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Urinary 3-Phenoxybenzoic Acid in U.S. Children and Adolescents: Temporal and Demographic Patterns in NHANES, 1999–2002 and 2007–2018

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Abstract

Background: Pyrethroid pesticides are widely used, and children may experience exposure through multiple nonoccupational pathways. Urinary 3-phenoxybenzoic acid (3-PBA) is a commonly used biomarker of recent pyrethroid exposure. **Methods:** In this repeated cross-sectional analysis, we analyzed U.S. National Health and Nutrition Examination Survey (NHANES) data for participants aged 3–19 years from 1999–2002 and 2007–2018. Urinary 3-PBA data were unavailable for 2003–2006. Descriptive statistics for urinary 3-PBA concentrations were creatinine-corrected and estimated by age group and survey cycle. For regression analyses, urinary 3-PBA concentrations were not creatinine-corrected; instead, log-transformed urinary 3-PBA was modeled with urinary creatinine included as a covariate, along with survey cycle, age group, sex, race/ethnicity, and poverty–income ratio (PIR). Analyses incorporated subsample weights with SUDAAN software. **Results:** Among 7415 U.S. children and adolescents, the overall creatinine-corrected geometric mean urinary 3-PBA concentrations were 0.31 [95% CI: 0.25, 0.39] and 0.93 [0.80, 1.08] µg/g creatinine for survey cycles 1999–2000 and 2017–2018, respectively. Concentrations were higher in younger children than in older children. Urinary 3-PBA concentrations were generally higher in later survey cycles. Adjusted models showed that urinary 3-PBA concentrations were higher among younger children and children from lower-income households and were lower among non-Hispanic Black, Mexican American, and Other race/ethnicity groups compared with non-Hispanic White children. Survey cycle was positively associated with urinary 3-PBA in the 1999–2002 and 2007–2014 model but was not statistically significant in the 2015–2018 model. Sex was not consistently associated with urinary 3-PBA across the two analytic periods. **Conclusions:** Recent pyrethroid exposure, as reflected by urinary 3-PBA, was widespread and socially patterned among U.S. children and adolescents. Urinary 3-PBA varied by age group, survey cycle, race/ethnicity, and poverty–income ratio. These findings should be interpreted as exposure surveillance data rather than evidence of specific health effects. Ongoing biomonitoring, source-focused research, and studies with repeated exposure assessments would help to better understand the factors influencing pyrethroid exposure and its public health significance in children.

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1. Introduction

Pyrethroid pesticides are a widely used class of synthetic insecticides modeled from naturally occurring pyrethrins. Compared with pyrethrins, pyrethroids are more chemically stable and therefore may persist longer in environmental and consumer use settings, increasing the potential for human exposure [1–5]. In the United States, pyrethroids have been used in agricultural, residential, and public health applications, including products used in and around homes. In addition, pyrethroids are used in outdoor clothes and gear, pet flea and tick treatments, and head lice shampoos [1,6]. As a result, exposure is not limited to occupational settings and may occur through multiple pathways, including diet, indoor environments, and consumer products [1,5].

Children are an important population for surveillance of pyrethroid exposure. Relative to adults, children may differ in behaviors and exposure contexts that affect contact with environmental chemicals, including greater hand-to-mouth activity, more time spent on floors and other indoor surfaces, and higher food and water intake relative to body size [2,7,8]. Biomonitoring studies have shown that pyrethroid metabolites are commonly detected in the U.S. population [2,5,9]. Urinary 3-phenoxybenzoic acid (3-PBA) is a nonspecific metabolite of several pyrethroid insecticides, including permethrin, cypermethrin, deltamethrin, cyhalothrin, esfenvalerate, phenothrin, and fenpropathrin, and is commonly used as a biomarker for pyrethroid exposure [2,5,9]. 3-PBA was detected in ~79% of the 6–19 year old children and adolescents in the United States based on the U.S. data from the National Health and Nutrition Examination Survey (NHANES 2007–2012), suggesting widespread exposure to pyrethroids [9]. Median urinary 3-PBA concentrations were comparable between children and adolescents (0.49 μg/L) and adults (0.47 μg/L) in the general U.S. population. Given its broad applicability as a metabolite of multiple pyrethroid insecticides and its frequent detection in population biomonitoring studies, 3-PBA is commonly used as a biomarker of recent pyrethroid exposure. Among urinary pyrethroid metabolites measured in NHANES, 3-PBA has generally been detected more frequently than cis- and trans-DCCA. However, differences in detection frequency should not be interpreted solely as differences in population exposure because analytical sensitivity varies among metabolites and methods. For example, the analytical method described by Davis et al. reported an LOD of 0.1 μg/L for 3-PBA compared with 0.4 μg/L for trans-DCCA [10]. Accordingly, lower detection frequencies for DCCA metabolites may reflect, in part, concentrations near or below the analytical detection limits.

Epidemiologic and toxicologic studies have raised concerns about possible associations between pyrethroid exposure and adverse health outcomes in children, including neurodevelopmental, respiratory effects, and potential hematologic or carcinogenic relevance in children [1,11–16]. These studies provide important context for understanding the potential public health relevance of pyrethroid exposure [17–22]; however, interpreting their findings requires caution due to differences in study design, exposure assessment methods, and study populations. In addition, urinary biomarkers of nonpersistent pesticides primarily reflect recent exposure and may be influenced by short-term variability [5,12,17]. For that reason, a clear characterization of exposure patterns in the general pediatric population remains an important public health objective.

Nationally representative information on temporal and demographic patterns in urinary concentrations of 3-PBA among U.S. children remains limited, particularly across

multiple NHANES cycles and younger age groups. Previous NHANES reports provide cycle-specific biomonitoring estimates, and Lehmler et al. characterized demographic and socioeconomic correlates of urinary 3-PBA using NHANES 2007–2012. The present analysis extends this work by evaluating pediatric 3-PBA patterns across eight available NHANES cycles spanning 1999–2018, including the earlier 1999–2002 measurements and later 2013–2018 cycles, and by evaluating children aged 3–5 years when measurements became available in 2015–2018. The present study also applies a common analytic framework across the available cycles to characterize age, race/ethnicity, poverty–income ratio, and survey-cycle patterns in the pediatric population. Therefore, the objectives of this study are to (1) assess pyrethroid exposure in U.S. children and adolescents, as reflected by urinary 3-PBA concentrations, (2) characterize urinary 3-PBA concentrations over time and across demographic groups and identify associated demographic factors among U.S. children and adolescents aged 3–19 years using available NHANES data from 1999–2018, and (3) assess associations between urinary 3-PBA concentrations and family poverty–income ratio (PIR) as an indicator of socioeconomic status.

2. Materials and Methods

2.1. Data and Study Design

We conducted a repeated cross-sectional analysis of NHANES data, a nationally representative survey of the civilian, noninstitutionalized U.S. population conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention. NHANES uses a complex, multistage probability sampling design and combines interview, examination, and laboratory components to assess the health and nutritional status of the U.S. population. Public use data are released in 2-year survey cycles, and each cycle includes survey design variables and sample weights to support population-level inference [23].

The present analysis used eight NHANES cycles from 1999 to 2018 with available urinary 3-PBA data for children, including 1999–2000, 2001–2002, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018. Because urinary 3-PBA was not measured in the 2003–2004 and 2005–2006 cycles, those cycles do not appear in the analysis.

2.2. Study Population

This study included children and adolescents aged 3–19 years who participated in the NHANES cycles from 1999 to 2018 and had available urinary 3-PBA measurements. Participants were eligible for inclusion if they had non-missing data for urinary 3-PBA (variable URXOPM), urinary creatinine (variable URXUCR), age (variable RIDAGEYR), gender (variable RIAGENDR), race/ethnicity (RIDRETH1), and the poverty-to-income ratio (PIR; variable INDFMPIR). We excluded 710 participants due to missing creatinine data (n = 3), PIR (n = 706), or both (n = 1). Race/ethnicity was categorized as Non-Hispanic White, Non-Hispanic Black, Mexican American, or Other, which combined Other Hispanic and multi-racial or other racial/ethnic groups.

Age at examination (RIDAGEYR) was categorized as young children (3–5 years), school-age children (6–11 years), and adolescents (12–19 years) to reflect developmentally meaningful groups and to facilitate interpretation of exposure patterns across childhood and adolescence. Although age could also be modeled continuously, categorical age groups were used to emphasize clinically and behaviorally relevant stages of child development and to maintain comparability across descriptive and regression analyses. Family PIR (INDFMPIR) was categorized as low ($\leq$1.85), medium (>1.85 to <3.5), and high ($\geq$3.5) to distinguish lower-income from higher-income households using cut points commonly applied in pediatric and nutrition-related analyses.

2.3. Laboratory Analytical Methods

Urinary 3-PBA was measured using solid-phase extraction (SPE) to extract and concentrate the analytes from the urine matrix, followed by separation and quantification by liquid chromatography–isotope dilution tandem mass spectrometry. During the 1999–2002 cycles, 2 mL of urine was extracted with an SPE manifold using individual cartridges (Waters, Milford, MA, USA) [24]. For the 2007–2014 cycles, 1 ml of urine was extracted with a semi-automated SPE approach using a 96-well SPE plate [10]. For the 2015–2018 cycles, urinary 3-PBA was measured using 0.2 ml of urine with online SPE [25]. Comparability across analytical procedures was evaluated during method implementation. For the transition to the semi-automated method used for NHANES 2007–2014, regression and difference-plot analyses were used to compare results obtained with the preceding analytical procedure. For 3-PBA, the regression analysis yielded $R^2 = 0.983$, and the difference-plot slope was 0.0035 and was not significantly different from zero, supporting excellent repeatability between the analytical procedures [10]. The online-SPE method subsequently used for NHANES 2015–2018 was evaluated against the preceding method during laboratory method validation using urine samples with concentrations spanning the analytical measurement range. Regression and difference-plot analyses supported the suitability of the online-SPE method for its intended biomonitoring application; however, quantitative agreement statistics from this comparison were not reported in the published method manuscript. In addition, the laboratory participated in the German External Quality Assessment Scheme (G-EQUAS) for 3-PBA, providing independent external proficiency-testing evidence supporting analytical performance during the period in which the 2007–2018 NHANES specimens were analyzed. The limit of detection (LOD) was 0.1 µg/L for all eight cycles and detection rates for our study sample are summarized in Supplemental Table S1. For urinary 3-PBA values below the LOD, we used NHANES-imputed values, in which the LOD was divided by the square root of 2. This approach was applied consistently across all cycles. We adjusted urinary 3-PBA concentrations with their corresponding creatinine measurements to account for variation in urinary dilution.

Urinary creatinine was measured using colorimetric (Jaffé) or enzymatic methods, as specified in the corresponding NHANES laboratory procedure manuals. Published method-comparison studies of urinary creatinine have reported close agreement between Jaffé and enzymatic approaches [26,27]. In NHANES, urinary creatinine was measured using a Jaffé rate method on the Beckman CX3 analyzer (Beckman Instruments, Inc., Brea, CA, USA) in the 1999–2002 cycles and an enzymatic creatinase method on the Roche/Hitachi Modular P analyzer (Roche Diagnostics, Indianapolis, IN, USA) beginning in 2007. NHANES conducted crossover studies to evaluate comparability between these methods and developed adjustment equations for pre-2007 urinary creatinine concentrations when comparing them with measurements obtained from 2007 onward. Because urinary creatinine was used to calculate creatinine-corrected descriptive concentrations and was included as a covariate in the regression models, potential between-cycle differences in creatinine measurement were considered in the interpretation of temporal patterns.

2.4. Statistical Methods

For each 2-year NHANES cycle, we used the urinary pesticide subsample weight to account for the fact that urinary pesticide measurements were obtained from approximately one-third of NHANES participants rather than the full sample. These weights enable estimates that are representative of the U.S. population. The corresponding subsample weight variable was used for each survey cycle period (WTSPP4YR for 1999–2002, WTSC2YR for 2007–2014 & WTSB2YR for 2015–2018), together with the corresponding masked variance strata (SDMVSTRA) and PSU (SDMVPSU) variables, to account for the multistage sampling

design. When combining multiple 2-year cycles, we followed NHANES analytic guidance by rescaling the 2-year subsample weights so that the combined weights represented the average U.S. population across the pooled study period.

2.4.1. Descriptive Analysis

For descriptive analysis, we calculated creatinine-adjusted 3-PBA concentrations (in μg 3-PBA/g creatinine) by dividing the measured "raw" concentrations (in μg 3-PBA/L urine) with creatinine levels (in mg creatinine/dL urine) and multiplying by 100. Geometric means and medians for creatinine-adjusted urinary 3-PBA were calculated using SUDAAN version 11.0.3 (Research Triangle Institute, Research Triangle Park, NC, USA). SUDAAN accounts for the complex survey design using sample weights and calculating variance estimates. The 95% confidence intervals for geometric means were calculated based on the Taylor series linearization method [28]. For the medians, confidence intervals were adapted from the methods of Korn and Graubard (1998) and Woodruff (1952) [29,30].

2.4.2. Regression Analysis

Unadjusted urinary 3-PBA concentrations were natural-log-transformed prior to performing regression analyses. We used multiple linear regression to identify independent variables associated with 3-PBA concentrations in children. The regression models included NHANES cycle, age group, race/ethnicity, PIR, and sex. We included natural log-transformed urinary creatinine in the models to account for urine dilution. Thus, unlike the descriptive analyses, the regression outcome was not expressed as a creatinine ratio (μg/g creatinine). Instead, measured urinary 3-PBA (μg/L) was natural-log-transformed and modeled with natural-log-transformed urinary creatinine included as a separate covariate. Survey cycle was modeled as a continuous variable and coded as 1 for 1999–2000, 2 for 2001–2002, 5 for 2007–2008, 6 for 2009–2010, 7 for 2011–2012, 8 for 2013–2014, 9 for 2015–2016, and 10 for 2017–2018.

Due to a lack of urinary 3-PBA data for young children (3–5 years) from 1999 to 2014, we performed two sets of analyses using the models outlined below. For the first analysis, we examined independent variables associated with urinary 3-PBA concentrations among school-age children (6–11 years) and adolescents (12–19 years) across six NHANES cycles (1999–2000, 2001–2002, 2007–2008, 2009–2010, 2011–2012, 2013–2014). For this analysis, we sought to compare 3-PBA concentrations across time and between the two age groups. To evaluate whether the association between survey cycle and urinary 3-PBA differed by age group, we additionally tested an age group × survey cycle interaction in Model 1 and Model 2. Additionally, to evaluate the assumption of linearity in the survey-cycle effect in Model 1, we conducted a sensitivity analysis treating survey cycle as a categorical variable, with 1999–2000 as the reference category. For Model 2, which included only the 2015–2016 and 2017–2018 cycles, categorical coding of survey cycle represents the same two-level comparison as the primary cycle specification and therefore does not provide an independent assessment of linearity.

Because the urinary creatinine measurement method changed in 2007, we conducted a sensitivity analysis for Model 1 using the piecewise regression equations provided in the NHANES 2007–2008 analytical notes to adjust urinary creatinine concentrations from the 1999–2002 cycles. Post-2007 creatinine concentrations were unchanged and Model 2 included only post-2007 survey cycles and therefore was not included in this sensitivity analysis.

(1) Model 1: $\ln(\text{3-PBA}) = \beta_1(\text{Age Group: }_{\text{6–11 \& 12–19}}) + \beta_2(\text{Survey Cycle r: }_{\text{1999–2002 \& 2007–2014}}) + \beta_3(\text{Sex}) + \beta_4(\text{Race}) + \beta_5(\text{PIR}) + \beta_6(\ln(\text{Creatinine})) + \varepsilon$.

For the second analysis, we examined independent variables associated with urinary 3-PBA among young children (3–5 years), school-age children (6–11 years), and adolescents (12–19 years) in the two NHANES cycles with available urinary 3-PBA data for young children (2015–2016 & 2017–2018). This analysis compared 3-PBA concentrations across the three age groups.

(2) Model 2: $\ln(\text{3-PBA}) = \beta_1(\text{Age Group: }_{3\text{–}5,\ 6\text{–}11\ \&\ 12\text{–}19}) + \beta_2(\text{Survey Cycle:}_{2015\text{–}2018}) + \beta_3(\text{Sex}) + \beta_4(\text{Race}) + \beta_5(\text{PIR}) + \beta_6(\ln(\text{Creatinine})) + \varepsilon$.

3. Results

A total of 7415 participants aged 3–19 years from NHANES 1999–2002 and 2007–2018 were included in the analytic sample (Table 1). Of these, 4.6% were young children (3–5 years), 41.5% were school-age children (6–11 years), and 54.0% were adolescents (12–19 years), based on survey-weighted estimates. Overall, the creatinine-corrected geometric mean and median urinary 3-PBA concentrations for the 2017–2018 survey cycle were 0.93 [95% CI: 0.80, 1.08] µg/g creatinine and 0.76 [0.68, 0.90] µg/g creatinine, respectively. Concentrations were higher in younger age groups than in older age groups, both within each NHANES cycle and in the overall sample from 1999 to 2018 (Tables 2 and S2). Across the available NHANES cycles, descriptive geometric means and medians were generally higher in later survey cycles, although the pattern was not strictly monotonic across all cycles. The overall geometric mean was 0.31 [0.25–0.39] µg/g creatinine in NHANES 1999–2000 and 0.93 [0.80–1.08] µg/g creatinine in NHANES 2017–2018. Non-creatinine-corrected geometric means showed a similar overall pattern across cycles (Supplemental Table S3).

Table 1. Demographic characteristics of the study sample and descriptive statistics of urinary 3-PBA by age group, NHANES 1999–2002 and 2007–2018.

	Overall N (%)	**Young 3–5 yrs N (%)**	**School Age 6–11 yrs N (%)**	**Adolescents 12–19 yrs N (%)**
N	7415 (100)	831 (4.6)	3113 (41.5)	3471 (54.0)
		Sex		
Male	3785 (51.4)	417 (51.8)	1603 (50.7)	1765 (51.8)
Female	3630 (48.6)	414 (48.2)	1510 (49.3)	1706 (48.2)
		Race/ethnicity		
Non-Hispanic White	2102 (56.3)	266 (51.2)	872 (55.9)	964 (57.0)
Non-Hispanic Black	1954 (14.0)	207 (14.2)	869 (14.3)	878 (13.9)
Mexican American	1915 (13.8)	142 (16.8)	795 (14.4)	978 (13.0)
Other Races	1444 (15.9)	216 (17.8)	577 (15.5)	651 (16.1)
		PIR		
Low (≤1.85)	4333 (45.9)	476 (49.7)	1875 (48.1)	1982 (43.8)
Medium (>1.85 to <3.5)	1559 (24.0)	183 (24.1)	636 (24.0)	740 (24.0)
High (≥3.5)	1523 (30.2)	172 (26.1)	602 (28.0)	749 (32.2)

Note: Data for children aged 3–5 years were available only in NHANES 2015–2016 & 2017–2018. Percentages for each category are survey-weighted estimates.

Table 3 illustrates the multiple linear regression results for U.S. children and adolescents aged 6–19 years (NHANES 1999–2002 & 2007–2014), as indicated in Model 1. There was a significant increase in log-transformed urinary 3-PBA with each increase in survey cycle ($\beta = 0.13$, 95% CI = [0.09, 0.16]) after adjusting for children's age group, sex, race/ethnicity, PIR, and urinary creatinine. Compared to school-age children, adolescents had significantly

lower urinary 3-PBA (β = −0.49, 95% CI = [−0.62, −0.35]). Females had significantly higher urinary 3-PBA than males (β = 0.23, 95% CI = [0.12, 0.35]). Compared to Non-Hispanic White children, there were significantly lower urinary 3-PBA concentrations among Non-Hispanic Black (β = −0.36, 95% CI = [−0.49, −0.22]), Mexican American children (β = −0.42, 95% CI = [−0.55, −0.30]), and those in the Other category (β = −0.19, 95% CI = [−0.34, −0.04]). Children in the medium (β = −0.16, 95% CI = [−0.29, −0.02]) and high (β = −0.40, 95% CI = [−0.56, −0.25]) PIR categories had significantly lower urinary 3-PBA than those in the low PIR group (≤1.85, the lowest-income category). The age group × survey cycle interaction was not statistically significant ($p = 0.62$), providing no evidence that the association between survey cycle and urinary 3-PBA differed between school-age children and adolescents. As this interaction was not statistically significant, it was excluded from the final model. Results of the sensitivity analysis treating survey cycle as a categorical variable generally supported higher urinary 3-PBA concentrations in later survey cycles, although the cycle-specific estimates did not demonstrate a strictly monotonic increase across all cycles (Supplemental Table S4).

Table 2. Creatinine-corrected 3-PBA geometric means (μg/g) and 95% CI by age group and NHANES cycle.

	1999–2000	2001–2002	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018
Young (3–5 yrs)	N/A	N/A	N/A	N/A	N/A	N/A	1.57 [1.38, 1.77]	1.57 [1.33, 1.85]
School-Age (6–11 yrs)	0.45 [0.31, 0.64]	0.42 [0.34, 0.52]	0.52 [0.44, 0.62]	0.76 [0.55, 1.05]	1.11 [0.92, 1.33]	0.93 [0.70, 1.22]	0.99 [0.83, 1.19]	1.07 [0.93, 1.24]
Adolescents (12–19 yrs)	0.23 [0.18, 0.28]	0.28 [0.23, 0.33]	0.32 [0.24, 0.42]	0.35 [0.30, 0.40]	0.58 [0.46, 0.73]	0.55 [0.41, 0.72]	0.63 [0.54, 0.73]	0.69 [0.51, 0.93]
Overall	0.31 [0.25, 0.39]	0.33 [0.28, 0.40]	0.39 [0.33, 0.47]	0.49 [0.40, 0.60]	0.76 [0.66, 0.88]	0.69 [0.54, 0.86]	0.85 [0.75, 0.96]	0.93 [0.80, 1.08]

Note: N/A: not applicable; data for children aged 3–5 years were available only in NHANES 2015–2016 & 2017–2018.

Table 3. Multiple linear regression results for log-transformed urinary 3-PBA (Model 1) among U.S. children and adolescents aged 6–19 years, NHANES 1999–2002 and 2007–2014.

	β	95% CI	*p*-Value
Survey Cycle	0.13	0.09, 0.16	<0.0001
Age Group			
School Age (6–11 yrs)		Ref	
Adolescents (12–19 yrs)	−0.49	−0.62, −0.35	<0.0001
Sex			
Male		Ref	
Female	0.23	0.12, 0.35	0.0002
Race			
Non-Hispanic White		Ref	
Non-Hispanic Black	−0.36	−0.49, −0.22	<0.0001
Mexican American	−0.42	−0.55, −0.30	<0.0001
Other	−0.19	−0.34, −0.04	0.0157
PIR			
Low (≤1.85)		Ref	
Medium (>1.85 to <3.5)	−0.16	−0.29, −0.02	0.0239
High (≥3.5)	−0.40	−0.56, −0.25	<0.0001
ln(Urinary creatinine)	0.81	0.74, 0.89	<0.0001

Note: Model used log-transformed 3-PBA and creatinine values.

Results were materially unchanged in a sensitivity analysis using the NHANES creatinine adjustment equations for the 1999–2002 cycles. The survey-cycle coefficient was 0.12 (95% CI: 0.09, 0.15), compared with 0.13 (95% CI: 0.09, 0.16) in the primary analysis, and the direction and statistical significance of the remaining associations were unchanged.

Table 4 illustrates the multiple linear regression results for U.S. children and adolescents aged 3–19 years (NHANES 2015–2018), as indicated in Model 2. Young children had higher log-transformed urinary 3-PBA than school-age children ($\beta = -0.29$, 95% CI = [−0.46, −0.12]) and adolescents ($\beta = -0.65$, 95% CI = [−0.87, −0.44]), after adjusting for survey cycle, sex, race, PIR, and urinary creatinine. Results on race/ethnicity and PIR were similar to those from model 1. Non-Hispanic White children had higher concentrations than children in the Non-Hispanic Black ($\beta = -0.48$, 95% CI = [−0.64, −0.32]), Mexican American ($\beta = -0.56$, 95% CI = [−0.78, −0.34]), and Other category ($\beta = -0.36$, 95% CI = [−0.56, −0.16]). Children in the low PIR category had higher urinary 3-PBA concentrations than those in the medium ($\beta = -0.40$, 95% CI = [−0.56, −0.23]) and high ($\beta = -0.51$, 95% CI = [−0.69, −0.32]) categories. However, there was no difference between males and females. The age group × survey cycle interaction was also not statistically significant in Model 2 ($p = 0.46$), providing no evidence that the association between survey cycle and urinary 3-PBA differed across age groups during 2015–2018. As this interaction was not statistically significant, it was excluded from the final model. Because Model 2 included only two survey cycles, categorical coding of survey cycle represents the same two-level comparison as the primary specification and does not provide an independent assessment of linearity (Supplemental Table S5).

Table 4. Multiple linear regression results for log-transformed urinary 3-PBA (Model 2) among U.S. children and adolescents aged 3–19 years, NHANES 2015–2018.

	β	95% CI	*p*-Value
Survey Cycle	0.07	−0.11, 0.24	0.4550
Age Group			
Young (3–5 yrs)		Ref	
School Age (6–11 yrs)	−0.29	−0.46, −0.12	0.0017
Adolescents (12–19 yrs)	−0.65	−0.87, −0.44	<0.0001
Sex			
Male		Ref	
Female	0.01	−0.12, 0.13	0.9306
Race			
Non-Hispanic White		Ref	
Non-Hispanic Black	−0.48	−0.64, −0.32	<0.0001
Mexican American	−0.56	−0.78, −0.34	<0.0001
Other	−0.36	−0.56, −0.16	0.0011
PIR			
Low (≤1.85)		Ref	
Medium (>1.85 to <3.5)	−0.40	−0.56, −0.23	<0.0001
High (≥3.5)	−0.51	−0.69, −0.32	<0.0001
ln(Urinary creatinine)	0.79	0.66, 0.93	<0.0001

Note: Model used log-transformed 3-PBA and creatinine values.

4. Discussion

Using cross-sectional data from NHANES cycles conducted during 1999–2002 and 2007–2018, urinary 3-PBA concentrations among U.S. children and adolescents varied by age group, poverty–income ratio, race/ethnicity, and survey cycle; associations with sex

differed between the two analytic periods. A sex difference was observed in Model 1, in which females had higher urinary 3-PBA concentrations than males, but this association was not observed in Model 2 for 2015–2018. These findings demonstrate variation in urinary 3-PBA concentrations across demographic and socioeconomic groups and over time among U.S. children and adolescents.

Urinary 3-PBA concentrations were generally higher in later NHANES cycles among children and adolescents in the United States. However, neither the descriptive estimates nor the categorical-cycle sensitivity analysis demonstrated a strictly monotonic increase across every survey cycle. Accordingly, the findings are interpreted as an overall pattern of generally higher concentrations in later cycles rather than as evidence of a uniform linear increase over time. Among school children aged 6–11 years, geometric mean concentrations increased from 0.45 to 1.07 μg/g creatinine, and among adolescents aged 12–19 years, concentrations increased from 0.23 to 0.69 μg/g creatinine between NHANES cycles 1999–2002 and 2007–2018 (Table 2). Previous analysis of NHANES data reported similar trends across time [5,9]. A similar upward trend was also observed in Canada. Data from the Canadian Health Measures Survey (CHMS) [31] showed an increase in urinary 3-PBA concentrations among school children aged 6–11 years (0.32 to 0.66 μg/g creatinine) and adolescents aged 12–19 years (0.25 to 0.35 μg/g creatinine) across survey cycles 1 (2007–2009), 2 (2009–2011), 5 (2016–2017), and 6 (2018–2019). Although analytical methods evolved during the study period, available method-comparison and quality-assurance evidence supports comparability across these transitions. However, residual method-related variability cannot be entirely excluded and is discussed further in the Limitations.

The pattern of higher urinary 3-PBA concentrations in later survey cycles may reflect changes in pyrethroid use and exposure patterns over time, including potential residential, dietary, consumer-product, and other nonoccupational sources. In particular, organophosphate insecticides such as chlorpyrifos and diazinon were restricted for household use, leading to an increase in the residential use of pyrethroid insecticides, which are relatively less toxic and more widely available [32–36]. Children can be exposed to indoor and outdoor insecticides used at home, daycare, and schools, as well as factory-treated or spray-treated clothing/gear, via lice and scabies treatments, and through contact with pets treated with pyrethroid-containing formulations to control ticks and fleas [37–39]. Publicly available pesticide-use data from U.S. agencies provide additional context for the increasing 3-PBA concentrations observed in children and adolescents. The U.S. Geological Survey (USGS) Pesticide National Synthesis Project reports that several major pyrethroid insecticides, such as permethrin, cypermethrin, and deltamethrin, have been used widely in U.S. agriculture over the past two decades, with annual application amounts (in pounds) remaining substantial and in some cases increasing through the 2000s and 2010s [40]. Although USGS data primarily capture agricultural applications and do not include residential or vector-control uses, these trends suggest sustained, and in some cases rising, pyrethroid use nationwide. Such patterns may contribute to population-level exposure trends and provide context for the generally higher urinary 3-PBA concentrations observed in later survey cycles.

Additionally, results from both regression models showed higher urinary 3-PBA concentrations among younger children than among older children (Tables 3 and 4). This may be explained, at least in part, by behavioral pathways, physiological differences, and parental pesticide use targeted toward young children (lice and scabies treatments, pet products) [5,9,41]. Younger children tend to spend more time at home, playing and crawling on the floor, and engaging in hand-to-mouth activity at a higher frequency compared to older children [8]. Consequently, younger children may be more likely to be exposed to pyrethroids used in the home via ingestion, inhalation, and dermal absorption from dust and contaminated surfaces [5,9]. Younger children have a higher surface area-to-body mass

ratio and higher respiratory rates, which increase the potential for exposure via dermal contact and inhalation, respectively [7,42]. The descriptive geometric means presented in Table 2 were expressed relative to urinary creatinine and therefore may also be influenced by age-related differences in creatinine excretion. Creatinine-adjusted concentrations can appear higher in younger children because baseline creatinine excretion generally differs with age. This consideration applies specifically to the ratio-based descriptive estimates. In contrast, the regression analyses modeled unadjusted ln(3-PBA) and included ln(creatinine) as a separate covariate; therefore, creatinine-ratio effects should not be used to explain the adjusted age coefficients from Models 1 and 2. Similar trends have been noted in previous studies using NHANES data to evaluate the general U.S. population [41].

Our findings are consistent with previous studies reporting differences in urinary 3-PBA concentrations across race/ethnicity groups. In the present analysis, non-Hispanic Black, Mexican American, and Other race/ethnicity groups had lower adjusted urinary 3-PBA concentrations than non-Hispanic White children. The present study was not designed to determine the mechanisms underlying these differences, which may reflect multiple exposure-related, behavioral, dietary, environmental, or physiological factors. In addition, race/ethnicity should not be interpreted as a biological proxy for any specific exposure mechanism. For the creatinine-corrected descriptive estimates, demographic differences in creatinine excretion may influence concentrations expressed as μg/g creatinine. However, this explanation does not directly account for the race/ethnicity coefficients in Models 1 and 2 because those regressions modeled unadjusted ln(3-PBA) with ln(creatinine) included separately as a covariate [9,43]. Environmentally, differences in diet, pest control practices, and housing type also affect exposure pathways. Importantly, these differences should not be interpreted as evidence of lower health risks, as minority children are often disproportionately burdened by cumulative environmental stressors [44].

Children from lower-income households had higher adjusted urinary 3-PBA concentrations than those from medium- and high-PIR households, consistent with previous studies. Potential determinants of socioeconomic differences in pyrethroid exposure may include housing characteristics, pest-control practices, diet, occupational take-home exposures, and residential proximity to pesticide use; however, these factors were not directly evaluated in the present analysis and therefore cannot be established as explanations for the observed PIR association. Sex was not a consistent correlate across the two regression models: females had higher urinary 3-PBA concentrations in Model 1, whereas no difference between females and males was observed in Model 2 ($p = 0.93$). The reason for this difference between models is uncertain. The models represent different survey periods and somewhat different age compositions, and changes in exposure patterns or other unmeasured factors could potentially contribute to the observed difference. Because these potential explanations were not directly evaluated, the findings do not support a persistent sex-related difference in urinary 3-PBA concentrations. Changes in pyrethroid use over time, including their use in vector-borne disease prevention and mosquito control programs and shifts toward pyrethroids in some pest-management applications, may also contribute to exposure patterns and warrant further investigation. Such patterns highlight how differences in SES and pesticide-use practices may translate into discrepancies in pesticide exposure [45–48]. Although this study did not evaluate health outcomes, the findings are relevant in the context of prior epidemiologic and toxicologic literature suggesting associations between pyrethroid exposure and child health outcomes, particularly for neurodevelopmental and respiratory outcomes and other health concerns. Thus, understanding exposure distributions in children remains a public health priority [17–22]. In that context, the present results help identify exposure patterns and subgroups that may be important for future studies incorporating repeated exposure assessment, improved source characterization,

and direct measurement of health outcomes. The findings should therefore be interpreted as strengthening the surveillance base for future etiologic research rather than as evidence of specific health effects.

Several limitations should be considered when interpreting the results of this study. First, urinary 3-PBA is a nonspecific biomarker of recent pyrethroid exposure and does not identify the parent compound or exposure source [5]. Second, reliance on a single spot urine sample may not adequately capture within-person variability or longer-term exposure patterns, particularly for nonpersistent pesticides with short half-lives [1,5]. Third, the cross-sectional design of NHANES does not allow causal inference and does not support conclusions about the timing of exposure in relation to later health outcomes. Fourth, age-related differences in creatinine excretion may affect the interpretation of creatinine-adjusted concentrations in children [2]. Fifth, although the analytical procedures used to measure urinary 3-PBA evolved during the study period, available method-comparison and quality-assurance evidence supports comparability across these methodological transitions. The method used for NHANES 2007–2014 showed strong agreement with the preceding procedure for 3-PBA ($R^2 = 0.983$), with no significant trend in the difference analysis [10]. The subsequent online-SPE method used for 2015–2018 was evaluated against the preceding method across the analytical measurement range and was determined to be suitable for its intended biomonitoring application. In addition, participation in G-EQUAS provided independent external quality-assurance evidence for 3-PBA measurement. Nevertheless, because quantitative agreement statistics for the 2007–2014 to 2015–2018 method comparison were not reported in the published method manuscript, residual method-related variability cannot be entirely excluded when interpreting differences across survey cycles. Urinary creatinine methodology also changed during the study period; however, published method-comparison studies support close agreement between Jaffé and enzymatic urinary creatinine measurements, and NHANES conducted crossover evaluations of the method transition. Furthermore, results of our sensitivity analysis applying the NHANES adjustment equations to pre-2007 creatinine concentrations were materially unchanged, suggesting that the creatinine method transition did not materially affect the observed regression associations. Finally, although NHANES includes information on factors such as fasting duration and examination or urine-collection timing, these variables were not included in the primary models. Because urinary 3-PBA reflects relatively recent exposure, short-term factors related to dietary intake and specimen timing could contribute to within- and between-person variability. Other source-specific factors, including recent pesticide-product use and pet-related exposures, were not consistently characterized across the study period.

Despite these limitations, this study provides nationally representative information on urinary 3-PBA concentrations among U.S. children and adolescents across multiple NHANES cycles. These findings provide a basis for continued biomonitoring and future studies incorporating repeated exposure assessments and improved source characterization to better understand the determinants and public health relevance of pyrethroid exposure in children.

5. Conclusions

This analysis of NHANES 1999–2002 and 2007–2018 data identified differences in urinary 3-PBA concentrations among U.S. children and adolescents by age, poverty–income category, race/ethnicity, and survey cycle. Urinary 3-PBA concentrations were higher among younger children and those from lower-income households, but lower among children in the non-Hispanic Black, Mexican American, and Other race/ethnicity categories compared with non-Hispanic White children. Sex was not a consistent correlate of urinary 3-PBA across the two regression models. Among age-comparable school-age children and

adolescents, urinary 3-PBA concentrations were generally higher in later NHANES cycles, although the observed pattern was not strictly monotonic across all cycles. Available method-comparison and external quality-assurance evidence supports analytical consistency across methodological transitions; however, quantitative agreement statistics were not reported in the published literature for the transition to the 2015–2018 method, and residual method-related variability cannot be entirely excluded.

Because urinary 3-PBA is a biomarker of recent exposure and the analysis was cross-sectional, these findings should be interpreted as population-level biomonitoring patterns rather than evidence of long-term exposure, specific exposure sources, or health effects. Continued biomonitoring and studies incorporating repeated urinary measurements, improved source characterization, and consideration of short-term determinants of urinary 3-PBA could help clarify the determinants and temporal patterns of pyrethroid exposure among U.S. children and adolescents.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jox16070220/s1: Table S1: Detection frequency of urinary 3-PBA by NHANES cycle year; Table S2: Creatinine-corrected 3-PBA medians (μg/g) and 95% CI by age group and survey cycle; Table S3: Non-creatinine-corrected 3-PBA geometric means (μg/L) and 95% CI by age group and NHANES cycle; Table S4: Multiple linear regression results for log-transformed urinary 3-PBA with survey cycle modeled as a categorical variable (Model 1) among U.S. children and adolescents aged 6–19 years, NHANES 1999–2002 and 2007–2014; Table S5: Multiple linear regression results for log-transformed urinary 3-PBA with survey cycle modeled as a categorical variable (Model 2) among U.S. children and adolescents aged 3–19 years, NHANES 2015–2018.

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