HHS Public Access

Author manuscript

J Expo Sci Environ Epidemiol. Author manuscript; available in PMC 2024 June 02.

Published in final edited form as:

J Expo Sci Environ Epidemiol. 2024 March ; 34(2): 241–250. doi:10.1038/s41370-023-00524-2.

Pesticide Exposure and Asthma Morbidity in Children Residing in Urban, Multi-family Housing

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Abstract

Background: Children are potentially more susceptible to the adverse effects of pesticides due to more sensitive organ systems and lower capacity to metabolize and eliminate chemicals compared to adults. The health risks are particularly concerning children with asthma, living in low-income neighborhoods in multi-family housing because of their impaired respiratory health, and factors associated with low-income, multi-family environments.

Objective: To assess the association between pesticide exposure and asthma morbidity among children 7–12 years residing in low-income, multi-family housing.

Methods: The concentrations of seven urinary pesticide biomarkers: 3,5,6-trichloro-2-pyridinol (TCPy), 2-isopropyl-4-methyl-6-hydroxypyrimidine, para-nitrophenol (PNP), 3-phenoxybenzoic acid (3-PBA), 4-fluoro-3-phenoxybenzoic acid, trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid, and 2,4-dichlorophenoxyacetic acid (2,4-D) were measured. Children (n=162) were followed for one year with three measures of pesticides biomarkers. Associations between individual biomarkers and asthma attack, asthma related health care utilization, and fraction of exhaled nitric oxide (FeNO), adjusting for demographic and household factors were examined with Generalized Estimating Equations (GEE). Weighted

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Author contributions: DW had full access to the data and takes responsibility for the integrity of the data and accuracy of analysis; DW, FR, GC, AC, MO were involved in the design and conduct of the analysis; DW, FR, GA, TR, AC, MO, GC contributed to the drafting of the manuscript; DW, FR, GA, TR, AC, MO, GC were involved in the editing of the manuscript. All authors approved the manuscript for submission.

Competing Financial Interests Declaration

The authors declare no actual or potential competing financial interests.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Quantile Sum (WQS) regression was used to examine the effect of pesticide mixture on asthma attacks and asthma-related health care utilization (HCU).

Results: In adjusted GEE models, positive non-significant associations were found between PNP and HCU (adjusted Odds Ratio(aOR):2.05 95% CI:0.76 – 5.52) and null associations for 3-PBA and HCU (aOR:1.07 95% CI: 0.88–1.29). Higher concentrations of PNP and 2,4-D were associated with significantly lower FeNO levels (PNP: −17.4%; 2,4-D:−19.74%). The mixture was positively associated with HCU in unadjusted (OR: 1.56 97.5% CI: 1.08 – 2.27) but not significant in adjusted models (aOR: 1.40 97.5% CI: .86–2.29). The non-specific pyrethroid biomarker 3-PBA at baseline contributed the greatest weight to the index (45%).

Significance: There were non-significant associations between pesticide biomarkers and respiratory outcomes in children with asthma. There was a suggestive association between urinary pesticide biomarkers and HCU. Further studies with larger sample sizes could help to confirm these findings.

Keywords

Pesticides; Asthma; Pyrethroids; Organophosphorous; 2,4-D

Introduction

Asthma is a complex disease that is influenced by environmental factors and is associated with substantial morbidity in childhood.[1] Previous researchers have established a connection between environmental risk factors and poorer respiratory health Several studies have elucidated the harmful effects of pollutants and chemicals such as particulate matter, ozone, nitrogen dioxide[2,3] and agricultural pesticides.[4,5] However, there is limited information on pesticide exposure in non-occupational settings and its effect on pulmonary health in children.

Pesticides are commonly used in the United States in residential settings.[6] Children are particularly susceptible to pesticides due to more sensitive organ systems and lower capacity to metabolize and eliminate chemicals compared to adults.[7] Pesticide exposure occurs through multiple routes (dermal, oral, inhalation). The oral route via food intake is considered the most important exposure pathway for the general population.[8] However, non-dietary and inhalation routes may also be important exposure paths especially for children.[9] The health risks of pesticides are of particular concern for children with asthma who live in low-income, multi-family housing. These children are more susceptible due to their impaired respiratory health, and more vulnerable because of persistent pest infestation often found in urban, multi-family environments. [10,11]

Although the toxic potential of low-level exposure to pesticides is unclear, pesticide toxicity at high exposures is well known. [12–14] There is some evidence that organophosphorous and pyrethroid insecticides, and certain herbicides are toxic substances that have the potential to cause long lasting health effects even in low doses. [15–17] However, research assessing low-level chronic exposure in children, particularly for those at greatest risk, is lacking.

Another research gap is the lack of collective consideration of multiple classes of pesticides; to date, most researchers have focused on a single metabolite or pesticide class [4,6,9,18] even though pesticide exposures do not occur in isolation. In a study evaluating general population exposure to a wide range of pesticides, Li et al.[19] found that organophosphorous biomarkers accounted for 62–77% of the total daily urinary pesticide concentrations and pyrethroid metabolites accounted for 17–33% of the total daily pesticide concentrations. Other research has shown the general population is exposed to multiple classes of pesticides[8,20,21] and an association with non-respiratory outcomes. [22–24]Pesticides comprise many substances with dissimilar structures and diverse toxicity that may act through different mechanisms. Therefore, it is plausible that not just one, but several mechanisms are involved in the pathophysiological routes between pesticide exposure and respiratory health. Despite this, there are limited data on exposure to mixtures of pesticides on respiratory health in the general popualtion. A recent publication from the Agency for Toxic Substances and Disease Registry concluded that greater-than-additive action on neurologic end points is possible between certain pyrethroids and organophosphorous insecticides, however the relevance of these findings to relatively low environmental exposures to pyrethroid and organophosphorous insecticides is not well understood.[25] Therefore, although not conclusive, there is biological plausibility for the combined negative effects of pesticide exposure at least on neurologic endpoints. The evidence for respiratory outcomes has shown 2,4-dichlorophenoxyacetic acid (2,4-D), and pyrethroids and organophosphorous metabolites to be associated independently with respiratory outcomes.[26–30] However, there is limited evidence on their combined effects, especially in the general population. Research assessing potential health effects of pesticides would benefit from considering both the individual and mixture effects of common pesticides on asthma. The current study fills this important data gap.

The objectives of this study were to quantify urinary biomarker concentrations of select commonly used pesticides in children ages 6 to 13 years who reside in an urban environment and to assess the association between pesticide exposure biomarkers and various measures of asthma morbidity. The hypothesis is that greater concentrations of urinary pesticide biomarkers (individual and mixtures) are associated with more asthma attacks, greater likelihood of asthma related healthcare utilization, and more airway inflammation.

Subjects and Methods

Study Design and Population.

The study used data from the Green Housing Study (GHS), a multi-city prospective cohort sponsored by the Centers for Disease Control and Prevention (CDC), the Department of Housing and Urban Development (HUD), and the United States Environmental Protection Agency (EPA). Children ages 7 – 12 years with doctor-diagnosed asthma experiencing asthma-related symptoms (wheezing, or night-time awakenings) during the previous 6 months and who lived in HUD subsidized homes were eligible for the study. Children were recruited in Boston, Massachusetts, by Harvard University staff, Cincinnati, Ohio, by the University of Cincinnati staff, and New Orleans, Louisiana by Tulane University staff during community outreach events. Children were followed for 12 months, and data were

collected during three 5-day home visits (baseline, month 6, and month 12). Participants were recruited between September 2011 and March 2015. The study was reviewed and approved by the Institutional Review Boards of the CDC, Tulane University School of Public Health and Tropical Medicine and Harvard T.H. Chan School of Public Health. Written consent and assent were obtained from each caregiver and child, respectively.

Urinary Pesticide Metabolites.

During each home visit, study personnel collected one convenience spot sample from the child, and caregivers were given instructions on urine specimen collection and provided with specimen cups for collecting one first morning void (FMV) sample from the child within 5 days of the convenience sample. Caregivers were instructed to store the child's FMV sample in the home freezer until picked up by study personnel. Urine samples were transported to the study lab on ice packs and stored at −80 °C, then shipped frozen overnight to the CDC's Division of Laboratory Sciences for analysis. At CDC, the concentrations of the following seven pesticide metabolites in the two urine samples obtained at each home visit were measured: 3,5,6-trichloro-2-pyridinol (TCPy), 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMPY), *para*-nitrophenol (PNP), 3-phenoxybenzoic acid (3-PBA), 4-fluoro-3-phenoxybenzoic acid (4F-3PBA), *trans*-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (*trans*-DCCA), and 2,4-D. Urine metabolites were quantified as described in detail by Davis et al. using solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry.[31]The limits of detection (LODs) were: 0.1 μg/L for TCPy, IMPY, PNP, 3-PBA, and 4F-3PBA, and 0.15 and 0.6 μg/L for 2,4-D and *trans*-DCCA, respectively. Urinary creatinine was also measured at CDC.[32] FMV and convenience sample pesticide metabolite concentrations were adjusted for urine creatinine. Creatinine-adjusted FMV and convenience spot samples from each visit were then averaged.

Asthma outcomes.

Asthma attacks were assessed by questionnaire at each home visit and during phone calls at months 3 and 9. Caregivers of children were asked: "During the past 3 months, has the child had an episode of asthma or an asthma attack?" Responses were coded Yes, No, or Don't Know. Caregivers were then asked the number of asthma attacks that occurred in the previous three months. Asthma related health care utilization (hospitalization, emergency department visit or unscheduled clinic visit) in the previous 3 months was assessed by questionnaire during each home visit and during phone calls at 3 and 9 months too.

Airway inflammation.

Fractional exhaled Nitric Oxide (FeNO) was used as a measure of airway inflammation. Children performed FeNO measures using the NIOX-MINO according to the manufacturer's instructions. Briefly, the child inspired nitric oxide-free air via a mouthpiece until total lung capacity was achieved, followed immediately by exhalation through the mouthpiece into the measuring device. FeNO was measured at baseline, 6 and 12 months. For descriptive statistics children with FeNO greater than 35 ppb were considered to have eosinophilic inflammation, consistent with ATS guidelines.[33] Due to the limited information on the effect

of pesticides on airway inflammation, in regression models FeNO was considered as a continuous variable.

Covariates.

Factors previously found to be associated with asthma outcomes were considered as potential covariates. These included age, race/ethnicity, child sex, household income, caregiver education level, child insurance status, season, and regular asthma medication use collected via questionnaire. Tobacco smoke exposure was assessed via cotinine concentration in child's urine, [34] indoor air pollution level by assessing particulate matter less than 2.5 microns (PM2.5)[35], indoor allergen exposure assessed as the concentrations of allergens in bed dust samples, and allergic sensitization, assessed in serum as allergen-specific Immunoglobulin E (IgE) for several common indoor allergens. In addition, due to the multi-site nature of the study, site was considered as a covariate to assess potential differences among the populations of the three cities. To avoid the exclusion of possibly important confounders rather than avoiding the inclusion of weak confounders or non-confounders, variables found to be associated ($p<0.20$) with the asthma outcomes in bivariate analyses were included in multivariable models.[36]

Statistical Analysis.

Descriptive statistics included geometric means and standard deviations (SD) or medians and 95% confidence limits for continuous variables and number and proportion for categorical variables. For reporting geometric means, metabolite concentrations below LOD were imputed as LOD/√2.[37] Biomarkers detected in fewer than 60% of samples were excluded from analyses beyond descriptive statistics. Correlations between biomarker concentrations in FMV and convenience spot samples were assessed using Spearman's correlation for creatinine adjusted urinary metabolites at each urine collection. To calculate the intra-class correlation coefficient (ICC), a one-way random effects model was used to estimate within-person variance in pesticide biomarker concentrations at baseline, month 6, and month 12. Differences between a nationally representative sample of children from the National Health and Nutrition Examination Survey (NHANES) and the cohort of children in each city were assessed using a one sample median test (Sign Test) comparing site specific medians to the median among NHANES 2013–2014 children 6–11 years.

We investigated the association between individual pesticide biomarkers and number of asthma attacks (count), and asthma related health care utilization in the previous three months (binary), and natural log transformed FeNO (continuous). Bivariate and multivariable analyses for each exposure-outcome relationship were conducted using generalized estimating equation (GEE) models with compound symmetry correlation to account for clustering by city and repeated measures of exposure (i.e., pesticide biomarker concentrations) and outcomes. Poisson (asthma attack), binomial (HCU), or linear (FeNO) regression was used in GEE analysis depending on distribution of outcome, GEE analyses were completed in SAS 9.4 (Cary, North Carolina).

To account for the collinearity of exposure to multiple pesticides, we employed an extension of weighted quantile sum regression (WQS), termed "joint WQS" (JWQS)[38] WQS is a

statistical learning method that identifies a weighted sum of components in the mixture of pesticide biomarker concentrations that is most strongly associated with the health outcome of interest.[39] JWQS enables the assessment of exposures without implicit constraints on the relationship between the pesticide mixture across time points. The generalized weighted quantile sum (gWQS) package in R was used to conduct WQS using quasi-Poisson regression with deciles to categorize pesticide biomarker concentrations with 100 boot strap samples and 100 repeated holdout samples. The analysis was conducted for positive directions of association (i.e., adverse associations). Covariates were chosen based on bivariate results of the GEE analyses.

Results

Characteristics of the 162 children at baseline are described in Table 1. Forty-two percent of children were from New Orleans, 28% from Cincinnati, and 30% from Boston. The median age was 9.5 years, a majority identified as non-Hispanic black (71%), and most lived in households with an annual income of less than $25,000 per year (91%). All children had medical insurance. At the baseline visit, 30% of children reported having had an asthma attack in the previous three months, 11% reported asthma related health care utilization in the previous three months, and 16% had evidence of eosinophilic inflammation (FeNO >35 ppb).

Detection frequencies of pesticide biomarkers varied over the 12-month follow-up period (Table 2). The most commonly detected pesticide biomarkers were PNP (100%) followed by TCPy (99%). Only one pyrethroid biomarker was commonly detected (3-PBA) with a detection frequency of 93.2%. The herbicide 2,4-D was detected in 71% of urine samples. IMPY, 4F-3PBA, and *trans*-DCCA were detected in <60% of samples and will not be discussed further.

Geometric mean concentrations of the pesticide biomarkers are presented in Figure 1. TCPy had the highest concentration at each time point (Baseline: 1.33 μg/g creatinine, Month 6: 1.23 μg/g creatinine, Month 12: 1.44 μg/g creatinine) and 2,4-D had the lowest concentration (Baseline: 0.33 μg/g creatinine, Month 6: 0.31 μg/g creatinine, Month 12: 0.24 μg/g creatinine). The ICCs over the year ranged from 0.06 for TCPy to 0.43 for 3-PBA. The Spearman correlation between pesticide biomarkers concentrations at each time point are presented in Figure 2. Correlations ranged from negative 0.14 between PNP at baseline and 3-PBA at month 12 to 0.42 between 3-PBA at baseline and 3-PBA at month 6. Convenience and FMV spot sample concentrations of PNP, TCPy, 3-PBA and 2,4-D were significantly correlated at each time point. Correlations ranged from 0.39 (PNP at baseline) to 0.75 (TCPy at baseline).

Pesticide median concentrations differed significantly by study site (Table S1). Children in Boston had the highest median concentration of PNP, whereas children in Cincinnati had the highest median concentrations of TCPy and 3-PBA. New Orleans children had the highest median concentration of 2,4-D. Comparing children in the GHS to those from NHANES, a nationally representative sample, GHS children had significantly lower pesticides biomarker concentrations (Table S1).

Results of bivariate analyses can be found in Table S2. Daily medication use, and dust mite (*Dermatophagoides pteronyssinus* and *D. farinae*) and cockroach (*Blatella germanica*) sensitization were associated ($p<0.20$) with the number of asthma attacks in the previous three months. BMI, daily medication use, dust mite sensitization, season, and age were associated with health care utilization. Sex, race, household income, sensitization to dog, dust mite (both *D. pteronyssinus* and *D. farinae*), cockroach, cat, and mouse, site, season and age were associated with FeNO.

Unadjusted and adjusted associations for each pesticide biomarker are presented in Table 3. For asthma attacks, associations with urinary biomarkers were not significant in unadjusted or adjusted models. In unadjusted models for asthma related HCU, TCPy and 3-PBA were inversely associated with HCU while PNP and 2,4-D were positively associated. None of the associations reached statistical significance. In models adjusting for BMI, medication use, dust mite sensitization, season and age, PNP and 3-PBA were positively associated with health care utilization (PNP: OR 2.05 95% CI: 0.76–5.52; 3-PBA: OR: 1.07 95% CI 0.88–1.29) but did not reach statistical significance. In models evaluating the association between pesticide biomarkers and FeNO, PNP and 2,4-D were significantly associated with decreased FeNO (PNP: −17.4%; 2,4-D:−19.74%).

Using JWQS regression we evaluated exposure to a mixture of the four most commonly detected pesticides biomarkers, TCPy, 2,4-D, 3-PBA and PNP,on asthma attacks and asthma related health care utilization over the year. The mean number of asthma attacks was 1.5 (range 0 – 20) and 20% of children reported at least one incidence of asthma related health care utilization during the year. The mixture index was not associated with asthma attacks in unadjusted models (IRR: 0.95 97.5% CI: 0.78,1.16) or in models adjusting for daily medication use, and sensitization to dust mites and cockroach (IRR: 0.98 97.5% CI: 0.83,1.17). In unadjusted models the pesticide mixture index was associated with HCU (OR: 1.56 97.5% CI: 1.08,2.27) with the greatest contribution coming from 3-PBA (55%), the mixture index remained positively associated with HCU in models adjusting for BMI, daily medication use, dust mite sensitization, season at baseline and child's age (OR: 1.40 97.5% CI 0.86,2.29) although not statistically significant. 3-PBA continued to contribute the greatest weight to the index (45%) followed by 2,4-D (28%), then PNP (15%) with TCPy contributing the least (10%) (Table 4.).

Discussion

We found that children's pesticide biomarker concentrations vary by geographic location, type of pesticide, and collection time point. The ICC revealed poor reproducibility between concentrations of urine pesticide biomarkers signifying that over the year of follow-up, pesticide biomarker concentrations varied considerably. A notable finding is that pesticide biomarker concentrations in this study population at each site were lower than in children from the general U.S. population (NHANES 2013–2014). We did not find significant associations between any of the individual pesticide biomarkers and the respiratory outcomes in the expected direction. We found a protective effect for PNP and 2,4-D on FeNO, which may relate in part to the fact that PNP is a biomarker of other compounds in addition to pesticides, this association may also simply be a spurious association in our

data set that would need confirmation in future studies. The variability across time and geography may help explain inconsistent associations between pesticides and respiratory health currently found in the literature although we cannot rule out other factors for these associations.

Examining the effect of individual pesticide biomarkers on asthma morbidity, our results suggest higher concentrations of PNP and 3-PBA result in a greater likelihood of asthma-related health care utilization, although neither association reached statistical significance. Of the individual metabolites assessed, the strongest associations were seen with PNP. Significant negative associations were found between PNP, 2,4-D and FeNO. Associations with asthma attack were small and non-significant.

Our results add to the research evaluating pesticides and asthma. In a recent systematic review examining the respiratory and allergic effects in children exposed to pesticides,[40] of the seventeen studies evaluating organophosphorous pesticides or multiple pesticide exposure, eleven reported positive associations, four found no associations, and two had no clear findings. An important note is that a majority of the studies were conducted in populations exposed via agricultural proximity or work. Of the three studies that evaluated pesticides in populations not including agricultural areas, only one included measurement of a biomarker of exposure.[41] In that study the authors found no clear association between asthma and biomarkers of diakylphosphates (DAP) a non-specific marker of OPs. The remaining two studies evaluated pesticide exposure via questionnaire and found children exposed to pesticides had higher odds of having respiratory disease (OR= 1.71; 95% CI: 1.20–2.43)[42]; and asthma diagnosis before 5 years was significantly associated with exposure to pesticides in the first year of life (OR: 2.39; 95% CI: 1.17–4.89)[43]. So, it appears that exposure to pesticides is related to impaired respiratory health however, differences in which pesticides were evaluated, methods of exposure assessment, and outcomes make direct comparisons across studies difficult.

We found a significant positive association between the pesticide mixture index and asthma-related health care utilization in unadjusted models. In adjusted models, the association remained positive, however the effect was attenuated and crossed the null. The pesticide index was predominately weighted by the pyrethroid biomarker 3-PBA and the herbicide 2,4-D which may indicate these biomarkers as the drivers of the effect. Therefore, evaluating the association of not only the individual metabolites but the combined exposures, which most closely mimics real world exposure, is important. Although not significant the results suggest there may be an increased risk of asthma related health care utilization even among children with biomarker concentrations lower than those in the general population. Therefore, there is a need to increase our understanding of the potential effects of pesticides in less-studied populations, such as those residing in low-income, multi-family, housing.[44,45]

The exact mechanism through which pesticides may affect asthma morbidity is unknown, although pesticide exposure may contribute to the exacerbation of asthma by irritation, inflammation immunosuppression, or endocrine disruption.[6] The different mechanisms, classes, and mixtures of pesticides have made it difficult to assess individual effects of pesticide exposure on asthma morbidity. This may explain the varying results observed in

the current study and previous research when looking at different pesticides and respiratory outcomes.

An unexpected finding is the negative association between FeNO and PNP and 2,4-D. One possible explanation for PNP may be related to exposure of cigarette smoke in participants' homes. PNP is also a metabolite of nitrobenzene which is a compound found in tobacco smoke.[46] Urinary cotinine measurements suggest there was smoking in the homes of some of the participants and we know that smoking may induce a decrease of exhaled NO levels in both healthy persons and those with asthma. Several mechanisms, such as an inhibited bronchial epithelial iNOS-related production of NO or an increased catabolism of NO, have been postulated to explain this decrease.[47] Based on the presence of nitrobenzene (a parent compound of PNP) in tobacco smoke and the biologic relationship between tobacco smoke and FeNO, it is plausible that in our study PNP was acting as a surrogate for tobacco smoke and therefore decreased FeNO levels. However, this study was not designed to evaluate sources of pesticides.

The study has a few limitations. Although urinary biomarkers of pesticide exposure are considered the gold-standard for exposure assessment, the relatively short biological half-life of these biomarkers may lead to misclassification of exposure over longer time periods. To overcome this limitation, we used biomarker concentrations from six spot samples to represent pesticide exposure over one year. This is important because we found that pesticide biomarker concentration is not consistent throughout the year. Therefore, the repeated measures of biomarkers strengthen the results of the study. The study was also limited by a relatively small sample size and low variation in study outcomes which may have resulted in non-significant findings. In addition, the use of simple imputation for pesticide biomarker concentrations below the LOD may result in impaired estimates of variances and covariances. Biomarker concentrations were adjusted for creatinine although there is currently controversy over the most appropriate method to adjust for creatinine;[48] the decision to adjust biomarkers concentrations for creatinine was made to ensure the ability to use all 6 urine samples over the course of the year while still considering the potential urinary dilution. A sensitivity analysis was conducted with unadjusted concentrations and differences in effect estimates were not significant (data not shown). Finally, the study sample may not be generalizable to all children.

The current study has several strengths. Many epidemiological studies of pesticide exposure have used questionnaire-based measurements, job titles, or relative distance to pesticide sources as a surrogate of pesticide exposures for individuals.[4] Of the studies conducted in children, many used only one or two bio-specimens to assess exposure. The epidemiological studies supported by quantification of biomarkers in urine, like the current study, lead to more (highly) validated conclusions on the associations between human exposure to organophosphorous or pyrethroid insecticides and health outcomes compared to those using questionnaire-based measurements. [18] In addition, the study evaluated not only the individual metabolites but their mixture.

Conclusions

Our hypothesis was not entirely supported. In this prospective study, there is suggestive evidence that urinary concentrations of pesticide biomarkers are positively associated with asthma related health care utilization. However, we saw no effect on asthma attacks and protective effects with a biomarker of airway inflammation. The study provides unique insight into the potential adverse association between exposure to pesticides and asthma morbidity in children thanks to the repeated measures design, biomarker-based exposure assessment, and assessment of pesticides exposure as a mixture. Future studies with larger sample sizes, more frequent longitudinal assessment of pesticide biomarkers, and different combinations of pesticides could better explore the relationship between pesticide exposure and asthma morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank the children and their parents for their participation and our community partners for their assistance throughout the study. We also thank Mark Davis and William Roman for the measurement of the pesticide biomarkers and Connie Sosnoff for the measurement of cotinine.

Funding Sources

This study was funded by the Centers for Disease Control and Prevention (CDC) grant #5UO1EH000990 with supplemental funding from the U.S. Environmental Protection Agency (EPA) interagency agreement #DW-75-9584500 and the U.S. Department of Housing and Urban Development (HUD) interagency agreement # I-PHI-01062.

Data availability Statement

Individuals who would like to access data can contact Dr. Werthmann (dwerthma@tulane.edu) with a specific request for data access.

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Impact Statement:

Pesticide exposure among children in the urban environment is ubiquitous and there is a dearth of information on the impact of low-level chronic exposure in vulnerable populations. This study suggested that pesticide exposure at concentrations below the national average may not affect asthma morbidity in children. However, different biomarkers of pesticides showed different effects, but the mixture suggested increasing pesticide exposure results in asthma related HCU. The results may show that children with asthma may be at risk for negative health outcomes due to pesticides and the need to further examine this relationship.

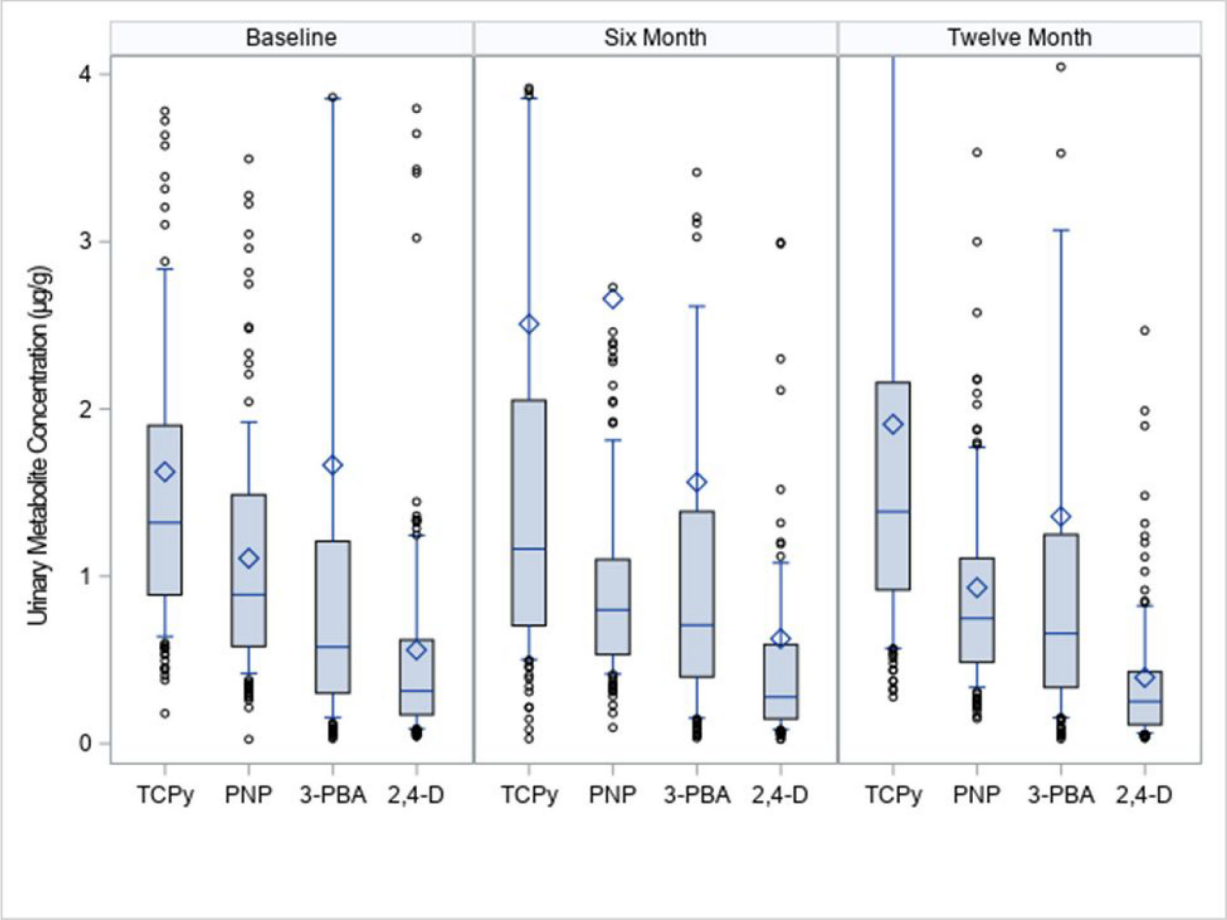

Figure 1.

Mean, median, interquartile range, 10th and 90th percentiles of pesticide biomarker concentrations (µg/g creatinine) by visit.

TCPy: 3,5,6-trichloro-2-pyridinol; PNP: *para*-nitrophenol; 3-PBA: 3-phenoxybenzoic acid; 2,4-D: 2,4-dichlorophenoxyacetic acid

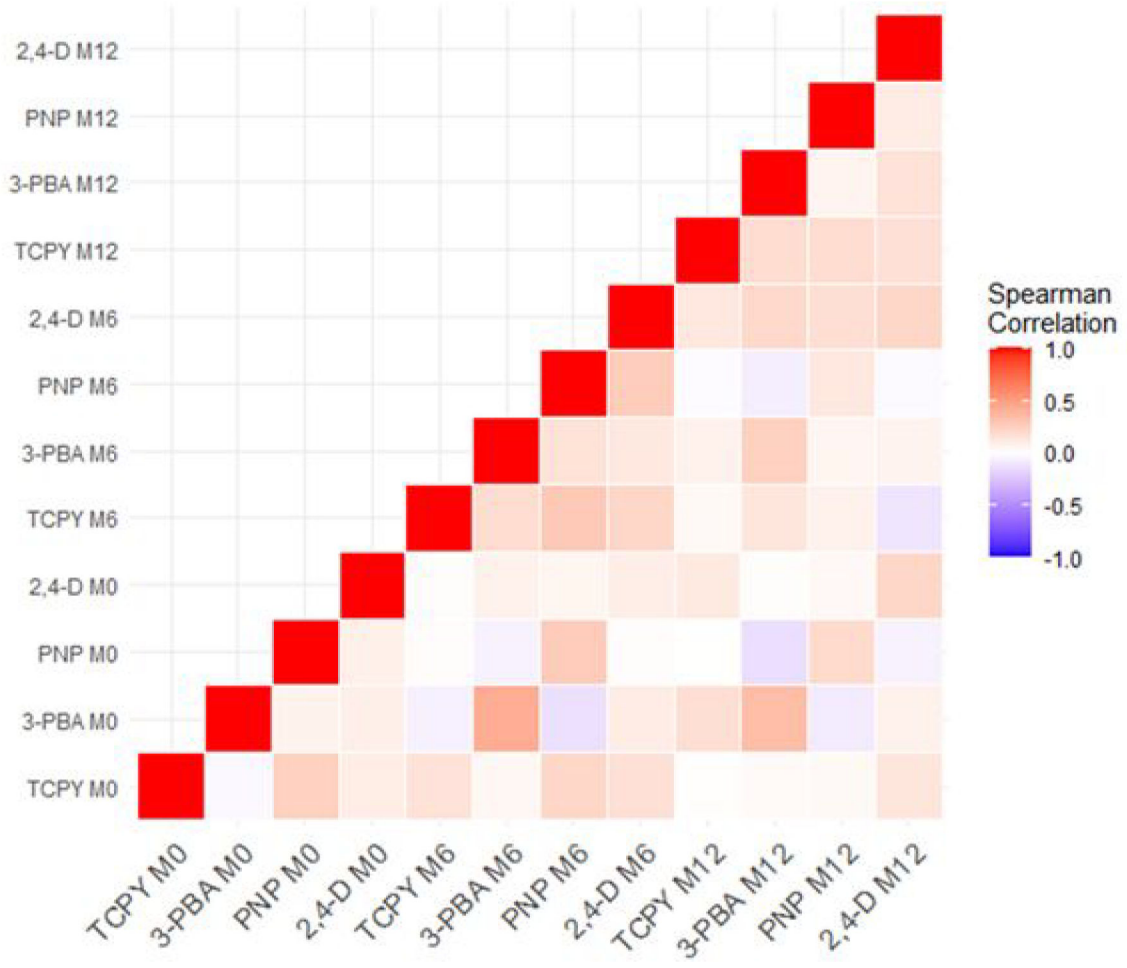

Figure 2.

Spearman Correlations between pesticide biomarkers at each time point

TCPy: 3,5,6-trichloro-2-pyridinol; ;PNP: *para*-nitrophenol; 3-PBA: 3-phenoxybenzoic acid; 2,4-D: 2,4-dichlorophenoxyacetic acid M0: Month 0 (baseline); M6: Month 6; M12: Month 12

Table 1.

Characteristics of 162 children enrolled in the Green Housing Study at baseline (2011–2015)

		Baseline				
		site			All sites	(%)
		Boston	Cincinnati	New Orleans		
		N=49	N=45	N=68	N=162	
Child Age (Years)	**N**	49	45	68	162	-
	Mean	10	9.6	9.6	9.7	-
Child Sex						
Female		23	19	35	77	47.5
Male		26	26	33	85	52.5
Child Ethnicity						
Non-Hispanic White		2	0	0	2	1.2
Non-Hispanic Black		3	45	67	115	71.0
Non-Hispanic Asian		27	0	0	27	16.7
Non-Hispanic Other		1	0	0	1	0.6
Hispanic Other		5	0	0	5	3.1
Hispanic White		10	0	0	10	6.2
Hispanic Black		1	0	1	2	1.2
BMI						
Underweight (<95th percentile)		3	0	8	11	6.8
Healthy (5th–85th percentile)		24	25	40	89	54.9
Overweight (>85th to 95th percentile)		14	5	9	28	17.3
Obese (≥95th percentile)		8	15	11	34	21.0
Annual Household Income						
≥ $25,000		10	1	1	12	7.4
< $25,000		39	44	64	147	90.7
Missing		0	0	3	3	1.9
Caregiver Education						
Greater than High School		9	22	21	52	32.1
High School/GED		25	13	29	67	41.4
Less than High School		15	10	15	40	24.7
Missing		0	0	3	3	1.9
Sensitization Status (n=157)						
Dog		8	12	13	43	27.4
Dust mite (Der f) *		21	15	43	79	50.3
Dust mite (Der p) *		22	16	39	77	49.0
Cockroach		14	19	21	54	34.4

	Baseline				
	site			All sites	(%)
	Boston	Cincinnati	New Orleans		
	N=49	N=45	N=68	N=162	
Cat	20	9	7	36	22.9
Mouse	11	0	8	19	12.1
Asthma Attacks Previous 3 months					
0	30	30	52	112	69.1
1	8	5	7	20	12.3
>1	10	10	8	28	17.3
Missing	1	0	1	2	1.2
Unscheduled Doctor/ER Visits previous 3 months (n=160)	5	5	7	17	10.6
Hospitalizations previous 3 months	0	0	1	1	0.6
Airway Inflammation (FeNO >35 ppb)	9	8	9	26	16.0
Daily Medication Use	10	25	13	48	29.6
Allergen Detected (n=116)					
Dog	5	8	11	24	14.8
Cat	4	6	3	13	8.0
Dust mite	4	11	25	40	24.7
Mouse	0	0	2	2	1.2
Cockroach	5	15	14	34	21.0
Season					
Fall	23	12	8	43	26.5
Spring	6	10	32	48	29.6
Summer	13	16	1	30	18.5
Winter	7	7	27	41	25.3
		Boston	**Cincinnati**	**New Orleans**	**All sites**
Number of Asthma Attacks in the previous three months	**N**	48	45	67	160
	Mean	1.1	0.9	0.7	0.9
	Std	2.4	2	2.5	2.4
	Min	0	0	0	0
	Median	0	0	0	0
	Max	12	12	20	20
FeNO (ppb)	**N**	45	33	68	146
	Mean	23.2	22.4	17.3	20.2
	Std	14.9	19.4	17.8	17.5
	Min	5	5	5	5
	Median	17	16	11	14
	Max	63	66	101	101
FEV_1% Predicted	**N**	47	42	68	157

	Baseline				
	site			All sites	(%)
	Boston	Cincinnati	New Orleans		
	N=49	N=45	N=68	N=162	
	Mean	98.1	96	90.3	94.1
	Std	18.5	12.7	21.7	18.9
	Min	63.8	69.8	53	53
	Median	98.1	94.9	88.9	93.1
	Max	159.6	121.1	185	185
$PM_{2.5}$ ($\mu g/m^3$)	N	44	43	65	152
	Mean	18.6	51.4	32.5	33.8
	Std	24	54.6	43.1	44
	Min	0.9	0.4	0.3	0.3
	Median	11.9	39.1	16	16.8
	Max	130.5	298.4	197	298.4
Cotinine (ng/mL)	N	48	35	68	151
	Mean	2.1	49.3	16	19.3
	Std	8.4	144.2	28.2	73.5
	10^{th} percentile	0.2	1.3	0.5	0.3
	Median	0.5	16.7	4.6	3.1
	95^{th} percentile	3.9	134.0	59.9	57.9

* Der f = *Dermatophagoides farinae*, Der p = *Dermatophagoides pteronyssinus*, Std : Standard Deviation

Table 2.

Percent of average urine samples (n) with pesticide metabolite concentrations (μg/L) below the limit of detection (<LOD), median, and interquartile range at each visit

		Baseline (N=162)			Month 6 (N=145)			Month 12 (N=142)			Overall (N=449)		
Organophosphorous Insecticide	**LOD (μg/L)**	**% <LOD**	**n**	**Median (IQR)**	**% <LOD**	**n**	**Median (IQR)**	**% <LOD**	**n**	**Median (IQR)**	**% <LOD**	**n**	**Median (IQR)**
TCPy	0.1	0	145	1.6 (0.9–2.7)	2.7	140	1.6 (1.1–3.1)	0	139	2.1 (1.3–3.1)	0.9	424	1.8 (1.1–2.9)
IMPY	0.1	59.7	58	0.2 (0.2–0.4)	42.4	80	0.3 (0.2–0.4)	66.1	47	0.2 (0.2–0.4)	56.1	185	0.2 (0.2–0.4)
PNP	0.1	0	145	1.1 (0.7–1.8)	0	143	1.1 (0.8–1.6)	0	139	1.1 (0.7–1.6)	0	427	1.1 (0.7–1.7)
Pyrethroid Insecticide													
3-PBA	0.1	6.2	134	0.8 (0.5–1.7)	6.2	135	1.2 (0.6–2.3)	9.3	126	1.0 (0.7–2.2)	7.2	395	1.0 (0.5–2.1)
trans-DCCA	0.6	82.7	25	5.6 (3.3–9.5)	82.6	25	4.4 (1.9–7.0)	82	25	3.3 (2.5–10.1)	82.4	75	4.2 (2.5–9.5)
4-F-3PBA	0.1	85.4	21	0.3 (0.2–0.8)	82.6	25	0.3 (0.2–0.4)	82	25	0.4 (0.2–1.1)	83.3	71	0.3 (0.2–0.8)
Herbicide													
2-4-D	0.15	24.8	109	0.6 (0.4–0.9)	25.6	107	0.6 (0.4– 09)	35.9	89	0.6 (0.4–1.0)	28.7	305	0.6 (0.4–0.9)

TCPy: 3,5,6-trichloro-2-pyridinol; IMPY: 2-isopropyl-4-methyl-6-hydroxypyrimidine; PNP: para-nitrophenol; 3-PBA: 3-phenoxybenzoic acid; 4F-3PBA: 4-fluoro-3-phenoxybenzoic acid; *trans*-DCCA: *trans*-3, -(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid

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Table 3.

Unadjusted and adjusted associations between a 1 μg/g creatinine increase in commonly detected (>60% samples) urinary pesticide biomarkers and asthma outcomes

	Asthma Attacks (no.)						Health Care Utilization (Y v N)						FeNO (ln)					
	Unadjusted			Adjusted *			Unadjusted			Adjusted**			Unadjusted			Adjusted***		
Biomarker	**IRR**	**95% CI**		**IRR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**		**β**	**95% CI**		**β**	**95% CI**	
TCPy	1.00	0.97	1.03	1.02	0.97	1.07	0.97	0.82	1.15	0.90	0.66	1.23	0.004	−0.001	0.01	0.13	−0.04	0.29
PNP	1.01	0.99	1.02	1.00	0.94	1.05	1.29	0.69	2.42	2.05	0.76	5.52	0.002	0.001	0.003	**−0.19** †	−0.35	−0.04
3-PBA	0.97	0.91	1.04	0.97	0.86	1.10	0.96	0.86	1.07	1.07	0.88	1.29	−0.01	−0.03	0.01	−0.02	−0.04	−0.01
2,4-D	0.97	0.77	1.21	1.02	0.79	1.30	1.29	0.94	1.76	0.82	0.48	1.38	−0.07	−0.16	0.03	**−0.22** †	−0.32	−0.12

* adjusted, dust mite sensitization, cockroach sensitization

** adjusted for BMI, daily medication use, HDM, season, age

*** adjusted for sex, race, income, dog, dust mite, cockroach, cat, and mouse sensitization, site, season and age

†: significant at p<0.05

TCPy: 3,5,6-trichloro-2-pyridinol, PNP: *para*-nitrophenol, 3-PBA: 3-phenoxybenzoic acid, 2,4-D: 2,4-dichlorophenoxyacetic acid

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Table 4.

Unadjusted and adjusted pesticide mixture index weights from WQS regression for asthma related health care utilization

	Unadjusted	Adjusted*
TCPy M0	4.9%	2.9%
TCPy M6	2.4%	3.1%
TCPy M12	3.2%	4.7%
TCPy Year Total	**10.5%**	**10.7%**
2,4-D M0	4.7%	7.6%
2,4-D M6	11.7%	12.8%
2,4-D M12	7.9%	7.9%
2,4-D Year Total	**24.3%**	**28.3%**
3-PBA M0	45.7%	40.3%
3-PBA M6	5.2%	0.6%
3-PBA M12	4.3%	4.5%
3-PBA Year Total	**55.2%**	**45.4%**
PNP M0	5.9%	10.0%
PNP M6	.8%	3.3%
PNP M12	3.0%	2.1%
PNP Year Total	**9.7%**	**15.4%**

M0: Baseline, M6: 6 Month, M12: 12 Month

*adjusted for BMI, daily medication use, HDM, season, age