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Urinary Phthalate Exposure and Kidney Outcomes in Chronic Kidney Disease: Evidence from Longitudinal and Experimental Approaches

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Objectives : Urinary phthalate metabolites, due to their rapid metabolism, reflect only short-term exposure, making single measurements insufficient for assessing long-term health effects. This study investigates the association between urinary phthalate metabolites and kidney function by utilizing repeated measurements in chronic kidney disease (CKD) patients.
Methods : This study included CKD patients from the SKETCH (Study on Kidney disease and EnvironmenTal Chemicals, NCT04679168) cohort, who were followed quarterly over one year. Urine samples collected at each visit were analyzed for nine phthalate metabolites. The associations between phthalate metabolites and kidney outcomes were assessed using a Cox proportional hazards model. To support mechanistic plausibility, in vitro assays were conducted using HK-2 human renal proximal tubular epithelial cells. Cells were exposed to MCPP at concentrations of 10 nM and 100 nM, and cell viability was assessed at 24, 48, and 72 hours using the CCK-8 assay.
Results : Among 285 CKD patients (eGFR ≥45: n=112; <45 mL/min/1.73m²: n=173), urinary MCPP (aHR 1.02, 95% CI 1.01–1.04) and DiNP (aHR 1.02, 95% CI 1.01–1.03) were significantly associated with increased risk of kidney dysfunction. These associations were evident only in patients with eGFR <45, while no significant effects were observed in those with eGFR ≥45. In patients with eGFR <45, MCPP showed a consistent harmful effect in diabetics. DiNP increased risk in subgroups with diabetes, BMI ≥25, or smoking, but was associated with decreased risk in non-diabetic, normal-weight, or non-smoking patients. In vitro, MCPP exposure (10 nM and 100 nM) significantly reduced HK-2 cell viability in a time-dependent manner, supporting its direct nephrotoxic potential.
Conclusions : Repeated measurements of urinary phthalate metabolites revealed that MCPP and DiNP are significantly associated with kidney dysfunction, particularly in patients with eGFR <45. The

findings highlight the importance of considering kidney function and individual characteristics when evaluating phthalate exposure risks.