> and promote vasoconstriction, platelet adhesion, and release of inflammatory cytokines by human coronary artery endothelial cells.<sup>173,174</sup>

As illustrated above, oxidative stress might represent a common pathway that mediates renal injury associated with exposure to environmental chemicals. This mechanism has biological plausibility and justifies further investigation when examining the adverse effects of these chemicals. The possibility remains that other functional disturbances contribute to the adverse cardiorenal effects elicited by the described compounds, including effects on modifiable patient-associated factors, such as obesity (Figure 1).

#### Intrauterine environment

The ‘thrifty phenotype’ hypothesis<sup>175,176</sup> suggests that early life adaptations to poor *in utero* nutritional conditions can produce a profile of maladaptation *ex utero*, where the ability to acquire energy results in increased adiposity.<sup>153,154</sup> This effect can present in childhood and contributes to an elevated risk of cardiometabolic and renal disorders in later life.<sup>175–178</sup> An association between phthalates and low birth weight,<sup>179</sup> as well as data associating increases in maternal BPA levels with reductions in estimated fetal weight,<sup>180</sup> is consistent with the hypothesis that prenatal exposure to environmental oxidant stressors could contribute to cardiorenal risks through intrauterine maladaptation.

The influence of organic contaminants during human development has been studied for several classes of compounds. Prenatal exposure to BPA might be associated with an increased risk of respiratory disease during childhood.<sup>181</sup> Maternal exposure to phthalates during the prenatal period<sup>182</sup> (based on urinary excretion) and PAH<sup>183</sup> (based on maternal and umbilical cord serum levels), have been associated with altered mental, psychomotor, and behavioural function at 3 years of age. A review of eight epidemiologic studies, (including six non-occupational and two occupational exposure studies) found no consistent association between maternal blood and/or umbilical cord concentrations of PFOS and PFOA and birth weight or other anthropometric measurements, such as head circumference and developmental milestones at 6 and

18 months of age.<sup>184</sup> In contrast to studies that have documented adverse pulmonary and neurocognitive effects of prenatal exposure to organic contaminants, no studies have investigated the effects of exposure to organic contaminants during the prenatal period or during infancy on renal structure or function.

### Conclusions

The effects of environmental chemicals on GFR described in this Review are unlikely to cause clinically overt adverse effects. Prolonged cumulative lifetime exposure to an array of compounds, however, in conjunction with age-associated decline in kidney function and other comorbid conditions, might accelerate the rate of deterioration in kidney function and progression to CKD. The effects on albuminuria are also modest and might reflect generalized endothelial dysfunction rather than alterations in the glomerular filtration barrier. Regardless of the underlying mechanism, changes in low-grade albuminuria that are attributed to environmental chemicals are associated with an increased risk of cardiovascular events.<sup>185</sup> The modest changes noted in blood pressure could be associated with an increased incidence of cardiovascular events, if achieved at the population level. Worsening hyperuricaemia after exposure to toxins might cause hypertension, aggravate endothelial dysfunction, and elicit effects consistent with metabolic syndrome.<sup>186</sup> The co-expression of such alterations might increase the risk of CKD over an individual's lifespan.

Reducing exposure to environmental chemicals can be achieved by comprehensive modification of the regulations governing the use of these compounds, and would produce large economic benefits as compared to the costs incurred in preventing cardiorenal disease [Au:OK?].<sup>187,188</sup> BPA-associated cardiovascular diseases are estimated to cost US\$1.5 billion annually in the United States.<sup>189</sup> Importantly, the adverse cardiorenal effects of environmental chemicals is likely to persist into the future as industry shifts its use from

regulated compounds to alternative replacements, such as bisphenol S, di-isodecyl, and di-isononylphthalate.

The majority of data presented in this Review reflect cross-sectional assessments of environmental toxins. The effect of long-term exposure to these toxins, either singly or in combination and at different stages of development [Au:OK?], on longitudinal changes in kidney function have not been determined. Longitudinal studies are now needed to guide regulatory strategies for heightened control or complete elimination of these molecules to reduce or prevent human exposure and lower the risk of target organ damage including the kidney. We recommend that industry, regulatory agencies, medical societies and the scientific community prospectively implement protocols to determine the safety of organic contaminants before their introduction into widespread use. Furthermore, ongoing surveillance is required to detect the emergence of unanticipated adverse effects.

### Review criteria

The PubMed database was searched for English-language and full-text articles published from 1980 to May 2014 using the following search terms: "bisphenol A OR BPA", "polychlorinated dibenzo-p-dioxins OR polychlorodibenzo-4-dioxin OR PCDD", "polychlorinated biphenyls[MeSH Terms] OR polychlorinated biphenyl\* OR PCB", "perfluoroalkyl OR perfluoroalkyls OR perfluoroalkyl acid\* OR perfluoroalkyl compound\* OR perfluoroalkyl substance\* OR PFAA[tiab] OR PFAAs[tiab]", "phthalates OR phthalate OR phthalic acids[tiab] OR Phthalic Acids[Mesh:noexp] OR Diethylhexyl Phthalate[Mesh] OR dehp OR Dibutyl Phthalate[Mesh]", "polycyclic hydrocarbons, aromatic[MH:noexp] OR polycyclic aromatic hydrocarbon OR polycyclic aromatic hydrocarbons", "halogenated diphenyl ethers OR halogenated diphenyl ethers OR polybrominated diphenyl ethers OR polybrominated diphenyl ether OR PBDE OR PBDES" in conjunction with either "renal function OR Kidney Function OR Glomerular Filtration rate OR eGFR OR uric acid OR blood pressure OR hypertension". [Au:OK?]

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#### Acknowledgements

The preparation of this review was supported in part by an NIH-NIDDK grant (number DK100307) awarded to L.T. and H.T., and an NIH-NIEHS grant (number ES022972) awarded to L.T. The authors would like to thank Judy Chen, Bryn Mawr College, Bryn Mawr, PA, USA for her assistance in finalizing the literature review that was conducted for preparation of this manuscript.

#### Author contributions

All authors researched data, provided substantial contribution to discussion of content and contributed equally to writing the article and to review and/or editing of the manuscript before submission.

**Supplementary information** is linked to the online version of the paper at [www.nature.com/nrnephrol](http://www.nature.com/nrnephrol).

**Author biographies**

Anglina Kataria graduated from State University of New York–Stony Brook. She is completing her medical school training at New York University School of Medicine and will start a residency in paediatrics in July 2015.

Leonardo Trasande is an internationally renowned leader in children's environmental health. He is the principal investigator of a study of the effects of prenatal and childhood phthalate and bisphenol exposure on obesity and cardiovascular risk in Generation R, funded by an NIH Research Project Grant (R01; grant number ES022972). He has been awarded another NIH Research Project Grant (R01; grant number DK100307) to study the effect of dietary contaminants in children with chronic kidney disease. He is also the principal investigator of an NIH Research Project Cooperative Agreement (U01; grant number OH010394) to compare the cardio-metabolic and respiratory profiles of children exposed to the World Trade Center disaster to a matched comparison group. Finally, he is the recipient of a Fogarty–National Institute of Environmental Health Sciences GeoHealth Hub grant (grant number TW005962) to study the impact of air pollution on children's health in Northwest China. He serves on the American Academy of Pediatrics' Executive Committee of the Council for Environmental Health, and the Science and Technical Advisory Committee for the World Trade Center Health Program.

Howard Trachtman is an internationally recognized leader in paediatric nephrology with a primary focus on glomerular diseases. He was a joint principal investigator in the multicentre FSGS Clinical Trial and the principal investigator for the Novel Therapies in Resistant FSGS Clinical Trial. He is a co-investigator on the Nephrotic Syndrome Study Network (NEPTUNE) Cohort study and is leading an effort to establish a new cohort of paediatric patients with new-onset nephrotic syndrome prior to renal biopsy. He is co-investigator for the CureGN Cohort study which aims to recruit a cohort of 2,400 paediatric and adult patients with prevalent primary glomerular disease (minimal change disease, FSGS, membranous nephropathy, and IgA nephropathy). His collaboration with Dr Trasande has culminated in a NIH Research Project Grant R01 award (grant number DK100307) to study the impact of environmental exposures in paediatric patients with glomerular and non-glomerular causes of CKD.

**Subject ontology terms**

[Health sciences / Nephrology / Kidney diseases / Toxin-induced nephropathy \[URI /692/4022/1585/2763\]](#)

[Health sciences / Diseases / Kidney diseases / Chronic kidney disease \[URI /692/699/1585/104\]](#)

[Earth and environmental sciences / Ecology / Environmental economics \[URI /704/158/843\]](#)

[Health sciences / Cardiology / Cardiovascular biology / Cardiovascular diseases / Hypertension \[URI /692/4019/592/75/243\]](#)

[Physical sciences / Nanoscience and technology / Nanotoxicology / Ecotoxicology \[URI /639/925/928/833\]](#)

**Competing interests**

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**Supplementary Information**

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## 000 The impact effects of environmental chemicals on renal function

*Anglina Kataria, Leonardo Trasande and Howard Trachtman*

The identification of modifiable risk factors that are associated with declining renal function is required to stem the increasing incidence of chronic kidney disease worldwide. In this Review, Howard Trachtman and colleagues discuss the impact of environmental chemicals on cardiorenal function. They highlight the ubiquity of exposure to environmental chemicals in the general public, the main sources of contamination, and the predominant adverse effects that might affect renal function.