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Glyphosate Exposures and Kidney Injury Biomarkers in Infants and Young Children

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Abstract

The goal of this study was to assess biomarkers of exposure to glyphosate and assess potential associations with renal function in children. Glyphosate is used ubiquitously in agriculture worldwide. While previous studies have indicated that glyphosate may have nephrotoxic effects, few have examined potential effects on kidney function in children. We leveraged three cohorts across different phases of child development and measured urinary levels of glyphosate. We evaluated associations of glyphosate with three biomarkers of kidney injury: albuminuria (ACR),

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Author Contributions Statement

L.T. conceived and designed the study. M.M. and R.G. supported data and specimen collection for Starting Early, while S.S., K.W. and D.C. supported data collection for Healthy Start and PEEPS. K.K. and R.K. characterized samples and performed analysis for urinary glyphosate. D.M. processed samples to measure renal injury biomarker levels, while H.T. supported interpretation. L.T. and S.I. drafted the main manuscript text, performed statistical data analysis, interpreted the results, and prepared tables 1–4. All authors discussed the results, reviewed, and commented on the manuscript. All authors gave their final approval of this manuscript.

CONFLICT OF INTEREST

The authors have no financial conflicts of interest to disclose

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neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury marker 1 (KIM-1). Multivariable regression analyses examined associations of glyphosate with kidney injury biomarkers controlling for covariates. We identified glyphosate in 11.1% of the total participants. The herbicide was particularly detected more frequently in the neonate population (30%). Multivariable regression models failed to identify significant associations of log-transformed glyphosate with any of the kidney injury biomarkers, controlling for covariates age, sex, and maternal education. While we confirm detectability of glyphosate in children's urine at various ages and stages of life, there is no evidence in this study for renal injury in children exposed to low levels of glyphosate. Further studies of larger sample size are indicated to better understand putative deleterious effects of the herbicide after different levels of exposure.

Graphical Abstract

Capsule

Glyphosate is detectable in the urine of 11% of infants and young children (30% of neonates). However, there is no association with albuminuria or biomarkers of renal tubular injury.

Keywords

Glyphosate; nephrotoxicity; children; environmental exposures; renal biomarkers

1. Introduction

Genetically modified organism (GMO) crops now comprise 90% of corn and soybean planted in the US. While 2000 and 2004 National Academy of Sciences reviews identified no health hazards,(1) they focused primarily on genetic modifications in GMOs, and concerns were raised in both reports about potential health effects of herbicides such as glyphosate used to limit weeds.

Initial biomonitoring studies of glyphosate infrequently detected glyphosate in farmers and their families, or otherwise identified levels below the EPA reference dose which is subject to change over time.(2) There is limited information about glyphosate exposure in

occupational settings and in the general population (3) In particular, there are little data on glyphosate exposure in pediatric patients, especially infants and toddlers (4, 5). These studies preceded the rapid increase in glyphosate that has occurred since 2000. More recent work has detected higher levels in food(6) and humans,(7). Average urinary glyphosate levels in occupationally exposed subjects range from 0.26 to 73.5 $\mu\text{g/L}$ while urinary levels due to environmental exposure are considerably lower, 0.16 to 7.6 $\mu\text{g/L}$ (3). Recent studies document effects in animals at environmentally relevant levels including oxidant stress,(8, 9) anti-androgenicity, and anti-estrogenicity,(10) and possible carcinogenicity.(11, 12) In particular, substantial bioaccumulation has been documented in kidney,(13). Nephrotoxicity has been shown to correlate with an altered metatranscriptomic profile, specifically with disturbances in the expression of genes associated with fibrosis, necrosis, phospholipidosis, mitochondrial membrane dysfunction and ischemia.(14)

Recent studies have identified the kidney as a susceptible organ to glyphosate. Previous studies have associated glyphosate exposure with changes in renal function, kidney injury, and chronic kidney disease of unknown etiology.(15–17) There is growing evidence linking glyphosate exposure with the epidemic of chronic kidney disease of unknown origin in farm workers in Central America, Sri Lanka and central India (18). However, the few available studies have yielded limited information with the majority being case-control studies, and none have examined children. Most of these studies were performed in occupational settings on agricultural workers. There is a paucity of studies on glyphosate exposures effects on kidney function in children.

Children are well known to be vulnerable to the effects of environmental contaminants, due to their greater consumption of food and water per unit body weight, as well as their developing organ systems. There are limited studies that have examined potential health effects of early life exposure to chemicals, especially pesticides. Therefore, we conducted the following study in which we leveraged three cohorts across different phases of child development (newborns, infants and younger children) to test the hypothesis that the prevalence and levels of glyphosate exposure are significant in infants and young children. Our second objective was to evaluate associations of glyphosate (as measured in urine) with three urinary biomarkers of kidney injury. In addition to albuminuria, a marker of glomerular injury,(19, 20) we measured concentrations of neutrophil gelatinase-associated lipocalin (NGAL),(21) and kidney injury marker 1 (KIM-1),(22) markers of distal and proximal tubular injury, respectively.

2. Methods

2.1 Study Populations

We briefly describe a longitudinal birth cohort of children (Starting Early), in whom urine samples were measured at 10–19 months of age, as well as two cross-sectional studies Preventing Environmental Exposures in Pregnancy (PEEPS), and Bright Start which represent older children (ages 3–8) and newborns (<30 days), respectively. The three cohorts are comprised of chronologically ordered categories of age in children as follows: Bright Start (newborns), Starting Early, and PEEPS. Inclusion in the present study was determined if sufficient urine was available for the experimental testing. All research was performed in

accordance with relevant guidelines/regulations. In particular, informed consent was obtained from participants' parents or their legal guardians for use of collected samples for use in future studies such as this one of glyphosate exposure.

The detailed descriptions of the three cohorts are provided in the Supplemental Materials

2.2 Urine collection and storage

Urine samples for each cohort were obtained at study visits using age-appropriate methods (urine bags and cotton balls in untrained babies and infants, freshly voided urine in trained children) and immediately transferred to sterile polyethylene cups. Within 2 hours after collection from the infants, urine was transferred to cryovials for storage at -80°C prior to laboratory analysis. We measured urinary markers of kidney injury NGAL, and KIM1 using Luminex xMAP technology (see below). Urine albumin and creatinine were measured using standard methods of quantitative spectrophotometry at the ARUP National Reference Laboratory (Salt Lake City, Utah) and the results were used to calculate ACR (Albumin-to-Creatinine Ratio [mg:mg]).

2.3 Analysis of urine samples for glyphosate

200 μL of urine sample was transferred into a 15-mL polypropylene (PP) tube and spiked with the labeled internal standard mixture ($2\text{-}^{13}\text{C}$, 99%; ^{15}N , 98+% Glyphosate), allowed to stand at room temperature for 30 min and then diluted to 1.0 mL (5-fold dilution) with 1% formic acid in water. The diluted sample was vortexed for 1 min, centrifuged and filtered through a nonsterile regenerated cellulose (RC) membrane filters ($0.2\text{ }\mu\text{m}$; Phenomenex, Inc., Torrance, CA, USA). The filtrate then transferred into an auto sampler vial for LC-MS/MS analysis. An Agilent 1260 Series HPLC system (Agilent Technologies Inc., Santa Clara, CA, USA) coupled with an ABSCIEX 4500 QTRAP mass spectrometer (Applied Biosystems, Foster City, CA, USA) running under negative mode electrospray ionization was used for the analysis. An anion-exchange column, Dionex IonPac AS 21 ($2\text{ mm} \times 250\text{ mm}$, $7\text{ }\mu\text{m}$) was employed for the separation of target chemicals under isocratic elution condition with a mobile phase consist of 1% formic acid in water and acetonitrile (95:5) mixture. Isotopic dilution mass spectrometry with MRM mode of analysis was used for selective quantification of the target chemicals. The QA/QC protocols included matrix spike (mean spike recoveries ($n=5$) for glyphosate was 109.5%) and procedural blanks (non-detected or $<\text{LOQ}$). Mid-point calibration standard and HPLC grade water were injected between every 20 samples analyzed to check the instrument detection linearity and carry-over effects, respectively. The limit of detection (LOD) and the limit of quantification (LOQ) were calculated as three and ten times of signal to noise ratio, respectively. LOD for glyphosate was 0.1 ng/mL , and LOQ was 0.33 ng/mL .

2.4 Analysis of kidney injury biomarkers

NGAL was measured in human urine using the Luminex performance human kidney Biomarker kit (FCSTM16-01, R&D Systems). Urine samples were thawed and diluted 1:10 in calibrator diluent and protocol followed manufacturer's instructions. Data were captured on a Luminex MAGPIX instrument with xPonent 4.2 software. Standard curve R^2 values were 0.98 and high and low quality controls were within expected range. KIM-1 was

measured in human urine using the Milliplex MAP Human Kidney Injury Magnetic Bead Panel Kit (HKI1MAG-99K, EMD Millipore) Urine samples were thawed and diluted 1:2 in assay buffer and protocol followed manufacturer's instructions. Data were captured on a Luminex MAGPIX instrument with xPonent 4.2 software. Standard curve R^2 values were 0.97 and high and low quality controls were within the expected range.

2.5 Statistical Analysis

We first described the demographics of our study population (N=108), including age, sex, maternal education, race/ethnicity, BMI category, and intervention arm in the case of the Starting Early group. Body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, was used to measure adiposity in the Starting Early group. We used standardized BMI z scores given that BMI varies widely by age and sex, following the Centers for Disease Control and Prevention year 2000 norms.(23) Overweight and obese were categorized as BMI z-score of 1.036 or greater (85th percentile for age and sex) and 1.64 or greater (95th percentile), respectively. We calculated median glyphosate, albuminuria, KIM-1, and NGAL levels, as well as interquartile ranges for all biomarkers and percent detected for glyphosate levels by study group. We also described mean and standard deviation in each one of the mentioned biomarkers of interest in the total population.

Univariate regressions examined log-transformed glyphosate concentrations and their detectability (using logistic regression) as dependent variables with covariates examined singly. We created dummy variables for maternal education with one category for those children whose mothers did not complete a high school education and another for those whose mothers at least completed high school, and created a dummy variable for missing values (N=34) that we used as reference. We also created an ordinal variable reflecting the age of the children in increasing order from youngest to oldest type as follows: Healthy Start, Starting Early, and PEEPS (N=108). We also performed univariate analyses by study arm in the Starting Early sample (N=66).

Multivariable analyses of continuous log-transformed glyphosate exposure examined age, sex, and maternal education as predictors (N=108). We assessed differences in detectability of glyphosate using multivariable logistic regressions with age, sex, and maternal education as predictors. All regressions examining predictors of log-transformed glyphosate were retransformed from the logarithmic scale.

We then examined associations of glyphosate with kidney injury. First, we calculated Pearson correlation coefficients for all log-transformed kidney injury markers KIM-1, NGAL, and ACR, as well as log-transformed glyphosate levels. For glyphosate levels below the limit of detection (LOD), we imputed values equal to LOD/square root of 2. We also performed univariate and multivariable regressions of urinary log-transformed glyphosate as predictor of log-transformed kidney injury markers KIM-1, NGAL, and ACR, controlling for age, sex and maternal education. Sensitivity analyses were also included; we performed univariate and multivariable regressions of creatinine-adjusted urinary log-transformed glyphosate as predictor of log-transformed kidney injury markers KIM-1, NGAL, and ACR. Statistical analysis was performed with Stata/IC Version 14 (StataCorp: College Station, TX).

3. Results

The population was largely Hispanic, and comprised roughly equal numbers of males and females (Table 1). Only 4% of our participants had a mother with a college degree but the majority of parents in our study population graduated from high school (62.1%). The mean urinary glyphosate concentration was 0.278 ± 0.228 $\mu\text{g/mL}$, with a range of 0.105–2.125 $\mu\text{g/mL}$. We identified glyphosate in 11.1% of the participants. The herbicide was detected in 7.6–30% of the three cohorts: 30% of neonates had glyphosate exposure above the LOD, followed by PEEPS cohort (12.5%) and Starting Early (7.6%). We also observed a wide detection range in NGAL biomarkers. We also noted that 40% of children in the Starting Early cohort were overweight or obese.

Younger children had higher urinary levels of glyphosate in both univariate (-0.04 ng/mL , 95% CI: -0.07 , -0.01 ; Table 2) and multivariable (-0.16 ng/mL , 95% CI: -0.22 , -0.09) regressions. Children with mothers without a high school diploma had slightly lower levels of urinary glyphosate (-0.17 ng/mL , 95% CI: -0.25 , -0.08) relative to those with mothers who attained a high school education (-0.16 ng/mL , 95% CI: -0.24 , -0.07) in our multivariable regression. However, we found no other significant associations of demographic covariates with glyphosate in univariate or multivariable models. Similarly, we found no statistically significant associations of demographic factors in relationship to detectability of urinary glyphosate in children.

No univariate regressions with urinary glyphosate identified a statistically significant association with increased renal biomarker injury (KIM-1: 0.974 ng/mL , 95% CI: -17.92 , 27.78 ; NGAL: -663.8 pg/mL , 95% CI: -2462 , 2641 ; ACR: -0.287 mg/g , 95% CI: -6.773 , 10.91 ; Figure 1A, 1B, and 1C respectively and Table 4). Multivariable regressions with urinary glyphosate failed to identify statistically significant associations of log-transformed glyphosate with KIM-1, NGAL, or ACR (KIM-1: -20.88 ng/mL , 95% CI: -54.89 , 28.02 ; NGAL: -60.53 pg/mL , 95% CI: -291.2 , 331.2 ; ACR: 0.3714 mg/g , 95% CI: -0.8725 , 2.335 ; Table 4). In sensitivity analyses of univariate and multivariable regressions with creatinine-adjusted log-transformed glyphosate, there was also no statistically significant evidence for increased levels of markers for renal injury (Table 4). In additional sensitivity analyses without the newborns similar results were reported with no statistically significant associations of log-transformed glyphosate with kidney injury biomarkers (Table 4).

4. Discussion

The main findings of this study are the substantial and frequent prevalence of glyphosate in children across the first decade of life in three independently assembled samples. We identified glyphosate in 11.1% of the total participants, and the herbicide was detected more frequently in the neonate population (30%). However, urinary concentrations detected in the neonates, toddlers, and young school age children was significantly lower than levels documented in adults with occupational or environmental exposure (3). No association of urinary glyphosate was found with any of the three renal biomarkers (KIM-1, NGAL or ACR).

Urinary excretion of albumin and serum creatinine concentration are conventional biomarkers for renal dysfunction. Novel biomarkers such as urinary excretion of KIM-1 and NGAL have been developed and it has been that they have diagnostic utility for earlier detection of acute kidney injury (AKI) prior to significant loss of function (24). While their use is fairly well established in adult patients, there is ongoing work to establish diagnostic cut-off values in pediatric patients including neonates (25–27). Their use would be especially helpful in glyphosate-induced nephrotoxicity occurring predominantly in the human proximal tubules.(28, 29) Urinary microalbumin, and serum or plasma creatinine, have been utilized to evaluate chronic exposures to glyphosate herbicide in human and animal studies.(21, 30) KIM-1 also predicted renal damage from acute exposures in animal studies.(31) This is the first study to our knowledge examining kidney injury biomarkers in relationship to glyphosate exposure in children.

This study has a number of limitations. We leveraged convenience samples in this initial study. We were limited in interpretation within and across the three populations, given the small sample size and distinct differences in demographic and other factors of the three cohorts. A greater sample size perhaps could have given more accurate results. Recognizing the limited sample size, we were limited in our adjustment for covariates in our multivariable models. Thus we were unable to collect data about place of residence and the time of the year the samples were collected. We focused on known factors that may represent vulnerability to exposures and disease, such as age, gender, or maternal education. Age is associated with differential development to vulnerability stages, and younger populations tend to be more susceptible to exposures than their older counterparts through lactation.(32–35) Glyphosate effects have been also shown to be sex-dependent in animal studies (36–38). We used maternal education as a proxy for family educational attainment or socio-economic status (SES) which are well-known factors for different levels of chemical exposures in children or renal injury outcome.(39–43)

We emphasize that low sample size also limited us to perform analyses in the three cohorts in conjunction, in lieu of stratified analysis. We acknowledge that the strength of any conclusion about the frequency of detecting glyphosate in newborns is limited by the sample size. The source of the glyphosate in the newborns, which was detected more frequently than in the other groups but not at high levels, could be via lactation or infant formula. It is possible that immature or different metabolic pathways for glyphosate in neonates, kidney injury during delivery, or lactation may have affected the findings in this age group. However, the addition of neonates in our study evaluating the association of glyphosate and kidney injury biomarkers may have biased findings towards the null. Our results also suggest that glyphosate levels declined with increasing age. The differences by age may represent differences in dietary behavior and access to foods free of contamination or improved elimination of the herbicide, though further research is needed.

Previous larger scale case-control studies have shown in the past changes in renal function, kidney injury, or chronic kidney disease of unknown etiology (CKDu) upon glyphosate exposure, especially of adult occupational exposures(15–17, 44) There are limited prospective studies and the majority focus on highly exposed workers in the occupational setting. Further evaluation in children may enable more direct assessment of the renal

toxicity of glyphosate. Longitudinal studies are suggested for further evaluation of the exposures from an early age. These could explore more in detail the mechanisms that underlie a potential association between glyphosate and renal biomarkers across different age groups.

Several strengths in this study are notable. Our study is the first to document the prevalence of glyphosate exposures in young children through age 8 years. Our frequent detection of glyphosate suggests the need for inclusion and biomonitoring of glyphosate exposures in national surveys or screenings in populations of interest, which could provide more information in regards to these exposures and outcomes. Glyphosate biomonitoring could be added into studies such as the National Health and Nutrition Examination Survey (NHANES). Our study is novel in that we examine specific renal biomarkers in relationship to glyphosate in a young population.

The lack of evident renal toxicity in association with glyphosate exposure in young children does not exclude a potential adverse impact of longer term exposure to the pesticide. Problems during labor and delivery can compromise renal perfusion leading to increased excretion of tubular injury biomarkers in the neonatal period.⁽⁴⁵⁾ This could interfere with the ability to detect an independent effect of glyphosate in this age group. In addition, the regenerative capacity of the renal tubular epithelium in infants and young children may mask an adverse effect of the pesticide on tubule integrity. Urinary biomarkers such as NGAL and KIM-1 have been demonstrated to be useful biomarkers of tubular injury even without reduced kidney function, highlighting their utility in detecting subclinical insults to the kidney.⁽⁴⁶⁾ Further research could explore more in detail the association between glyphosate and kidney injury biomarker types across different age groups in larger cohorts, and assess whether more prolonged exposure could have progressive deleterious effects.

5. Conclusions

In this study, we identify frequent prevalence of levels of glyphosate (11.1%), present across all three age ranges, and particularly present in the youngest population of neonates. There is no evidence for renal injury in young children exposed to low levels of glyphosate. Further studies of larger sample size are indicated to better understand the potential deleterious effects of the herbicide after different levels, routes, and duration of exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- We leveraged three cohorts across different phases of child development and measured urinary levels of the herbicide, glyphosate, and evaluated associations with biomarkers of kidney injury.
- We identified glyphosate in 11.1% of the participants. The herbicide was detected more frequently in neonates (30%). There were no significant associations of log-transformed glyphosate with any kidney injury biomarker, controlling for covariates age, sex, and maternal education.
- Further studies of larger sample size are indicated to better understand putative deleterious effects of glyphosate after different levels of exposure

Figure 1A.

The dot plot illustrates the urinary KIM-1 level in participants enrolled in the different studies

Figure 1B.
The dot plot illustrates the urinary NGAL level in participants enrolled in the different studies

Figure 1C.

The dot plot illustrates the urinary albumin:creatinine ratio (ACR) in participants enrolled in the different studies

Table 1.Study Population (N=108)¹

Demographics		N	%
Male (Sex)		56	51.9
Study	Bright Start (Neonates)	10	9.3
	Starting Early	66	61.1
	Intervention Arm	39	59.1
	Control Arm	27	40.9
	PEEPS	32	29.6
Maternal Education	None	7	9.5
	Elementary/Middle	21	28.4
	High School/General Equivalency Diploma	35	47.3
	Some college	7	9.5
	College grad	3	4.1
	Other	1	1.4
Race/Ethnicity	Hispanic	67	90.5
	Non-Hispanic White	5	6.8
	Non-Hispanic Black	1	1.4
	Non-Hispanic Asian	1	1.4
BMI Categories ²	Underweight	2	3.0
	Normal	40	60.6
	Overweight	12	18.2
	Obese	12	18.2

Distribution of Glyphosate and Kidney Injury Biomarkers		
	Mean (SD)	Detection Range (Min. & Max. Concentrations)
Glyphosate (ng/mL)	0.278 (0.228)	0.105–2.125
KIM-1 (ng/mL)	80.17 (76.92)	12.38–560.6
NGAL (pg/mL)	12,486 (21,934)	530.7–131,196
ACR ³ (mg/g)	26.23 (25.43)	1.414–119.0

Distribution of Glyphosate and Kidney Injury Biomarkers by Study Groups (N=108)			
Study	Healthy Start (Neonates)	Starting Early	PEEPS
Glyphosate (ng/mL), Median (IQR)	<LOD (<LOD-1.06)	<LOD (<LOD-LOD)	<LOD (<LOD-LOD)
Percent Detected	30.0%	7.58 %	12.5%
KIM-1 (ng/mL), Median (IQR)	88.9 (71.0–114)	47.1 (33.8–71.7)	76.5 (40.3–140.2)
NGAL (pg/mL), Median (IQR)	3,770 (2,520–7,200)	9,080 (3,880–18,700)	1,920 (1,240–5,770)
ACR ³ (mg/g), Median (IQR)	9.45 (6.00–34.3)	28.0 (19.1–42.4)	5.66 (3.54–9.00)

¹Maternal Education 34 missing, Race/Ethnicity 34 missing, BMI 42 missing, KIM-1 9 missing, NGAL 13 missing, 480 and ACR 12 missing.

²Underweight (Below -1.036 SD); Normal (Between -1.036 and $+1.036$ SD); Overweight (Between $+1.036$ and $+1.64$ SD); Obese (Above $+1.64$ SD)

³Albumin-to-creatinine ratio.

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Table 2.

Univariate and Multivariable Regressions for Demographic Predictors of Urinary Glyphosate.

	Univariate ¹		Multivariable ²	
	Glyphosate	OR Glyphosate below LOD	Glyphosate	OR Glyphosate below LOD
Age	-0.04 (-0.07, -0.01) *	1.48 (0.53, 4.10)	-0.16 (-0.22, -0.09) *	3.02 (0.84, 10.9)
Sex	-0.01 (-0.05, 0.03)	1.30 (0.56, 7.10)	-0.01 (-0.05, 0.09)	1.73 (0.44, 6.78)
Arm	0.01 (-0.01, 0.03)	0.34 (0.04, 3.20)	-	-
Education <HS	-0.02 (-0.06, 0.03)	1.44 (0.31, 6.62)	-0.17 (-0.25, -0.08) *	3.16 (0.48, 20.7)
Education ≥HS	0.005 (-0.04, 0.05)	1.81 (0.45, 7.32)	-0.16 (-0.24, -0.07) *	6.23 (0.84, 46.2)
Z-BMI	0.002 (-0.008, 0.01)	1.11 (0.43, 2.86)	-	-

* P-value <0.05

¹ Age N=108, Sex N=108, Arm N=66, Z-BMI N=66, and Maternal Education (N=108).² Note that Maternal Education had imputed missing observations as a reference category to be included in multivariable analyses with N=108.

Table 3.Pearson Correlations across Kidney Injury Biomarkers, and Glyphosate¹

	Glyphosate	KIM-1	NGAL	ACR
Glyphosate	X	0.00880	−0.0526	−0.00690
KIM-1	0.00880	X	−0.137	−0.263 *
NGAL	−0.0526	−0.137	X	0.512 *
ACR	−0.00690	−0.263 *	0.512 *	X

¹ Glyphosate, KIM-1, NGAL, and ACR were log-transformed.

* P-value <0.05

Table 4.

Multivariable Regressions of Creatinine-adjusted Urinary Log-transformed Glyphosate as Predictor of Log-transformed KIM-1, NGAL, ACR Biomarkers¹

All ages N=108 [§]			
Increment per one log unit increase	KIM-1	NGAL	ACR
Glyphosate Univariate	0.974 (−17.92, 27.78)	−663.8 (−2462, 2641)	−0.287 (−6.773, 10.91)
Glyphosate Multivariable	−1.55 (−14.93, 17.62)	−887.8 (−1800, 662.2)	−5.05 (−14.14, 9.85)
Creatinine-adjusted models [¶]			
Glyphosate Univariate	−1.648 (−15.22, 17.47)	−640.5 (−3242, 4079)	7.603 (−9.522, 32.88)
Glyphosate Multivariable	−3.70 (−13.47, 10.26)	−819.8 (−1688, 657.8)	0.858 (−13.80, 22.43)
Non-neonates N=98 ^{§§}			
Increment per one log unit increase	KIM-1	NGAL	ACR
Glyphosate Univariate	−5.351 (−24.13, 27.39)	1489 (−4383, 17944)	3.002 (−10.66, 35.99)
Glyphosate Multivariable	−3.568 (−14.90, 15.96)	395.3 (−5128, 12782)	12.05 (−37.98, 106.6)
Creatinine-adjusted models ^{¶¶}			
Glyphosate Univariate	−4.89 (−20.66, 22.43)	2083 (−5679, 23234)	8.24 (−16.60, 54.17)
Glyphosate Multivariable	−3.73 (−14.45, 14.88)	132.8 (−5165, 11668)	10.37 (−25.33, 72.33)

[§]KIM-1 N=99; NGAL N=95; ACR N=96. Multivariable regression models controlling for demographic covariates age, sex, and maternal education, where maternal education missing observations were imputed as the majority category “Equal or Greater Than High School”.

[¶]Creatinine-adjusted regression models KIM-1 N=95; NGAL N=92; ACR N=96.

^{§§}KIM-1 N=89; NGAL N=86; ACR N=86. Multivariable regression models controlling for demographic covariates age, sex, and maternal education, where maternal education missing observations were imputed