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Renal Function and Exposure to Bisphenol A and Phthalates in Children with Chronic Kidney Disease

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Abstract

Rationale and objective: Exposure to Bisphenol A (BPA) and phthalates is ubiquitous among adults and children in the United States. Among children and adolescents, those with chronic kidney disease (CKD) are potentially at greater risk of adverse effects from BPA and phthalate exposure. The objective of this study was to evaluate BPA and phthalate exposure among children with CKD and evaluate associations with three measures of kidney function.

Study design: Cross sectional study

Setting, participants, and measurements: The CKD population was represented by the Chronic Kidney Disease in Children (CKiD) Study, a multicenter, prospective cohort study of children with impaired kidney function in the US. The main outcome was assessment of the relationship between chemical exposures and clinical laboratory findings at enrollment into CKiD. Data collected at baseline from participants 1–17 years old (N=538) were analyzed. Urinary BPA and phthalate levels were evaluated at this time point. Data from the National Health and Nutrition

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Examination Survey (NHANES), a nationally representative pediatric population, were used for comparison to the CKiD cohort.

Results: Urinary BPA and phthalate levels in the CKiD population were consistently lower than levels detected in healthy children. Additionally, BPA was not significantly associated with blood pressure, proteinuria, or estimated glomerular filtration rate (eGFR). Within the CKiD population, for select individual and combined phthalates, there was an inverse relationship with the urinary protein:creatinine ratio (LMW phthalates, −9.53 percent change; 95% CI: −14.21, - 4.21; p=0.001), and in most cases, a positive relationship with eGFR (LMW phthalates, a 3.46 unit increase in eGFR, 95% CI: 1.85, 5.07; p<0.001).

Limitations: Lack of longitudinal data, limited assessment of diet and nutritional status

Conclusion: In the study cohort, children with CKD did not have increased exposure to BPA and phthalates. Longitudinal studies with repeated measures are likely to be more informative about the possible health effects of prolonged exposure to BPA and phthalates in pediatric patients with CKD

Keywords

chronic kidney disease; bisphenol A; phthalates; children; blood pressure; glomerular filtration rate; urinary protein:creatinine ratio

Introduction

Environmental exposure to Bisphenol A (BPA) and phthalates is nearly ubiquitous among adults and children in the United States (1–3). These possible endocrine disruptors are among the most widely used chemicals in consumer and industrial products (4). BPA is used in the production of polycarbonate plastic and expoxy resins used to coat metal products such as food cans, bottle tops, and water supply pipes, and is commonly found in food packaging, drink containers, and medical devices (5, 6). Phthalates are categorized by size and low molecular weight (LMW) phthalates are commonly found in scented personal hygiene products, such as hair care products and cosmetics (7). High molecular weight (HMW) phthalates are added to vinyl plastics, which are used in food packaging, construction materials, and intravenous tubing (8). A categorization of the different phthalate metabolites is presented in Table 1. BPA and phthalates have been associated with obesity, low grade albuminuria, and increased blood pressure in children.

Though routes of exposure include skin absorption and inhalation (9–11), BPA exposure occurs most often through dietary intake of canned foods (12). Phthalate exposure is mainly through ingestion of leached food packaging and absorption of personal care products applied to the skin (7, 8). Although the FDA has maintained that BPA is safe at current levels, it has banned its use in sippy cups and baby bottles, children and adolescents remain at risk because they consume more food per unit of body weight, and cumulative exposure to phthalates and BPA will be greater across the lifetime (13). Studies have, in fact, shown that urinary concentrations of BPA in children and adolescents are higher than those in adults (2).

Chronic Kidney Disease (CKD) is a serious health condition that is a growing public health and clinical concern worldwide (14, 15). CKD is associated with progressive decline in glomerular filtration rate (GFR), which compromises kidney excretion of BPA and phthalates (16). Among children and adolescents, those with CKD are potentially at a far greater risk of exposure to BPA and phthalates. Patients with CKD often undergo medical procedures involving the use of medical devices that contain phthalates, such as diethylhexyl phthalate (DEHP), a combined phthalate metabolite (5, 8). DEHP is often added to polyvinyl chloride (PVC) based medical supplies that are used for intravenous, blood, and nutritional solutions and respiratory gases. These items leach various amounts of different phthalates into the solutions administered to patients. In addition, the coatings of some pharmaceutical drugs, including various antibiotics, antihistamines, and laxatives, include phthalate plasticizers that may be absorbed into the intestinal tract (8). Children with CKD are, therefore, less able to limit their exposure to possible endocrine disruptors in medical devices and pharmaceutical drugs compared to healthy children, who can opt to avoid certain food packaging and personal care products. Moreover, the patients have limited capacity to excrete these toxic molecules because of reduced kidney function.

The primary objective of our study was to evaluate exposure to BPA and phthalates among children with CKD. In addition, we sought to examine possible associations between BPA and phthalate exposure and three measures of kidney function, namely: estimated GFR (eGFR), blood pressure (BP), and proteinuria, as measured by urinary protein to creatinine ratio (UPCR). To our knowledge, ours is the first study to examine cross-sectional exposure to BPA and phthalates among children with CKD, and to assess the possible associations of BPA and phthalate levels with eGFR.

Concise Methods

Data Source and Sample

The Chronic Kidney Disease in Children (CKiD) Study is a multicenter, prospective cohort study of children with mild to moderate impaired kidney function in the United States (17). The design of the CKiD Study, including enrollment criteria, has been published previously (17).

For this study, data and specimens collected during the baseline study visit of participants between 1– 17 years of age were analyzed. Study participants were not fasting at the tie of collection of biospecimens. All samples were collected and stored in polycarbonate-free tubes that were suitable for analysis of BPA and phthalate levels. This was part of the standard procedures of the CKiD study and no quality assurance or quality control testing was done to validate this aspect of the project. The majority of samples were collected between the years 2005 and 2008, while some were collected between 2009 and 2014. The New York University School of Medicine Institutional Review Board exempted this project from review on the basis of its analysis of an already collected and de-identified dataset.

We compared the concentration of chemicals in our study population with the levels reported by the Fourth National Report on Human Exposures to Environmental Chemicals (tables updated to January 2017), in which the Centers for Disease Control and Prevention (CDC)

analyzed data released by the National Health And Nutrition Examination Survey (NHANES) (18). We examined geometric mean BPA and phthalate levels in children ages 12–19 in the years 2007–2008 when the environmental chemicals were assayed.

Measurement of Urinary BPA and Phthalates

Twenty two phthalate metabolites and BPA in urine samples were measured at the Wadsworth Center, New York State Department of Health. Specifically, we analyzed the phthalate metabolites reported in Table 1. BPA and phthalate metabolites levels were assayed in freshly voided samples that were obtained at the baseline visit in the CKiD study and subsequently stored in a biorepository. We excluded the following chemicals for which 50% or more of the samples contained concentrations below the limit of detection: MCHP, MICOP, MCINP, MPEP, MOP, MINP.Urinary creatinine concentrations were also measured in these specimens. Detailed methods about the measurements of these chemicals and the assays used are provided in the Appendix.

Measures of Renal Function and Blood Pressure

Estimated glomerular filtration rate (eGFR) was calculated using the modified equation formulated by Schwartz and colleagues:

eGFR (ml/min/1.73 m^2) = 0.413 × L (cm)/serum creatinine (19). This formula was used because the older Jaffe reaction that was used to measure serum creatinine concentration has been replaced by an enzymatic method that results in lower determinations.

The urinary protein to creatinine ratio (UPCR) was measured by obtaining a first morning urine sample. The log-transformed UPCR was also calculated because UPCR had a skewed distribution.

Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured at the CKiD baseline visit in a standard fashion using an aneroid sphygmomanometer. Three BP measurements were taken at 30 second intervals using the subject's right arm. Values for blood pressure were standardized to z-scores according to the National High Blood Pressure Education Program Fourth Report (20).

Demographics and other characteristics

In CKiD, information was collected about date of birth, gender, race and ethnicity (Caucasian, African American, American Indian, Asian, Multi-racial, Hispanic/Latino, and Other), birth weight, gestational age, body mass index (BMI) and BMI z-scores, subjects' underlying kidney disease, including age of onset, and other disease comorbidities.

Statistical Analysis

We conducted descriptive, univariate, bivariate and multivariable analyses with Stata Version 14.1. Urinary metabolite concentrations of chemicals were log-transformed to account for skewed distributions.

We analyzed combined phthalate metabolites in groups corresponding to their use in product categories. We expressed the low-molecular weight (LMW) phthalate concentration as the

sum of the molar concentrations of MEP, MBP, MIBP, MMP, MIDP and MCPP. The high-molecular weight (HMW) phthalate concentration was calculated as the sum of the molar concentrations of MECPP, MEHHP, MEOHP, MBZP, MHXP, MHPP, MCMHP, MIDP, and MCHPP. DEHP was calculated as the sum of the molar concentrations of MECPP, MEHHP, MEOHP, MHPP, and MCMHP. Dioctyl phthalate (DOP) was calculated as the sum of the molar concentrations of MCPP and MCHPP. We adjusted for urinary dilution by including urinary creatinine in all regression models.

We performed univariate and multivariable regressions of the log-transformed micromolar concentrations of phthalate metabolite groups (LMW, HMW, DEHP and DOP) and BPA with eGFR, SBP and DBP z-scores, and UPCR. In secondary multivariable analyses, we also analyzed individual phthalates. In addition, we stratified our analyses by both sex and the presence of glomerular disease. The diagnosis of glomerular disease was based on clinical findings (hematuria, hypertension, edema, and a confirmatory kidney biopsy), Since our statistical analysis examined urinary levels of multiple chemicals, we accounted for the risk of multiple comparisons by applying a more stringent threshold level to define statistical significance, namely a P value less than 0.01 (21). As such, we adjusted the p-value for significance from 0.05 to 0.01 by taking into account BPA and the four combined phthalate metabolites (LMW, HMW, DEHP and DOP), which were the five primary chemicals considered.

For univariate models, we adjusted for urinary creatinine. For multivariable models, we adjusted for BMI z-scores, demographic characteristics (race/ethnicity, age, and gender), birthweight, prematurity, presence of glomerular disease, use of relevant medications such as ACE-inhibitor and angiotensin receptor antagonist, urinary creatinine, and urinary cotinine. The latter factor was included because of its association with kidney function. A measure of tobacco use, cotinine was analyzed categorically based on available clinical information to account for passive exposure to tobacco (<20 ng/mL cotinine concentration) (22, 23). When BP was not the outcome, we adjusted for systolic and diastolic blood pressure as well. In supplemental analyses using multivariable models, we also included serum albumin as a covariate for all three outcomes. These clinical and laboratory measures were selected as covariates because they are associated with severity and progression of CKD and exposure to the environmental chemicals. Inclusion of all of these factors was justified because they are linked to the three measures of kidney function and elimination of any one might have altered the results. As a sensitivity analysis, we removed prematurity and birth weight from the models and assessed whether the coefficients changed by ≤15% as a potential for confounding.

Results

Population Characteristics and Chemical Exposures

We analyzed 538 participants who had available baseline and serial specimens from the CKiD Study. This enabled both the current cross-sectional study and the preparation of future reports describing the relationship of longitudinal exposure to the environmental chemicals on kidney function. The subset of participants included in this study is comparable to the complete cohort enrolled into CKiD (24, 25). Table 2 shows the study

population's characteristics and Table 3 summarizes levels of environmental chemicals collected in participants' urine samples. Specifically, the geometric mean for urinary BPA was 0.69 ng/mL (95% CI: 0.61, 0.78), and the geometric mean for urinary phthalates ranged from 0.03 ng/mL (95% CI: 0.02, 0.03) for DOP to 32.76 ng/mL (95% CI: 28.27, 37.97) for phthalic acid (PA).

We found that levels of BPA and phthalates reported in NHANES and analyzed by the CDC were consistently higher than those found in our analysis of samples from CKiD participants. Sample collection and storage and analytic procedures were similar in the CKiD and NHANES cohorts. For example, the geometric mean for urinary BPA levels was 2.45 ng/mL (95% CI: 2.14, 2.80) among children 12–19 years of age in NHANES, substantially higher than the geometric mean reported in the CKiD analyses. Similarly, for phthalates, we found consistently higher concentrations across the years in NHANES compared to the levels in our study population. CDC data with geometric means and 95% confidence intervals are reported in Table 3 for comparison. We are unable to perform statistical comparisons between the information provided by CKiD and the National Report on Human Exposure to Environmental Chemicals (Updated Tables, January 2017) for continuous variables because raw data is unavailable in the report prepared by the CDC and only percentiles and geometric means are provided. We were able to compare categorical data in the two study populations.

To evaluate possible exposure differences across the study period, we compared urinary samples obtained by CKiD in 2005–2008 and 2009–2014 with data obtained by the CDC during the corresponding years. We found minimal differences in urinary BPA and phthalate concentrations between the two periods examined (Appendix, Table A1).

We also examined whether chemical levels significantly differed between children with glomerular and non-glomerular CKD. Urinary concentrations of BPA and combined and individual phthalate metabolites did not significantly differ between these two groups of children and adolescents with CKD.

Univariate Analyses

For both univariate and multivariable regression analyses, the precise number of participants fluctuated depending on the availability of covariate values collected through CKiD. Univariate regression analyses were performed for log transformed BPA and single and combined phthalate metabolites adjusted for urinary creatinine to account for urinary dilution. These results are presented in the Appendix (Tables A2–A4). There was no significant association between BPA and any index of kidney function. No log transformed single or combined phthalate metabolite had a significant association with SBP or DBP z-scores (Appendix, Table A2). For eGFR, a one log unit increase in MMP, MEP, MIBP, MECPP, MEHHP, MEOHP, MHPP, and LMW phthalates were associated with significant increases in eGFR, while MCMHP, MCHPP, MIDP were associated with significant decreases in eGFR (Appendix, Table A3). Secondary analyses of single phthalate metabolites revealed an inverse association between specific chemicals, namely MMP, MBP, MIBP, MECPP, MEHHP, MHXP and MHPP, and UPCR.

Multivariable Analyses

In multivariable analyses, there were no associations between BPA exposure and any index of kidney function. Associations between specific phthalate metabolites, both single and combined, and health outcomes are reported in Tables 4 (BP) and 5 (eGFR). Secondary multivariable analyses were also performed to isolate the single phthalate metabolites that may have been driving significant associations. No single or combined phthalate metabolites were found to have a significant association with either SBP or DBP z-scores (Table 4). For eGFR, a one log unit increase in LMW phthalates was significantly associated with a 3.46 unit increase in eGFR (95% CI: 1.85, 5.07; p<0.001). For individual chemicals, a one log unit increase in MMP was significantly associated with a 3.97 unit increase in eGFR (95% CI: 2.45, 5.48; p<0.001). A similar association was identified for MEP (with a 1.84 unit increase in eGFR; 95% CI: 0.60, 3.09; p=0.004), MIBP (with a 5.26 unit increase in eGFR; 95% CI: 3.76, 6.77; p<0.001), MECPP (with a 2.35 unit increase in eGFR; 95% CI: 1.44, 3.26; p<0.001), MEHHP (with a 2.40 unit increase in eGFR; 95% CI: 1.15, 3.64; p<0.001), MEOHP (with a 1.85 unit increase in eGFR; 95% CI: 0.78, 2.91; p=0.001), and MHPP (with a 2.00 unit increase in eGFR; 95% CI: 1.08, 2.93; p<0.001). We also identified a −2.30 unit change in eGFR (95% CI: −3.74, −0.85; p=0.002) for each log unit increase in MCMHP, and a −1.55 unit change in eGFR (95% CI: - 2.49, −0.61; p=0.001) for MCHPP (Table 5).

In addition, we found a significant inverse association between UPCR and MMP, such that for each log unit increase of MMP we identified a −17.98 percent change in UPCR (95% CI: −24.94, −10.14; p<0.001). A similar association was identified for MBP (−22.74 percent change; 95% CI: −34.54, −9.08; p=0.002), MIBP (−28.07 percent change; 95% CI: −36.84, −18.18; p<0.001), MECPP (−10.20 percent change; 95% CI: −15.80, −4.95; p<0.001), MEHHP (−13.23 percent change; 95% CI: −20.34, −5.38; p=0.001), MEOHP (−9.23 percent change; 95% CI: −15.04, −2.91; p=0.005), MBZP (−16.21 percent change; 95% CI: −25.74, −5.50; p=0.004), MHXP (−7.71 percent change; 95% CI: −11.46, −3.66; p<0.001), MHPP (−8.69 percent change; 95% CI: −12.40, −4.70; p<0.001), and LMW phthalates (−9.53 percent change; 95% CI: −14.21, −4.21; p=0.001) (Table 6).

We also performed multivariable analyses stratified by sex and the presence of glomerular disease. Overall, the results of the stratified analyses (Appendix, Tables A5–A10), were largely consistent with our results from non-stratified multivariable analyses.

In addition, we performed sensitivity analyses with serum albumin, a marker for nutritional status, as a covariate in our multivariable model. The results are consistent with those from multivariable models without serum albumin as a covariate. We have highlighted those coefficients that changed at least 10% from multivariable analyses without serum albumin (Appendix, Tables A11-A13). Removal of prematurity and birthweight from the models had minimal effects on the findings and the coefficients for all chemicals and eGFR and proteinuria were changed by ≤15%. These data are summarized in Appendix Tables A14 and A15. Although we did not assess the impact of each individual covariate separately, we ran multiple models testing groups of covariates. The associations were robust to different model specifications without any one group of variables driving confounding.

Discussion

This study represents the first comprehensive assessment of exposure to organic pollutants in an at-risk population, namely children with CKD. The main finding of our analysis is that urinary BPA and phthalate levels in the study population of children with CKD were lower than in the general population. When we compared our analysis of the CKiD study with nationally representative data compiled by the CDC, we found that urinary BPA and phthalate levels in our CKD cohort were consistently lower than in healthy children. This was contrary to our expectation that children with CKD would have higher urinary levels of these chemicals as a result of increased risk of exposure.

The most parsimonious explanation for the lower urinary of BPA and phthalates is reduced intake of these chemicals. Pediatric patients with CKD may have healthier dietary habits than the general population. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), health problems associated with pediatric CKD, such as slowed growth and lack of energy, can be delayed or prevented with a diet that regulates intake of food, including protein, minerals, and vegetables, to an amount appropriate for a child's specific age, weight, and height (26). If children with CKD do, in fact, follow a healthy diet, which may include more fresh foods and less canned foods, they are likely exposed to less BPA and phthalates in food packaging. We considered this possibility and performed additional multivariable analyses with albumin incorporated as a covariate as a preliminary index of nutritional status and the findings were unchanged. However, additional studies are needed that incorporate more detailed assessment of diet and more sensitive markers of adequacy of nutrition to address the relationship between specific elements of the diet, environmental chemical exposure, and renal outcomes in children with CKD.

An alternative explanation for our findings is that CKD may be associated with tubulointerstitial fibrosis, and exposure to the environmental chemicals may exacerbate the tubular injury. The net result may be reduced tubular secretion of the molecules. Renal excretion accounts for most of the clearance of BPA and phthalates and their metabolites and tubular secretion is the primary route of elimination (27, 28). If this process is impaired, then it may result in retention of BPA and phthalates within the renal tubular epithelial cell with the potential for sustained injury. This underscores the need to develop better indices of exposure to environmental chemicals in patients with CKD because unlike healthy children the urinary concentrations may be influenced by kidney function per se and not be a sole reflection of exposure. Mean BPA and phthalate levels did not significantly differ between children with and without glomerular disease. This finding may reflect a comparable degree of tubular injury in both categories of CKD. However, the contribution of tubular secretion and delineation of the transport system requires further study. We plan to measure urinary excretion of biomarkers of tubular injury (neutrophil gelatinase-associated lipocalin [NGAL] and kidney injury molecule-1 [KIM-1]) in this cohort which should clarify the impact of BPA and phthalates on damage to the renal tubular epithelium in children with CKD.

When we explored the possible association of urinary BPA and phthalates and renal and cardiovascular health outcomes, BPA was not significantly associated with BP, UPCR, or eGFR and LMW phthalates were the only combined phthalates associated with eGFR and

UPCR in non-stratified multivariable analyses. Secondary analyses of individual phthalate metabolites revealed a positive significant association between select individual phthalate metabolites and eGFR. These findings regarding eGFR may be explained by a state of early glomerular hyperfiltration associated with exposure to BPA and phthalates. Glomerular hyperfiltration is conventionally defined as a GFR that is more than two standard deviations above the mean among healthy individuals. It reflects an adaptive response following nephron loss and has been proposed as a mechanism for progressive renal injury leading to end stage kidney disease (29, 30). To the best of our knowledge, no epidemiologic studies have examined an association between BPA and phthalates and glomerular hyperfiltration. However, a recent study found that podocytes from mice exposed to BPA *in vitro* had reduced viability, increased apoptosis, and diminished expression of nephrin and podocin. *In vivo* exposure to BPA caused increased albuminuria and GFR (31). Oxidant stress induced by exposure to BPA and phthalates may trigger hyperfiltration similar to what is observed in pediatric patients with type 1 diabetes mellitus (32). Thus, an increased eGFR may be associated with glomerular hyperfiltration and increased short-term clearance of BPA and phthalates. Early onset of hyperfiltration could contribute to latent and long-term decline of GFR among children with CKD, possibly accelerating progressive renal decline from a young age.

The lack of association between BPA and phthalate exposure and BP was based on the normative data in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (33). It is unlikely that the use of the modified BP tables in the recently released fifth report would substantially alter these findings (34).

Most of the phthalate metabolites that were positively associated with eGFR manifested a negative association with UPCR. A variety of studies have indicated that proteinuria is an important and independent risk factor for the progression of renal disease and decline in GFR in adults (35, 36) and children (37, 38) with CKD. We acknowledge that the phthalates individually have divergent effects on eGFR. The same two phthalates, MCMHP and MCHPP, that were significantly associated with reduced GFR also showed a trend in increased proteinuria. We anticipate that further longitudinal studies may serve to clarify these disparate associations observed to determine what if any effect the individual phthalates have on long-term kidney function in children with CKD.

Our cross-sectional results suggest that phthalates and BPA are not associated with decreased GFR or increased UPCR and BP in children with CKD. A cautionary note is warranted with regard to BPA. The potential adverse effects of bisphenols need to be readdressed to evaluate the safety of molecules, such as Bisphenol S (BPS), that have been introduced as replacements for BPA in the same consumer and medical products (39).

While cross-sectional studies provide a valuable snapshot of an association between outcomes and exposures, they have inherent limitations. Monoesters of phthalates typically have a half-life of approximately 12 hours (40), which may present difficulties in assessing renal and cardiovascular outcomes from sustained exposure. In order to account for the rapid elimination of these organic chemicals, it will be important to incorporate biomarkers of target organ injury into studies of the adverse effects of these environmental toxicants. Our

results may be explained by unaccounted confounding factors that may relate to children with CKD. Our findings may also be explained by the possibility of reverse causation among the sample, i.e. children with greater eGFR are able to excrete phthalates more efficiently. To overcome these limitations, longitudinal studies with repeated measures are underway and are likely to yield more informative findings about the possible adverse health effects of prolonged exposure to BPA and phthalates in children and adolescents with CKD.

Conclusion

To our knowledge, this cross-sectional study is the first to examine BPA and phthalate exposure in children with CKD and provides the basis for the evaluation of the long-term effects of these exposures in this at-risk population (41, 42). The results show that, in our study cohort, urinary excretion of BPA and phthalates is lower than in the general population. For select phthalate metabolite excretion, there was a direct relationship between eGFR and an inverse relationship with UPCR. There were no relationships with BP. Longitudinal studies are underway to evaluate the renal and cardiovascular outcomes in these children with CKD who might have increased exposure to BPA and phthalates and heightened vulnerability to the consequences compared to healthy children. Identification of environmental chemical exposures as a modifiable risk factor for kidney disease progression in children and adolescents could contribute to decreasing the disease burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of environmental chemicals with abbreviations

DEHP	
DOP	dioctyl phthalate
HMW	high molecular weight
LMW	low molecular weight
MBP	
MBZP	
MCHPP	
MCMHP	
MCHP	

MCINP

MCPP

MECPP

MEHHP

MEOHP

MEP

MHPP

MHXP

MIBP

MICOP

MIDP

MINP

MMP

MOP

MPEP

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Highlights

1. Exposure to short-acting organic chemicals is lower in children with chronic kidney disease (CKD) compared to healthy controls
2. Exposure to bisphenol A has no effect on kidney function in children with CKD.
3. Exposure to select phthalates is associated with increased in kidney function and reduced proteinuria in children with CKD
4. Longitudinal studies are needed to ascertain the long-term impact of these environmental chemicals.

Table 1.

Categorization of Phthalate Metabolites

Phthalate parent compound	Category	Metabolite
		Phthalic Acid (PA)
Dimethyl phthalate (DMP)	LMW[a]	Monomethylphthalate (MMP)
Diethyl phthalate (DEP)	LMW	Monoethylphthalate (MEP)
Di-N-butyl phthalate and	LMW	Mono-n-butylphthalate (MBP)
di-isobutyl phthalate (DBP)	LMW	Mono-isobutylphthalate (MiBP)
Butyl benzyl phthalate	HMW[b]	Monobenzyl phthalate (MBZP)
Dioctyl phthalate (DOP)	HMW	Mono(3-carboxypropyl) phthalate (MCPP)
	HMW	Mono-(7-carboxy-*n*-heptyl) phthalate (MCHPP)
Diethylhexyl phthalate (DEHP)	HMW	Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)
		Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
		Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)
		Mono-[(2-carboxymethyl) hexyl] phthalate (MCMHP)
Dihexyl phthalate (DHxP)	HMW	Mono-hexylphthalate (MHxP)
Diisoheptyl phthalate (DIHpP)	HMW	Mono-2-heptyl phthalate (MHpP)
Diisodecyl phthalate (DIDP)	HMW	Mono-(8-methyl-1-nonyl) phthalate (MIDP)
Diisopropyl phthalate (DiPP)	LMW	Monoisopropyl phthalate (MIPRP)

[a]LMW, low-molecular weight phthalates, are added to personal care product to preserve scent.

[b]HMW, high-molecular weight phthalates are used as plasticizers of polyvinyl chloride (PVC) to increase flexibility, and can be found in a variety of settings ranging from flooring, clear food wrap and intravenous tubing (Schettler, 2006).

Table 2.

Characteristics of the Study Population

Characteristics		Mean (SE) or n (%)
Sex	Female	194 (36.06)
	Male	344 (63.94)
Age at Study Visit (years)		10.77 (0.18)
Race	Caucasian	363 (67.47)
	African American (AA)	92 (17.10)
	American Indian, Native Hawaiian, Asian, Other	36 (6.69)
	More than one race (excluding AA)	24 (4.46)
	More than one race (including AA)	23 (4.28)
Hispanic or Latino Origin	Hispanic	75 (13.94)
	Not Hispanic	456 (84.76)
	Missing	7 (1.30)
Child's Primary Diagnosis	Glomerular	63 (11.71)
	Non-glomerular	475 (88.29)
Birth Weight (grams)		3078.58 (33.34)
Low Birth Weight	Yes	97 (18.03)
	No	411 (76.39)
	Missing	30 (5.58)
Premature Birth (gestational age less than 36 weeks)	Yes	62 (11.52)
	No	453 (84.20)
	Missing	23 (4.28)
Body Mass Index (BMI)		19.87 (0.23)
BMI Z-Score *		0.41 (0.05)
Systolic BP		106.01 (0.56)
Systolic BP Z-Score †		0.32 (0.05)
Diastolic BP		65.69 (0.51)
Diastolic BP Z-Score †		0.52 (0.04)
Currently Taking ACE Inhibitor	Yes	241 (44.80)
	No	297 (55.20)
Currently Taking ARB	Yes	47 (8.74)
	No	491 (91.26)
Urinary Cotinine (ng/mL)		6.69 (2.20)
Urine Creatinine (mg/dL)		554.98 (27.55)
Estimated GFR (ml/min| $1.73m^2$)		51.48 (0.75)
Urinary Protein to Creatinine Ratio		0.86 (0.07)
Serum albumin (g/dL)		4.35 (0.02)

* BMI z-score based on age and gender.

[†]Blood pressure z-scores based on age, gender, and height.

Table 3.

Distribution of the Urinary Concentrations of the Examined Chemicals (ng/mL) in the CKiD Study and the Fourth National Report on Human Exposure to Environmental Chemicals

Chemical (CKiD, N=538)	CKiD Median (IQR)	CKiD Geometric Mean (95% CI)	CDC Geometric Mean (95% CI)
BPA	0.78 (0.18, 1.66)	0.69 (0.61, 0.78)	2.45 (2.14, 2.80)
Single Phthalate Metabolites			
PA	42.18 (14.73, 95.95)	32.76 (28.27, 37.97)	N/A*
MMP	2.00 (1.06, 3.41)	1.96 (1.79, 2.14)	N/A
MEP	14.46 (6.71, 40.11)	17.39 (15.48, 19.52)	98.6 (79.1, 123)
MCPP	2.14 (1.34, 3.64)	2.36 (2.19, 2.55)	3.81 (3.15, 4.61)
MBP	8.58 (5.11, 14.45)	8.71 (8.08, 9.38)	N/A
MIBP	3.31 (1.97, 6.31)	3.38 (3.10, 3.68)	10.2 (8.53, 12.3)
MECPP	0.77 (0.41, 6.73)	1.61 (1.38, 1.89)	44.3 (35.2, 55.9)
MEHHP	3.12 (1.53, 8.60)	3.86 (3.46, 4.30)	29.8 (22.5, 39.3)
MEOHP	1.46 (0.69, 4.999)	1.91 (1.69, 2.17)	16.9 (12.8, 22.3)
MBZP	7.22 (3.99, 15.51)	7.68 (7.00, 8.41)	11.6 (9.56, 14.2)
MHXP	0.20 (0.09, 0.48)	0.18 (0.16, 0.21)	N/A
MHPP	0.82 (0.18, 1.73)	0.54 (0.47, 0.63)	N/A
MCMHP	11.85 (6.59, 24.2)	12.69 (11.56, 13.92)	N/A
MCHPP	5.47 (0.65, 12.06)	3.22 (2.74, 3.78)	N/A
MIDP	0.01 (0.01, 0.96)	0.06 (0.05, 0.07)	N/A
MIPRP	0.10 (0.1, 1.09)	0.34 (0.30, 0.40)	N/A
Combined Phthalate Metabolites			
LMW Phthalates	0.19 (0.11, 0.39)	0.22 (0.20, 0.24)	N/A
HMW Phthalates	0.16 (0.09, 0.29)	0.17 (0.16, 0.19)	N/A
DEHP Metabolites	0.09 (0.05, 0.18)	0.10 (0.09, 0.11)	N/A
DOP Metabolites	0.02 (0.01, 0.05)	0.03 (0.02, 0.03)	N/A

MOP (83% <LOD), MCINP (56% <LOD), MCHP (76%), MINP (75%), MPEP (70%), and MCIOP (50%) were excluded from analyses because of the high percentage of <LOD. For all chemicals included in the table and analysis, the number of samples below LOD was <50%.

*N/A refers to those chemicals which are not evaluated in the Fourth National Report on Human Exposure to Environmental Chemicals or had too many values >LOD.

Table 4.

Multivariable Linear Regression Analysis of Systolic and Diastolic Blood Pressure Z-Scores with Log Transformed Urinary BPA and Phthalate Metabolites

Chemical (N=452)	Changes in Systolic Blood Pressure Z-Scores (95% CI)	Changes in Diastolic Blood Pressure Z-Scores (95% CI)
BPA	−0.004 (−0.08, 0.07)	−0.02 (−0.09, 0.05)
Single Phthalate Metabolites		
PA	0.01 (−0.05, 0.07)	0.001 (−0.05, 0.06)
MMP	−0.03 (−0.12, 0.07)	−0.05 (−0.15, 0.04)
MEP	0.01 (−0.07, 0.09)	−0.01 (−0.09, 0.06)
MCPP	−0.06 (−0.17, 0.05)	−0.02 (−0.13, 0.08)
MBP	−0.04 (−0.16, 0.08)	0.01 (−0.11, 0.12)
MIBP	−0.11† (−0.21, −0.01)	−0.05 (−0.15, 0.04)
MECPP	0.03 (−0.03, 0.09)	0.01 (−0.05, 0.06)
MEHHP	0.02 (−0.06, 0.10)	0.03 (−0.04, 0.11)
MEOHP	0.02 (−0.05, 0.08)	0.02 (−0.04, 0.09)
MBZP	−0.03 (−0.12, 0.06)	−0.03 (−0.12, 0.06)
MHXP	−0.002 (−0.07, 0.06)	−0.01 (−0.07, 0.05)
MHPP	−0.07† (−0.13, −0.01)	−0.05 (−0.11, 0.005)
MCMHP	−0.03 (−0.12, 0.06)	−0.0004 (−0.09, 0.09)
MCHPP	−0.04 (−0.10, 0.02)	−0.02 (−0.08, 0.03)
MIDP	−0.02 (−0.06, 0.02)	−0.01 (−0.04, 0.03)
MIPRP	−0.01 (−0.07, 0.04)	−0.03 (−0.08, 0.03)
Combined Phthalate Metabolites		
LMW Phthalates	0.01 (−0.10, 0.11)	−0.01 (−0.11, 0.09)
HMW Phthalates	−0.02 (−0.13, 0.08)	0.01 (−0.09, 0.11)
DEHP Metabolites	−0.002 (−0.10, 0.09)	0.01 (−0.08, 0.10)
DOP Metabolites	−0.05 (−0.15, 0.06)	−0.02 (−0.11, 0.08)

Adjusted for the following covariates: sex, age at visit, race, ethnicity, glomerular disease, birth weight, low birth weight, prematurity, BMI z-score, use of ACE-I/ARB, urinary creatinine, and urinary cotinine.

† The p-value <0.05 but exceeds Bonferroni-corrected p-value <0.01.

Table 5.

Multivariable Linear Regression Analysis of Estimated Glomerular Filtration Rate (ml/min|1.73m^2) with Log Transformed Urinary BPA and Phthalate Metabolites

Chemical (N=451)	eGFR Changes (95% CI)
BPA	−0.70 (−1.87, 0.47)
Single Phthalate Metabolites	
PA	0.56 (−0.36, 1.49)
MMP	**3.96 (2.45, 5.48) P<0.001**
MEP	**1.84 (0.60, 3.09) P=0.004**
MCPP	1.24 (−0.48, 2.95)
MBP	2.26[†] (0.39, 4.13)
MIBP	**5.26 (3.76, 6.77) P<0.001**
MECPP	**2.35 (1.44, 3.26) P<0.001**
MEHHP	**2.40 (1.15, 3.64) P<0.001**
MEOHP	**1.85 (0.78, 2.91) P =0.001**
MBZP	−0.35 (−1.85, 1.14)
MHXP	1.15[†] (0.13, 2.17)
MHPP	**2.00 (1.08, 2.93) P<0.001**
MCMHP	**−2.30 (−3.74, −0.85) P=0.002**
MCHPP	**−1.55 (−2.49, −0.61) P =0.001**
MIDP	−0.44 (−1.02, 0.13)
MIPRP	0.81 (−0.10, 1.72)
Combined Phthalate Metabolites	
LMW Phthalates	**3.46 (1.85, 5.07) P<0.001**
HMW Phthalates	0.39 (−1.30, 2.09)
DEHP Metabolites	1.01 (−0.51, 2.53)
DOP Metabolites	−0.80 (−2.42, 0.82)

Adjusted for the following covariates: sex, age at visit, race, ethnicity, glomerular disease, birth weight, low birth weight, prematurity, BMI z-score, use of ACE-I/ARB, SBP and DBP z-scores, urinary creatinine, and urinary cotinine.

[†]The p-value <0.05 but exceeds Bonferroni-corrected p-value <0.01.

Table 6.

Multivariable Linear Regression Analysis of Urinary Protein to Creatinine Ratio with Log Transformed Urinary BPA and Phthalate Metabolites

Chemical (N=436)	UPCR* (95% CI)
BPA	−0.12 (−6.25, 6.61)
Single Phthalate Metabolites	
PA	−5.94 (−11.51, 0.04)
MMP	**−17.98 (−24.94, −10.14) P<0.001**
MEP	−8.74† (−16.57, −0.11)
MCPP	−10.44† (−18.83, −0.85)
MBP	**−22.74 (−34.54, −9.08) P=0.002**
MIBP	**−28.07 (−36.84, −18.18) P<0.001**
MECPP	**−10.20 (−15.80, −4.95) P<0.001**
MEHHP	**−13.23 (−20.34, −5.38) P=0.001**
MEOHP	**−9.23 (−15.04, −2.91) P=0.005**
MBZP	**−16.21 (−25.74, −5.50) P=0.004**
MHXP	**−7.71 (−11.46, −3.66) P<0.001**
MHPP	**−8.69 (−12.40, −4.70) P<0.001**
MCMHP	3.20 (−3.76, 11.00)
MCHPP	3.95 (−1.10, 9.39)
MIDP	0.55 (−2.61, 3.86)
MIPRP	−5.14 (−10.80, 0.93)
Combined Phthalate Metabolites	
LMW Phthalates	**−9.53 (−14.21, −4.21) P=0.001**
HMW Phthalates	−7.15† (−13.01, −0.45)
DEHP Metabolites	−6.35† (−11.45, −0.60)
DOP Metabolites	−0.90 (−8.60, 7.83)

Adjusted for the following covariates: sex, age at visit, race, ethnicity, glomerular disease, birth weight, low birth weight, prematurity, BMI z-score, use of ACE-I/ARB, SBP and DBP z-scores, urinary creatinine, and urinary cotinine.

*UPCR changes are presented as percent change in the original unit of measurement for one log unit increase of the chemicals examined.

†The p-value <0.05 but exceeds Bonferroni-corrected p-value <0.01.