Kidney Medicine

Organic Pollutant Exposure and CKD: A Chronic Renal Insufficiency Cohort Pilot Study

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Rationale & Objective: This study aimed to assess the effect of exposure to organic pollutants in adults with chronic kidney disease (CKD).

Study Design: This was a cross-sectional and longitudinal analysis.

Setting and Participants: Forty adults enrolled in the Chronic Renal Insufficiency Cohort (CRIC).

Exposures: Exposure at baseline and longitudinally to various organic chemical pollutants.

Outcomes: The outcomes were as follows: death; composite of congestive heart failure, myocardial infarction, and stroke; event-free survival from kidney failure or ≥50% decline in estimated glomerular filtration rate (eGFR); and longitudinal trajectory of eGFR.

Analytical Approach: We used high-performance liquid chromatography with tandem mass spectrometry to measure urinary concentrations of bisphenols, phthalates, organophosphate pesticides, polycyclic aromatic hydrocarbons, melamine, and cyanuric acid at years 1, 3, and 5 after enrollment in the CRIC. Univariate and multivariable logistic regression were used to examine the association of individual compounds and classes of pollutants with the outcomes. The Cox proportional hazards model and Kaplan-Meier method were used to calculate hazard ratios and 95% CIs for each class of pollutants.

Results: Median baseline eGFR and urinary protein-to-creatinine ratio were 33 mL/min/1.73 m^2 and 0.58 mg/g, respectively. Of 52 compounds assayed, 30 were detectable in ≥50% of participants. Urinary chemical concentrations were comparable in patients with CKD and healthy individuals from contemporaneous National Health and Nutrition Examination Survey cohorts. Phthalates were the only class with a trend toward higher exposure in patients with CKD. There was an inverse relationship between exposure and the eGFR slopes for bisphenol F, mono-(3-carboxypropyl) phthalate, mono-benzyl phthalate, mono-[2-(carboxymethyl)hexyl] phthalate, and melamine. There were no associations between organic pollutant exposure and cardiovascular outcomes.

Limitations: Small sample size, evaluation of single rather than combined exposures.

Conclusions: Simultaneous measurement of multiple organic pollutants in adults with CKD is feasible. Exposure levels are comparable with healthy individuals. Select contaminants, especially in the phthalate class, may be associated with more rapid deterioration in kidney function.

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Human exposure to toxic chemicals in the environment is ubiquitous.[1,2] In addition, a wide range of organic chemicals are released into the environment from industrial activities and the use of plastics in personal care, lifestyle activities, and food preparation.[3] Exposure to these organic pollutants has been associated with adverse effects on kidney structure and function, including reduced glomerular filtration rate (GFR) and tubular abnormalities.[3] These compounds, including bisphenols (BPs), phthalates, organophosphate pesticides, polycyclic aromatic hydrocarbons (PAHs), melamine, and cyanuric acid (CYA), are incorporated into household and workplace products and medical devices.

We have examined the effect of exposure to several organic pollutants in the Chronic Kidney Disease in Children (CKiD) study, a multicenter, long-term observational cohort of pediatric patients with chronic kidney disease (CKD). Overall, although there was evidence of a relationship between the level of chemical exposure and intrarenal oxidant stress and tubular injury, the effect on kidney function based on blood pressure, estimated glomerular filtration rate (eGFR), and proteinuria was minimal over the course of follow-up.[4–13]

It is unknown whether the effect of exposure to organic pollutants differs in adults versus children with CKD. To address this knowledge gap, we conducted a pilot study in adults with the following objectives: determine the feasibility of evaluating a comprehensive panel of organic pollutants in urine samples collected from adults with CKD who were enrolled in a longitudinal cohort study; and obtain preliminary data on the association between exposure to organic pollutants and the trajectory of kidney function over time as well as the incidence of cardiovascular (CV) complications. We measured levels of 6 organophosphate pesticide metabolites (dialkylphosphates [DAPs]), 8 BPs, 28 phthalate metabolites (PhMs), 10 PAH metabolites, melamine, and CYA in urine from 40 patients with CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC). Associations between chemical exposures and baseline kidney function, CV markers, markers of bone

PLAIN-LANGUAGE SUMMARY

The effect of exposure to organic pollutants has not been studied in adults with chronic kidney disease. (CKD). To fill this gap, we measured the exposure to a wide range of chemicals that are found in plastics, personal care products, and food preparation. Overall, the exposure was similar to that noted in the healthy population living in the United States. Only select compounds, mainly phthalates, demonstrated a trend with a more rapid decline in kidney function. These findings provide a useful reference for future studies that aim to evaluate organic pollutant exposure in patients with CKD. This is significant because these exposures represent a modifiable risk factor for disease progression through alterations in diet or lifestyle.

and mineral metabolism, CKD progression, and CV outcomes were analyzed.

METHODS

Patients and Data Sources

Participants were chosen from the CRIC, an observational study that enrolled adults aged 21-74 years with a range of kidney disease severity. The original CRIC project was approved by the IRB at each participating center with informed consent obtained from all participants. Informed consent for the current study was waived because the project involved use of de-identified clinical and laboratory data and biosamples.

CRIC participants underwent extensive clinical evaluation every 6 months starting from enrollment.[14] Based on the availability of samples for measurement, baseline for the current study was 1 year after enrollment in the CRIC. Data on the quality of life, dietary assessment, physical activity, health behaviors, cognitive functions, health care resource utilization, measures of kidney function, and the occurrence of new and worsening CV disease were collected, and urine and blood specimens were collected at years 1, 3, and 5. eGFR was estimated using the CRIC-specific equation, which has been validated for use in this population.[15]

The following criteria were applied sequentially to the full CRIC cohort: available TransDry 24-hour urine samples at years 1, 3, and 5; nonmissing echocardiogram data (left ventricle mass index) at years 1 and 4; nonmissing coronary calcification assessment (total Agatston score) at years 1 and 4; nonmissing calibrated fibroblast growth factor 23 (FGF23) at years 1 and 3; nonmissing serum 25-hydroxyvitamin D level (determined using liquid chromatography-mass spectrometry or mass spectrometry) at years 1 and 3; and nonmissing calibrated total parathyroid hormone at years 1 and 3. Fig 1 summarizes the serial reduction in sample size following each step. This process yielded 47 CRIC participants meeting all 6 criteria, of whom 40 were randomly selected for full chemical analyses. This number was determined by the available funding which enabled measurement of the panel of organic pollutants at the 3 time points (1, 3, and 5 years) in 40 CRIC participants.

Chemical Analysis

Quality control procedures and results as well as a full list of chemicals and abbreviations for chemical names are provided in Item S1 and Table S1. Briefly, urinary DAPs were measured using a method described elsewhere.[16] Six DAPs were targeted. Briefly, urine samples were extracted using weak anion-exchange cartridges (Biotage WAX; Waters Corp) and measured on an ABSciex 5500 Q-Trap mass spectrometer (Framingham) coupled to a Waters Acquity Class I ultra-high liquid chromatograph (UHPLC; Waters Corp).

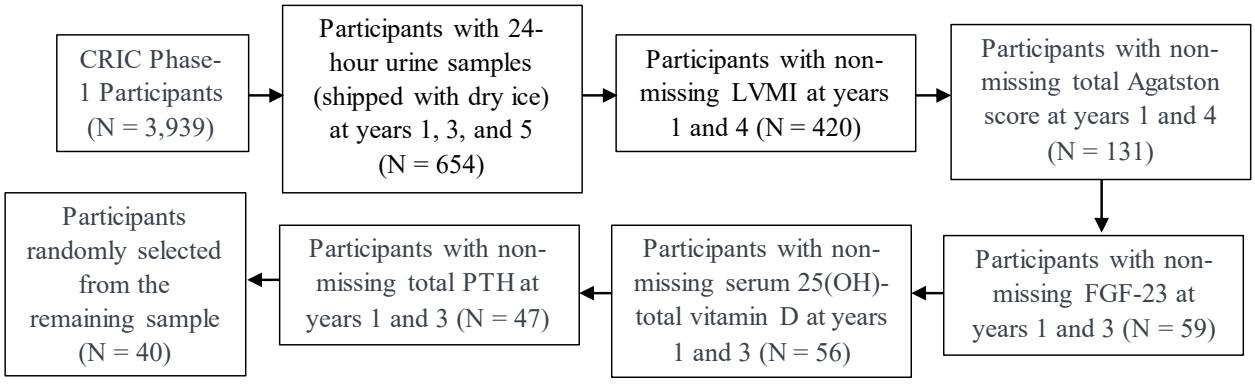

Figure 1. A flowchart of sample selection. The schematic summarizes the serial reduction in sample size following the application of the following criteria to the full CRIC cohort: available TransDry 24-hour urine samples at years 1, 3, and 5; nonmissing echocardiogram data (left ventricle mass index) at years 1 and 4; nonmissing coronary calcification assessment (total Agatston score) at years 1 and 4; nonmissing calibrated fibroblast growth factor 23 (FGF23) at years 1 and 3; nonmissing serum 25-hydroxyvitamin D level (determined by liquid chromatography-mass spectrometry or mass spectrometry) at years 1 and 3; and nonmissing calibrated total parathyroid hormone at years 1 and 3.

Eight BPs and hydroxylated polycyclic aromatic hydrocarbons (OH-PAHs) were measured using a method described elsewhere.[17] Urine sample preparation entailed enzymatic deconjugation (β-glucuronidase from *E. coli* K12; Roche Diagnostics GmbH), followed by liquid-liquid extraction (ethyl acetate: pentane: toluene = 5:4:1 [v/v/v]). Analyte determination was conducted on an ABSciex 5500 Q-Trap mass spectrometer (Framingham) coupled to a Shimadzu LC-30 AD HPLC (Shimadzu Corp).

Melamine and CYA were analyzed using a method reported earlier.[18] Briefly, urinary melamine and CYA were extracted separately using liquid-liquid extraction following acidification (for CYA) or basification (for melamine). Analyte determination was performed on an ABSciex 5500 Q-Trap mass spectrometer (Framingham) coupled to a Shimadzu LC-30 AD HPLC (Shimadzu Corp).

Twenty-eight urinary PhMs were analyzed using methods reported earlier.[17] Briefly, sample preparation entailed enzymatic deconjugation (β-glucuronidase from *E. coli* K12; Roche Diagnostics GmbH), followed by solid-phase extraction using reversed-phase cartridges (Bond Elut NEXUS; Agilent Technologies). Analyte determination was performed on an ABSciex 5500+ Q-Trap mass spectrometer coupled to an ExionLC HPLC (SCIEX, Redwood City). Details of the instrumental parameters have been reported elsewhere.[16-19]

Statistical Methods

For baseline data, counts and proportions (in percentage) were calculated for categorical variables, whereas means and standard deviations (SDs) or medians and 25th and 75th percentiles were calculated for continuous variables. Three clinical outcomes, death; a composite of congestive heart failure, myocardial infarction, and stroke; and event-free survival from kidney failure or a ≥50% decline in eGFR, were considered in the statistical analysis. In addition, we analyzed associations with longitudinal change in eGFR and urine protein-to-creatinine ratio.

Associations of exposure with these outcomes were assessed for specific compounds and for each class of compounds based on the sum of the urinary levels of the molecules within the class. The classes included BPs, organophosphates, PAHs, CYA, melamine, and phthalates. Individual compounds were removed from a class if measurements were below the limit of detection in ≥50% of the participants. The Cox proportional hazards model and Kaplan-Meier method were used to calculate hazard ratios and 95% confidence intervals for each class.

For continuous outcomes, Pearson correlation coefficients between compound classes and CV outcomes (total Agatston score, ejection fraction, and left ventricle mass index) were calculated; the Pearson correlation coefficient between annual change in eGFR and baseline exposure to each compound class was assessed. Primary analyses were based on the raw urinary concentrations with sensitivity analyses using concentrations normalized to the urinary creatinine concentration. Additional survival analyses used time-updated measurements of the chemical compounds in longitudinal analyses. Post hoc analyses were conducted to explore the effect modification of associations of phthalate concentration with eGFR decline by body mass index (BMI) and to assess whether associations differed for high- versus low-molecular weight phthalates.[20,21] All analyses were conducted in R version 4.0.3 (R Foundation for Statistical Computing). Statistical significance was defined as a *P* value less than 0.05. This study was approved by the Institutional Review Board of the New York University Grossman School of Medicine (i21-01319).

RESULTS

Description of the Cohort

Baseline characteristics are summarized in Table 1. The median age was 58 years with a predominance of men. The race, ethnicity, geographic distribution, socioeconomic status, underlying disease, and key clinical and laboratory features, including presence of diabetes, hypertension, or CV disease, were comparable in the subgroup and the complete CRIC cohort. The median eGFR was 33 mL/min/1.73 m^2, and the urinary protein-to-creatinine ratio was 0.58 mg/mg.

Urinary Concentrations of Environmental Chemicals

Of the 52 compounds assayed, 30 were measurable in the majority of study participants with only 3 below the lower limit of detection in all participants. Overall, the exposure in the patients with CKD were comparable with values measured in healthy control participants enrolled in contemporaneous National Health and Nutrition Examination Survey (NHANES) studies (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx) (Table 2). The only class of molecules with a trend toward higher exposure levels in patients with CKD was phthalates. Three PhMs were undetectable in all patients: mono-methyl phthalate (mMP), cyclohexane-1,2-dicarboxylic acid-mono(-hydroxy-isononyl) ester (mHNCH), and cyclohexane-1,2-dicarboxylic acid-monocarboxy isooctyl ester (mCOCH). Urinary excretion of BPF and cyanuric acid were also higher in patients with CKD versus healthy individuals.

Effects on Kidney Function

In univariate analyses, point estimates were consistent with greater annual decline in eGFR with higher baseline concentrations of OH-PAHs and the phthalates, although neither association achieved significance (Fig 2). Results were similar for the individual chemicals (Fig S1). Univariate analyses using time-updated exposures to the individual compounds demonstrated a wide range of associations with the eGFR trajectory (Table 3) without consistent trends. Eight compounds, including DETP, 2-hydroxyphenanthrene

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics of 40 CRIC Adult Participants

Characteristic	Median or Count (25th and 75th Percentiles or Percent)
Age (y)	58.0 (43.0-64.3)
Sex	
Female	14 (35.0%)
Male	26 (65.0%)
Race	
African American	17 (42.5%)
White	21 (52.5%)
Other	2 (5.0%)
Ethnicity	
Hispanic	3 (7.5%)
Non-Hispanic	36 (90.0%)
Other	1 (2.5%)
Education	
High school or less	8 (20.0%)
College education or graduate	23 (57.5%)
Post-college education or graduate	9 (22.5%)
Annual income (in US dollars)	
≤20,000	6 (15.0%)
20,001-50,000	10 (25.0%)
50,001-100,000	15 (37.5%)
>100,000	4 (10.0%)
Unknown	5 (12.5%)
Geographical region in the United States	
Northeast	3 (7.5%)
Southeast	7 (17.5%)
Midwest	17 (42.5%)
Northwest	13 (32.5%)
Cause of kidney disease	
Diabetes	13 (32.5%)
Hypertension	6 (15.0%)
Other	21 (52.5%)
Cardiovascular disease	9 (22.5%)
Cancer	5 (12.5%)
Antihypertensive medications	
ACE inhibitors or ARBs	27 (67.5%)
Beta blockers	17 (42.5%)
Diuretics	19 (47.5%)
Calcium channel blockers	20 (50.0%)
Antihyperlipidemic drugs	
Lipid-lowering drugs	23 (57.5%)
Statins	22 (55.0%)
Vitamin D deficiency and mineral bone disease drugs	
Calcimimetic agents	0 (0%)
Calcium-containing phosphate binders	3 (7.5%)
Non–calcium containing phosphate binders	1 (2.5%)
Calciferols	1 (2.5%)
Activated vitamin D	2 (5.0%)
Antidiabetic drugs	6 (15.0%)
Insulin	15 (37.5%)
Sulfonylurea	5 (12.5%)
Steroids	2 (5.0%)
Blood pressure (mm Hg)	97.7 (90.4-107.8)
Urine protein-to-creatinine ratio (24-h and spot measure combined)	0.6 (0.1-1.9)
Estimated glomerular filtration rate (CRIC equation)	33.0 (22.9-47.1)
Serum albumin level (g/dL)	4.0 (3.7-4.3)
Total cholesterol (mg/dL)	175.0 (157.0-213.0)
Calcium (mg/dL)	9.2 (8.9-9.4)
Phosphate (mg/dL)	3.9 (3.4-4.2)
Parathyroid hormone (pg/mL)	98.0 (49.3-148.7)
25OH-vitamin D (ng/mL)	20.15 (14.1-30.2)
Fibroblast growth factor 23 (RU/mL)	184.5 (127.4-392.3)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; RU, relative units.

(PHEN), 3-PHEN, 1/9-PHEN, CYA, mHXP, mHPP, and mEHP, were associated with a significant improvement in the eGFR slope. In contrast, there were 8 individual molecules, namely BPF, 2-napthol (NAP), melamine, mCPP, mBZP, mEOHP, mECPP, and mCMHP that were associated with an estimated annual decline in eGFR exceeding −1.0 mL/min/1.73 m^2/y, among which BPF and mCPP were statistically significant. Results were qualitatively similar directionally in a sensitivity analysis using concentrations normalized to urinary creatinine (Table S2), although neither normalized BPF nor mCPP were significantly associated with the decline in eGFR. We were unable to show any additive effect of combinations of chemical exposures in this limited cohort. There were no significant associations between exposure to organic pollutants and increased levels of proteinuria for individual pollutants or class of compounds (Tables S3 and S4).

As shown in Table 4, the total level of exposure to all of the compounds assayed within the 5 classes of the organic pollutants in the aggregate were not different in those who experienced a 50% decline in eGFR, kidney failure, or mortality versus those who remained event free. Kaplan-Meier plots illustrating this composite outcome, however, were consistent with a trend for worse kidney survival in patients with phthalate and melamine exposure above versus below the median value (Fig 3). There was no difference in the association of time-updated exposure to phthalates as a class on the eGFR slope according to BMI with a binary cutoff at ≥30 (Table S5). Point estimates were not consistent with a greater adverse effect of exposure to high-molecular-weight versus low-molecular-weight phthalates on the rate of deterioration in kidney function over time (Table S6).

Table 2. Comparison of Environmental Chemicals Measured in the CRIC Cohort With NHANES Data

	CRIC			NHANES[a]		
Analytes	DF%	Median (ng/mL)	P95 (ng/mL)	Median (ng/mL)	P95 (ng/mL)	Survey year
Dialkylphosphate metabolites						
DMP	80	1.1	11.3	2.3	18.8	2011-2012
DEP	100	0.8	6.0	2.2	19.5	2011-2012
DMTP	100	2.3	23.2	1.5	25.1	2011-2012
DETP	83	0.3	1.8	< LOD	2.8	2011-2012
DMDTP	91	0.2	3.8	< LOD	3.2	2011-2012
DEDTP	40	< LOD	0.4	< LOD	< LOD	2011-2012
Bisphenols						
BPA	98	1.1	8.5	1.1	6.8	2015-2016
BPS	94	0.3	2.7	0.4	4.1	2015-2016
BPF	63	0.6	15.5	< LOD	8.2	2015-2016
Hydroxylated polycyclic aromatic hydrocarbon						
1-NAP	99	1.6	14.0	1.2	21.3	2013-2014
2-NAP	99	1.4	12.8	4.1	30.0	2013-2014
2/3/9-FLUO[b]	27	< LOD	2.1	0.5	5.1	2011-2012
2-PHEN	97	0.0	0.1	0.1	0.3	2011-2012
3-PHEN	91	0.0	0.1	0.1	0.4	2011-2012
1-PYR	44	< LOD	0.2	0.1	0.7	2013-2014
1/9-PHEN[c]	96	0.1	0.5	0.1	0.4	2013-2014
4-PHEN	26	< LOD	0.0	0.0	0.1	2011-2012
Melamine and derivatives						
Melamine	100	2.8	16.9	2.9	22.9	2003-2004
Cyanuric acid	100	21.2	61.2	5.7	19.3	2003-2004
Phthalate metabolites						
mMP	3	< LOD	< LOD	1.0	11.8	2011-2012
mEP	100	53.5	1,120	28.6	433	2015-2016
mCPP	96	1.9	8.5	1.1	8.6	2015-2016
mBzP	99	5.3	31.0	4.3	44.8	2015-2016
mEHP	80	1.3	38.4	1.1	6.0	2015-2016
mEOHP	100	13.2	183	3.7	19.0	2015-2016
mEHHP	100	20.7	252	5.7	28.3	2015-2016
mCIOP[d]	100	5.2	74.6	7.4	93.8	2015-2016
mCINP[e]	100	0.5	3.3	1.8	9.9	2015-2016
mHNCH	1	< LOD	< LOD	0.6	7.4	2015-2016
mCOCH	2	< LOD	< LOD	0.5	4.0	2015-2016
mBP/mIBP[f]	100	11.8	42.2	19.7	89.2	2015-2016
mECPP	100	24.7	255	9.0	46.2	2015-2016

Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; LOD, limit of detection; mCOCH, cyclohexane-1,2-dicarboxylic acid-monocarboxy isooctyl ester; mHNCH, cyclohexane-1,2-dicarboxylic acid-mono(hydroxy-isononyl) ester; mMP, mono-methyl phthalate; NHANES, National Health and Nutrition Examination Survey.
[a]The newest available data from NHANES are used for comparison.
[b]The median and P95 values of NHANES indicate the sum of 2-, 3-, and 9-FLUO;
[c]NHANES data indicate the median and P95 values for 1-PHEN;
[d]mCOP and mCIOP are not separated in NHANES;
[e]mCNP and mCINP are not separated in NHANES;
[f]NHANES data indicate the sum of mBP and mIBP.

Cardiovascular Outcomes

The level of baseline exposure to the 5 classes of the organic pollutants was not associated with the occurrence of the composite of heart failure, myocardial infarction, or stroke (Table 4). There was a general pattern of an inverse relationship between exposure of organic pollutant classes and measures of cardiac structure with better function at higher levels of exposure (Fig 4); however, most of the correlation coefficients were <0.2 and not significant. When examined at the level of individual compounds, strengths of association varied, but none of the individual compounds were associated with a consistent and significant pattern of worsening left ventricular mass, left atrial dimension, and Agatston score (Fig S2). Other than relationships between melamine or CYA exposure and serum FGF23 (inverse) and 25(OH)-vitamin D (direct) levels, there was no consistent association between the organic pollutants and these measures of calcium-phosphorus metabolism (Tables S7 and S8).

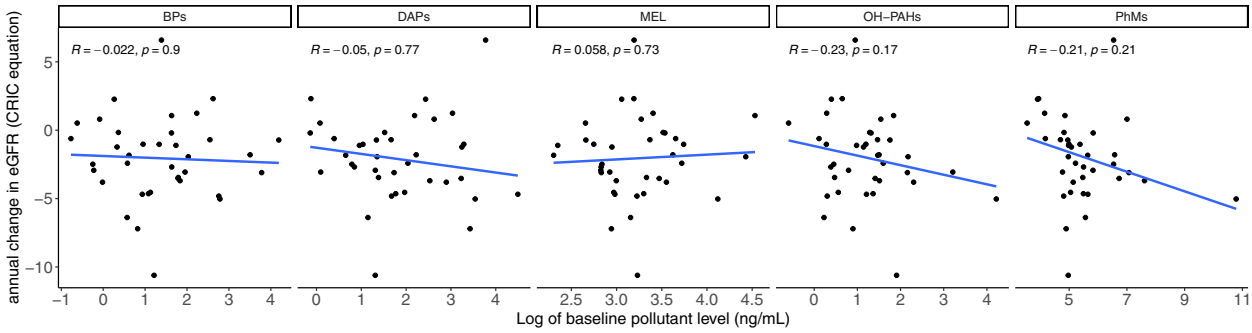

Figure 2. Scatter plots of annual change in eGFR versus log of baseline level of pollutant classes. Notes: eGFR was calculated using the CRIC equation with no race adjustment. Solid straight lines represent fitted values from a univariate linear regression. Pearson correlation coefficients and *P* values are denoted as R and *P*, respectively.

DISCUSSION

In this pilot project in the CRIC cohort study, we demonstrate the feasibility of assessing exposure to organic pollutants in multiple structural classes based on the urinary excretion of the chemicals. Our study is unique in that it represents a comprehensive survey of the largest number of organic chemical pollutants, including organophosphate pesticides, BPs, PAHs, melamine or CYA, and phthalates. It is the first study to our knowledge to measure the molecules serially over time in a well characterized cohort of adult patients with CKD and to compare the findings to healthy individuals in the United States. Although the sample size was limited and the number of clinical events was small, we did not detect significant associations between the degree of chemical exposure broadly by class or individual compound and kidney or clinical cardiac events. Based on collective analyses of unadjusted or creatinine-normalized concentrations, there were trends suggesting a greater rate of decline in kidney function with higher levels of exposure to a limited number of compounds, such as BPF and mCPP, that merit investigation in larger cohorts.

CKD imposes changes in lifestyle or diet that may influence exposure to the organic pollutants assessed in this study. In addition, many of these molecules are eliminated by kidney excretion. Thus, patients with long-standing kidney disease may be at increased risk of adverse consequences because of cumulative exposure to organic pollutants. However, our findings suggest that patients with CKD have levels of exposure to the full range of compounds that are comparable with healthy adults residing in the United States. The only exception may be phthalate exposure, which may be modestly increased. Further in-depth studies are needed to define the source of exposure to each class of compounds and whether intake can be modified with feasible interventions.

Overall, there was not a consistent trend indicating increased risk of adverse kidney or cardiac outcomes in relation to the level of exposure to the organic pollutants in patients with CKD. This included the composite outcome of 50% decline in eGFR or the need for kidney replacement therapy, eGFR slope, proteinuria, biochemical measures, mineral bone metabolism, cardiac calcification, or left ventricular hypertrophy. Further studies will be needed to determine whether these chemicals are associated with more subtle signs of kidney damage, such as tubular injury or oxidant stress. For many of the molecules, there was a positive association between increased levels of exposure and eGFR slope. It is worth noting that in a prior NHANES 2007-2016 study of 1,610 United States adolescents, select phthalates, namely MiBP, were positively associated with eGFR, indicating that this finding is not unprecedented.[22] Increased exposure may reflect parallel changes in personal behaviors or medical treatment that leads to improved kidney and heart function. For example, prescription of medications in capsule form, increased travel, or consumption of fruits without precautions regarding pesticide use may increase exposure to organic pollutants in subgroups of patients.[23,24]

The effect of environmental chemicals on kidney function has been investigated in numerous preclinical and clinical investigations. The effect of BPs, phthalates, PAHs, and melamine on eGFR and proteinuria has been assessed in healthy children and adults.[6,10,12,25] BP and phthalate levels have been measured and noted to be elevated in adults receiving kidney replacement therapy because these chemicals may be leached from plastic supplies during repeated hemodialysis treatments.[26,27] However, less data are available for patients with CKD not receiving dialysis. Large studies in the United States and Korea have explored the association of exposure to BPs, phthalates, and PAHs with the risk of developing CKD in adults. In a cohort of 9,008 participants enrolled in NHANES 2005-2016, of whom 12% had CKD, select phthalate, and BPs were associated with lower eGFR.[25] These compounds were also associated with higher levels albuminuria. In contrast, there was an uncertain effect on eGFR among 1,272 healthy adults enrolled in the Korean National Health Environmental Study from 2015 to 2017.[28] Neither of these studies focused

Table 3. Estimates, 95% Lower and Upper Confidence Limits and *P* Values for Classes of Compounds and Individual Pollutants Within Each Class Reported as Log of Concentration (ng/mL) With eGFR as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values

Pollutant Class	Estimate	LCL (2.5%)	UCL (97.5%)	*P* Value
Dialkylphosphate metabolites	0.324	−2.774	3.392	0.836
DMP	0.109	−1.598	1.816	0.901
DEP	−0.788	−4.420	2.845	0.672
DMTP	−0.366	−3.220	2.489	0.802
DETP	2.579	0.118	5.039	0.043
DMDTP	0.682	−1.640	3.004	0.566
Bisphenols	−1.694	−5.411	2.023	0.374
BPA	0.033	−4.168	4.235	0.988
BPS	1.281	−2.545	5.108	0.513
BPF	−2.883	−5.403	−0.362	0.027
Hydroxylated polycyclic aromatic hydrocarbon	0.312	−3.911	4.535	0.885
1-NAP	−0.136	−3.242	2.971	0.932
2-NAP	−1.005	−4.992	2.983	0.623
2-PHEN	4.970	0.518	9.423	0.031
3-PHEN	4.910	1.561	8.258	0.005
1/9-PHEN	3.970	0.336	7.604	0.035
Melamine and derivatives				
Melamine	−2.124	−5.911	1.662	0.274
Cyanuric acid	8.236	1.140	15.332	0.025
Phthalate metabolites	−0.340	−3.578	2.898	0.837
mEP	0.040	−2.541	2.622	0.976
mHxP	3.057	0.158	5.957	0.041
mCPP	−5.269	−9.300	−1.237	0.012
mBZP	−3.114	−7.310	1.083	0.149
mHPP	5.532	2.627	8.438	<0.001
mEHP	2.454	0.779	4.130	0.005
mEOHP	−1.107	−4.450	2.236	0.518
mEHHP	−0.818	−4.024	2.389	0.618
mCIOP	1.239	−2.533	5.010	0.521
mCINP	−0.901	−5.481	3.679	0.701
mPOHP	1.943	−1.163	5.048	0.223
mPCHP	−0.732	−6.217	4.754	0.794
mBP/mIBP	0.339	−3.943	4.621	0.877
mECPP	−1.090	−4.441	2.260	0.525
mCMHP	−1.813	−4.665	1.040	0.216

Abbreviations: LCL, lower confidence limit; UCL, upper confidence limit.

specifically on adults with CKD. Moreover, they were cross-sectional in design and did not measure longitudinal exposure over time. Finally, these studies did not comprehensively assay as large of a range of compounds as we measured in this pilot study.

Among the 5 classes of organic pollutants, phthalates were the only class in which exposure trended higher in CKD patients versus healthy controls. In addition, phthalates comprised the only class with more than 1 member in which there was an association between worse kidney function and increased levels of exposure. Alterations in kidney function in association with phthalate exposure have been linked to increased oxidant stress and/or inflammation in healthy children and children with CKD.[4,8] Overall, our results are consistent with previous reports that have detailed divergent effects of individual organic molecules within a class in a wide range of in vitro and in vivo assays.[25]

It is worth comparing the findings in this pilot study in adults with CKD and our earlier work in children who were enrolled in the CKiD cohort study. Among 618 children and adolescents who provided serial urine specimens over an average of 3 years, BPA and phthalate metabolites were not associated with eGFR or proteinuria. Only phthalic acid was associated with lower eGFR over time, such that for a 1-SD increase in log-transformed concentration, there was an average decrease in eGFR of 0.38 mL/min/1.73 m^2.[5] PAH metabolites, driven by 3-PHEN (3-hydroxyphenanthrene), were associated with increased eGFR and reduced proteinuria over time. However, they were consistently associated with increased excretion of biomarkers of tubular injury and oxidant stress.[6] Similarly, organophosphate pesticide

Table 4. Medians (25th and 75th Percentiles) of Log of Baseline Concentration (ng/mL) and Hazard Ratios (95% Confidence Intervals) for Pollutant Classes by Different Endpoints. Hazards ratios are provided for exposure levels above versus below the median concentration

	Death		
Pollutant Class	**Yes (n = 9)**	**No (n = 31)**	**Hazard Ratio[a]**
Dialkylphosphate metabolites	2.01 (1.48-2.73)	2.09 (1.50-2.78)	0.87 (0.48-1.57)
Bisphenols	1.62 (1.20-2.68)	1.13 (0.83-2.02)	1.38 (0.84-2.28)
Hydroxylated polycyclic aromatic hydrocarbon	1.99 (1.38-2.34)	1.15 (0.82-1.69)	1.82 (1.01-3.26)
Melamine and derivatives	3.27 (3.03-3.45)	3.34 (3.07-3.57)	1.23 (0.34-4.40)
Phthalate metabolites	5.55 (4.85-6.13)	5.67 (5.15-6.12)	1.28 (0.86-1.92)
	CHF, MI, stroke composite status		
Pollutant class	**Yes (n = 12)**	**No (n = 28)**	**Hazard ratio**
Dialkylphosphate metabolites	2.75 (1.97-3.23)	1.91 (1.41-2.46)	1.58 (0.92-2.70)
Bisphenols	1.31 (0.92-1.76)	1.44 (0.86-2.10)	1.11 (0.71-1.73)
Hydroxylated polycyclic aromatic hydrocarbon	1.76 (1.15-2.24)	1.15 (0.64-1.68)	1.74 (1.00-3.03)
Melamine and derivatives	3.22 (3.01-3.54)	3.32 (3.07-3.57)	1.01 (0.32-3.21)
Phthalate metabolites	5.24 (4.99-5.58)	5.74 (5.32-6.13)	1.25 (0.85-1.85)
	Surviving an ESKD with at least 50% eGFR decline		
Pollutant class	**Yes (n = 26)**	**No (n = 14)**	**Hazard ratio**
Dialkylphosphate metabolites	1.91 (1.44-2.71)	2.40 (1.89-2.81)	0.87 (0.62-1.23)
Bisphenols	1.44 (1.20-2.21)	1.14 (0.73-1.94)	0.92 (0.68-1.26)
Hydroxylated polycyclic aromatic hydrocarbon	1.44 (0.89-1.96)	1.26 (0.99-1.90)	1.01 (0.65-1.57)
Melamine and derivatives	3.25 (2.93-3.44)	3.48 (3.30-3.72)	0.63 (0.28-1.42)
Phthalate metabolites	5.68 (5.23-6.12)	5.37 (4.94-6.46)	1.12 (0.86-1.47)

Abbreviations: CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; ESRD, end-stage kidney disease; FLUO, hydroxyfluorenes; MI, myocardial infarction; NAP, naphthol; PHEN, hydroxyphenanthrenes; PYR, 1-hydroxypyrene.
[a]Hazard ratios are provided for exposure levels above versus below the median concentration.

exposure was associated with lower eGFR at baseline but not with a more rapid rate of disease progression.[7] These observations suggest that organic pollutants had only a marginal adverse effect on the trajectory of pediatric CKD during 3-5 years of observation. More prolonged follow-up is required to ascertain whether low-grade tubular injury caused by organic pollutants leads to a decline in eGFR across the lifespan.

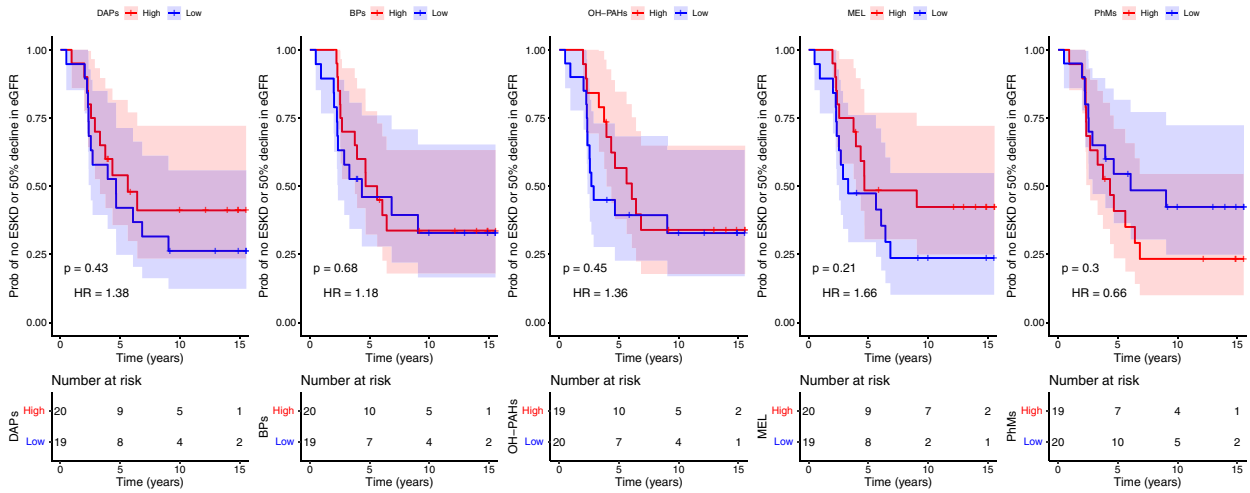

Figure 3. Kaplan-Meier plots for the outcome of kidney failure or 50% decline in eGFR stratified by pollutant classes. Notes: Ribbons denote 95% confidence intervals. Medians were used for pollutant class stratification (high versus low). Hazard ratios and *P* values were denoted as HR and *P*, respectively. The number of patients at risk for the outcome is provided under each plot. BPs, bisphenols; DAPs, dialkylphosphate metabolites; OH-PAHs, hydroxylated polycyclic aromatic hydrocarbon; Mel, melamine and derivatives; PhMs, phthalate metabolites.

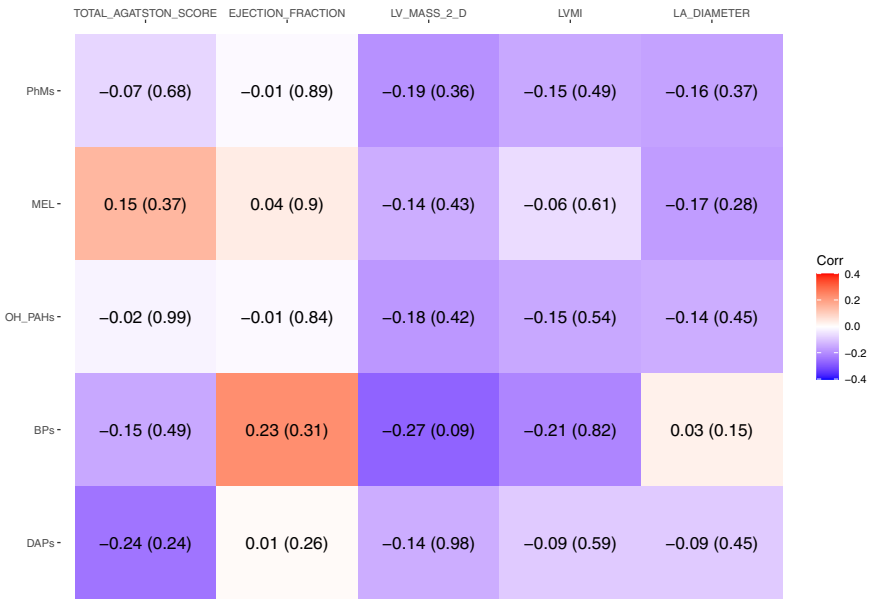

Figure 4. A correlation matrix of pollutant classes and cardiovascular outcomes. Color-coding reflects level of correlation. *P* values are provided in parentheses. BPs, bisphenols; DAPs, dialkylphosphate metabolites; OH-PAHs, hydroxylated polycyclic aromatic hydrocarbon; Mel, melamine and derivatives; PhMs, phthalate metabolites.

Several limitations of this study should be acknowledged. Given the small sample size, our ability to detect an association between exposure to the organic pollutants and CV or kidney outcomes was constrained. Concerns about evaluating the relationship between chemical exposure and clinical outcomes based on urinary excretion should be acknowledged. An interpretation of the effects of environmental exposures based on high urinary excretion levels may reflect reverse causation because of impaired reabsorption of the molecules rather than increased exposure. Although analysis of serum concentration of pollutants may be more adversely affected by declining kidney function, reverse causation remains a concern in the context of elevated urinary levels. However, we point out that the urinary concentrations of organic compounds were comparable in the CRIC participants and healthy adult controls from the United States. Moreover, the patients included in this study had fairly well-preserved kidney function (CKD stage 3), and it is unlikely that the degree of kidney functional impairment affected urinary excretion. We report findings based on urinary concentration. However, results were similar in sensitivity analyses with concentrations normalized to urinary creatinine, and prior studies have indicated that the general findings are comparable with and without normalization.[29] We evaluated the effect of the organic pollutants as single exposures. A more meaningful assessment of the effect of these chemicals on the trajectory of CKD may emerge by assessing combined exposures for potential interactions. This may better reflect lived experiences and novel analytic techniques that have been developed to perform such analyses.[25] Finally, we did not assay serum samples and were unable to assess the effect of exposure to polyfluorinated alkyl substances (PFAS).

Several strengths of the design of this pilot study should be noted. Use of data from participants in the CRIC Study enabled exploration of the relationship of exposure to an exhaustive list of clinical, laboratory, and radiological outcomes. The advanced methodology used to assay the chemicals is state-of-the-art and has been used in a number of investigations into the exposome in health and disease.

In conclusion, it is feasible to assess exposure to a wide range of organic pollutants in adult patients with CKD. The level of exposure in affected individuals is comparable with the healthy population in the United States. The findings suggest that a subset of molecules is associated with more rapid deterioration in kidney function, especially in the phthalate class. In view of the high costs and labor-intensive effort required to measure environmental chemical exposure, our findings provide a useful reference for future studies that aim to evaluate organic pollutant exposure in the CKD population. Further investigations of the effect of exposure to these chemicals on the trajectory of kidney function and CV disease may be more rewarding if the analyses focus on a panel of select molecules that have been demonstrated to be harmful in pilot studies like ours and if the follow-up is extended over a longer observation period.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Scatter plots of annual change in eGFR versus log of baseline level of individual pollutant compounds.

Figure S2: A correlation matrix of individual pollutant compounds and cardiovascular outcomes.

Table S1: Limit of Detection (LOD), Procedural Blank (BLK), Spike Recoveries of the Analytes in the Urine Matrix (at 10 ng/mL), and Proficiency Test results.

Table S2: Univariate Estimates, 95% Confidence Intervals, and *P* Values for Individual Pollutants (Normalized by Urine Creatinine and Log Transformed) With eGFR as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values.

Table S3: Univariate Estimates, 95% Confidence Intervals, and *P* Values for Individual Pollutants Reported as Log of Concentration (ng/mL) With the Protein-Creatinine ratio as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values.

Table S4: Univariate Estimates, 95% Confidence Intervals, and *P* Values for Pollutant Classes Reported as Log of Concentration (ng/mL) With the Protein-Creatinine ratio as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values.

Table S5: Adjusted Estimates, 95% Confidence Intervals, and *P* Values for Phthalate Classes Reported as Log of Concentration (ng/mL) Stratified by Body Mass Index (BMI) and Adjusting for Sex, Race, and Protein-Creatinine Ratio (PCR) With eGFR as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values.

Table S6: Adjusted Estimates, 95% Confidence Intervals, and *P* Values for Phthalate Compounds Reported as Log of Concentration (ng/mL) Adjusting for Sex, Race, and Protein-Creatinine Ratio (PCR) With eGFR as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values.

Table S7: Adjusted Estimates, 95% Confidence Intervals, and *P* Values for Individual Pollutants Reported as Log of Concentration (ng/mL) With Fibroblast Growth Factor 23 as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values.

Table S8: Adjusted Estimates, 95% Confidence Intervals, and *P* Values for Individual Pollutants Reported as Log of Concentration (ng/mL) with Serum 25-Hydroxyvitamin D as the Outcome of Interest From a Generalized Linear Model With Time-Updated Values.

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