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Impact of Chlorpyrifos Exposure on Lung Function in Egyptian Adolescent Agriculture Workers

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Abstract

Chlorpyrifos (CPF) is a widely used organophosphate insecticide that has been linked to detrimental health effects that range from neurological impacts to respiratory disease. The objective of this study was to assess respiratory symptoms associated with CPF exposure throughout the application season. Urine samples were collected from Egyptian adolescent applicators (n=206) and non-applicators (n=72) to assess 3,5,6-trichloro-2-pyridinol (TCPy), a biomarker for CPF exposure, along with spirometry measures to determine lung ventilatory function. Samples were collected over 7 months in 2016. Logistic regression was used to model the odds of reporting wheeze symptoms based on urinary TCPy concentrations while controlling for age and smoking in the household. Ordinal multinomial logistic regression was used to model the percent reference for forced expiratory volume in one second ($rFEV_1$) based on urinary TCPy concentration (μg/g creatinine). Wheezing increased with increasing pesticide exposure (OR = 1.74 (1.32 – 2.31)). There was no statistically significant relationship between $rFEV_1$ and TCPy concentration. Efforts to reduce pesticide exposure should be implemented to prevent the potential onset or exacerbation of any linked respiratory complications in adolescents.

Keywords

Spirometry; Pesticides; Adolescent; Occupational Exposure; Respiratory Health

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Introduction

Chlorpyrifos (CPF) is a widely used organophosphate insecticide applied for a broad range of insects and arthropods. CPF impacts the neurological system through the inactivation of acetylcholinesterase (AChE) and the overstimulation of the peripheral nervous system(1, 2). Agricultural workers are one of the most highly exposed populations especially when serving in the role of a pesticide applicator(3–5). Many adolescents around the world work as pesticide applicators. Previous studies have found that some of the health outcomes that may result from adolescent pesticide exposure include indicators of attention deficit hyperactivity disorder (ADHD), a decrease in intelligence quotient scores during neurodevelopment, impacted motor functioning, and respiratory and allergic symptoms(5–11).

While CPF has primarily been associated with neurological effects, there is some evidence that CPF may also predispose to respiratory complications(12). The respiratory tract serves as one of the target organ systems for organophosphate poisoning that is elicited through the inhibition of AChE in muscarinic and nicotinic receptors(13). Spirometric measurements such as forced expiratory volume (FEV_1), forced vital capacity (FVC), and a ratio of these two (FEV_1/FVC) have been utilized to determine lung ventilator function obstruction and restriction in adult pesticide applicators(14–16). At high levels of CPF exposure, where there is substantial AChE inhibition, there has been evidence showing the presence of adverse respiratory effects in adults. Decreased lung ventilator function is a less understood health outcome in the younger workforce that may increase with varying levels of occupational exposure experienced during the application of pesticides.

Studies conducted to analyze the impact of pesticides on adolescent lung ventilator function, though few, have shown evidence of deleterious effects with impacted spirometric measurements and reported symptoms. An inverse relationship of organophosphate exposure with lung ventilator function has been previously observed for adolescent populations(5, 9). This relationship warrants further investigation into how organophosphate exposure can impact adolescent populations especially when they serve in the role of pesticide applicators or are heavily involved in agricultural production as found in countries such as Egypt. The present study builds upon a previously conducted study with the same cohort of adolescent pesticide workers that was conducted in 2010. This previous study found non-significant results with reported higher odds of wheezing in applicators vs non-applicators and a non-significant inverse association between CPF exposure and lung function(9). These findings are similar with previous studies that have found limited to no association between CPF exposure and lung function. The impact of pesticide exposure on lung function and respiratory symptoms has yielded conflicting evidence between the exposure and outcome association. A systematic review in 2017 examining the relationship between occupation and environmental exposure to pesticides and lung function found tentative evidence with reduced FEV_1/FVC measures from exposure to ChE-inhibiting pesticides(17). Another study examining pesticide exposure in Ethiopian workers demonstrated better spirometry measures for applicators vs. non applicators with the only worsening symptom being that of chest tightness in applicators. However, the authors mentioned to consider the use of respiratory protective equipment in the applicator group as well as the potential impact of

the healthy worker effect due to the young age of the workers(18). The present study seeks to inform previous results with more up to date data, a larger sample of participants, multiple recorded measurements on individuals, and alternative statistical methods to evaluate the outcomes of interest.

The objective of this study was to further evaluate the association between occupational chlorpyrifos exposure and lung ventilator function within pesticide applicators and non-applicators across a longitudinal study in Egyptian adolescent males. In this study, our primary outcome of lung ventilatory function was measured with spirometry, and defined with the use of FEV_1, percent reference for FEV_1, and self-reported wheeze. Exposure to chlorpyrifos was measured through analysis of urinary 3, 5, 6-trichloro-2-pyrindinol (TCPy), a specific metabolite for this pesticide and expressed as μg/g creatinine. We hypothesized that higher concentrations of chlorpyrifos would lead to an inverse association of lung ventilatory function measured as worse FEV_1 results and the self-report of wheezing.

Methods

Study Population

This study is a part of the greater Egyptian Adolescent Study (EGAD), a longitudinal study whose goal was to evaluate occupational exposure to pesticides in Egypt from 2014 – 2017. Baseline questionnaires were administered during the enrollment period in 2014 and 2015 while non-applicators completed them only in 2015. The present study uses data that were collected in 2016. Urinary measures of pesticide exposure and spirometric measurements were collected in the months of April, May, August and December. Additionally, a short questionnaire was administered during these four months in 2016 to identify medical and lifestyle factors. This short questionnaire asked for the presence of wheezing which was used as a secondary outcome in addition to the spirometry results. The different recruitment sites included the field stations of Quesna, Shohada, Tala, and Berket El Saba, all located in the Nile Delta region in Egypt. All adolescent applicators employed at the four field stations were invited and agreed to participate, with a response rate of 100% as described in a previous study(11). Parental consent and child assent were obtained for all participants under the age of 18 and informed consent was obtained from those over the age of 18. Females were not a part of this study since they do not apply pesticides.

The subset population for this current study was limited to those who initially enrolled at an age less than 20 and had completed at least one spirometric measurement and urine analysis. Our applicator group (n = 206) were employed by the Ministry of Agriculture and were sampled in the summer months for the application of pesticides in farms owned by local families or neighbors. Common tasks included pesticide preparation (mixing and filling sprayers), application, and marking of field limits. Subsequently, our non-applicator group (n = 72) was recruited from the same communities. Participants were asked to provide urine samples for analysis of TCPy concentrations to estimate chlorpyrifos exposure throughout the year. Spirometry was concurrently conducted to further analyze FEV_1 and percent reference FEV_1 as measurement of lung ventilator function during four of the follow up visits (April, May, August, and December). Spirometry was conducted by occupational health physicians, who were trained on assessing respiratory functions using

different methodology. Due to budgetary reasons non-applicators were only evaluated during April and August. Non-applicators were included to assure a population with low pesticide exposure was available for comparison with adolescents who had higher CPF exposure. Sensitivity analysis was run excluding this group to evaluate if selection bias from self-selection into the applicator occupation biased our primary results. Biomonitoring data and spirometric data from these four visits were used in the primary analysis. A total of 68 applicators and 22 non-applicators were excluded from statistical models due to incomplete data on spirometric and urinary measures. This study was performed in line with the principles of the Declaration of Helsinki. The University of Iowa Human Subjects Office reviewed and approved informed consent and study procedures (IRB ID #201301760).

Measurements

The four testing sessions in 2016 were timed to span over the season of pesticide application, specifically before application (April), during, (May and August), and after (December). Both urine samples and spirometric measurements were collected at each session. Exposure estimates were done by assessing the individual biological metabolites of CPF and the outcome is the individual performance in ventilatory functions. Exposure and outcome measures, in addition to sociodemographic characteristics, were analyzed in the regression models to examine the effect of exposure to CPF on the ventilatory functions.

Urine samples were collected during in person testing sessions, placed on wet ice, and frozen aliquots were sent to the University at Buffalo for analysis of pesticide metabolites. The chlorpyrifos-specific metabolite, TCPy (3,5,6-trichloro-2-pyridinol), was analyzed by negative ion chemical ionization gas chromatography-mass spectrometry (GC/MS), with ^{13}C-^{15}N-3,5,6-TCPy as an internal standard, as described earlier(19). The within-run imprecision of this assay is very low, as shown by a < 2% coefficient of variation (CV) and an intra-class correlation coefficient of 0.997. The LOD for TCPy was 0.22 ng/ml. Creatinine concentrations were measured using the Jaffe reaction to obtain urinary TCPy concentrations expressed as micrograms TCPy per gram creatinine as described in a previous study(19). Duplicate samples and control samples were utilized in each analytical series for quality assurance. Average creatinine corrected urinary metabolite concentrations were calculated for each month.

Lung ventilatory function was determined through both spirometry and questionnaires. Pulmonary ventilator function tests were conducted in all four months of the present study. A Spirolab II spirometer was utilized to perform three maneuvers according to the American Thoracic Society as described in a previous study(9). FEV_1 and percent reference FEV_1 were recorded and calculated for each participant. Percent reference FEV_1 was calculated for each participant by dividing the measured value of FEV_1 by the predicted value for the same individual. The measurement of each participant was used as a percentage of the predicted values of each measure. These predicted values were estimated by the measuring devices according to the participant's characteristics (e.g. age, height, and gender). Predicted values and associated equations were calculated in accordance to the American Thoracic Society(20). Repeat spirometry sessions were performed at similar times within each month. Wheezing was defined as present or not present based on self-reported episodes of wheezing

since the last visit and recorded at the time of spirometric testing. At enrollment, a baseline questionnaire was administered through interviews and obtained information on age (number of years), education (number of years), body mass index (kg/m^2), time spent working (hours per day), city of enrollment (Qwesna, Shohada, Tala, or Berket El-Saba), use of personal protective equipment (yes/no for various PPE), and if anyone in the household currently smoked (yes/no).

Statistical Analysis

Descriptive statistics were reported on select variables between the two groups of pesticide applicators and non-applicators. The odds of reporting wheeze symptoms were evaluated using logistic regression modelling. TCPy (continuous and categorical) concentrations served as the exposure of interest while controlling for age and smoking in the household. Natural logarithmic transformation of TCPy concentrations were used in the models and verified to be normally distributed. Multinomial logistic regression was utilized to evaluate the increase in categorical level of percent reference FEV_1 with continuously increasing values of TCPy. Levels of percent reference FEV_1 were constructed in tertiles distinguishing low, middle, and high performance based on cohort results. Logistic regression models were utilized to individually compare the high and middle categories to the lowest to explore the potential for a non-linear relationship between percent reference FEV_1 and TCPy concentration. To account for the repeated measurements of the participants throughout the study we used Generalized Estimating Equations with an independent correlation structure. The SAS Proc GENMOD procedure was used for the analysis of the data (SAS version 9.4; SAS Institute, Inc., Cary, NC). An alpha of 0.05 was used to indicate statistical significance in evaluating odds ratios and parameter estimates. Additional variables were tested in the modelling process to identify correlations and potential confounding to construct the final model. Linearity between exposure and outcomes of interest were investigated by categorizing the TCPy values into quartiles. Sensitivity analysis was completed restricting to only pesticide applicators to compare results on the association between CPF exposure and percent reference FEV_1 categories in the group alone. Specimen collection in the months of May and December was completed for a subpopulation of applicators to measure exposure over time. Only the data collected from all participants during April and August collection periods were used in the analysis. Furthermore, only measures in April and August that did not have missing outcomes were used for our final models. There were a total of n = 370 measurements used in the analysis (n = 188 in April and n = 182 in August) with 57 missing spirometric measures and no participants measurement of wheeze.

Results

Table 1 presents baseline characteristics for adolescents during 2016 based on applicator status. The age range of all participants was 10 – 19 years old with an average age of 15 years old. Years of education and BMI were similar across both groups with just over 9 years of educational experience and approximately a BMI of 22 kg/m^2. Both applicator and non-applicator groups were found to have homogenous demographic characteristics. A breakdown of cities where participants were recruited shows that the majority of the applicators came from Qwesna (n = 72) and the minority from Berket El-Saba (n = 40).

For non-applicators, the majority were from Shohada (n = 23) and the minority were from Berket El-Saba (n = 13). Use of personnel protective equipment and clothing was also reported for applicators. The most used equipment or clothing among applicators included shoes, head covers/cap, and goggles with the least used being protective masks, covers, or respirators.

Table 2 presents the mean levels of urinary TCPy concentrations among both group as well as their mean levels of spirometric measures. The highest concentrations were found in the month of August for applicators with an average of 28.2 μg/g creatinine (SD: 44.4) The lowest levels for applicators were in December with mean 7.8 μg/g creatinine (SD: 4.4). Mean values of FEV_1 and percent reference FEV_1 were also calculated for both applicator and non-applicator groups. Both groups displayed decreasing trends for values of these spirometric measurements from the months of April to December. Applicators displayed a higher magnitude of average TCPy concentration over time.

The association between metabolite concentrations and wheeze based on our logistic regression analysis are displayed in Table 3. The unadjusted model examined the univariate relationship between the natural log transformed values of urinary TCPy and wheezing while the final model controlled for age and smoking in household. When adjusting for age and smoking in the household, an odds ratio of 1.74 (95% CI: 1.32 – 2.31) for experiencing wheezing per one unit increase in log TCPy was observed. Table 3 also shows the association between metabolite concentrations and wheeze with log TCPy categorized into quartiles instead of being treated as a continuous exposure. Results were statistically significant at only the highest category of exposure OR = 2.77 (95% CI: 1.49 – 5.15) in the adjusted model and OR = 2.10 (95% CI: 1.14 – 3.86) in applicator only adjusted model.

The association between CPF exposure (urinary TCPy concentration) and percent reference FEV_1 based on our ordinal regression analysis are displayed in Table 4. The full model controlled for both age and exposure to smoking in the household. There was not a statistically significant relationship observed for categories of FEV_1 and urinary TCPy (continuous or categorized). When including only the applicator group in our sensitivity analysis, an odds ratio of 1.23 (95% CI: 0.92 – 1.64) for having worse FEV_1 per one unit increase in log TCPy was observed. After categorizing urinary TCPy, odds ratios for worse FEV_1 were not statistically significant but an increasing magnitude of the likelihood to be in a worse lung function category occurred with higher urinary TCPy categories of CPF exposure.

Discussion

We observed an increased frequency of self-reported wheeze with higher levels of exposure to the organophosphate pesticide CPF. Mean levels of chlorpyrifos tended to be higher during the pesticide application months with reduced concentrations towards the latter end of the year. CPF exposure was variable across the population as indicated by the standard deviations of the mean exposures across the four months. Effective use of personal protective equipment among applicators was limited, potentially impacted by unavailable equipment or resources which led to low self-reported use.

Two previous studies have analyzed the effect of pesticide exposure on lung ventilatory function in adults. Hoppin et al. utilized data from the Agricultural Health Study (AHS) to analyze exposure to pesticides and respiratory outcomes in adult farmers (n = 17,920) and commercial applicators (n = 2,255) in Iowa and North Carolina(21). Results yielded evidence for an association between organophosphate exposure and the outcome of wheeze in both farmers (OR = 1.48, 95% CI: 1.00 – 2.19) and commercial applicators (OR = 1.96, 95% CI: 1.05 – 3.66) who had used chlorpyrifos for at least 20 days in a year(21). Analyzing these two populations individually, another study that utilized the AHS looked specifically at farmers and found an elevated odds ratio for the outcome of wheeze when exposed to chlorpyrifos 1.12 (95% CI: 1.01 – 1.25)(22). Commercial applicators who applied chlorpyrifos for more than 40 days per year, displayed an odds ratio of 2.40 (95% CI: 1.24 – 4.65)(23). An earlier study in the same communities of the current one showed that chlorpyrifos exposure (urinary TCPy) was found to have an inverse relationship with spirometric lung function measurements with a reported odds ratio of 3.41 (95% CI: 0.70 – 17.41) for the symptom of wheeze when comparing adolescent applicators and non-applicators in Egypt(9). Our final model found a statistically significant effect of increasing TCPy concentration leading to an increase in the likelihood of displaying wheezing symptoms per unit increase in log TCPy, OR = 1.74 (95% CI: 1.32 – 2.31). Analyzing TCPy as a categorical variable showed that relative to the lowest category, only the highest quartile was significantly different OR = 2.77 (95% CI: 1.49 – 5.15). The observed higher odds ratio suggests a possible threshold effect for self-reported wheeze and CPF exposure. Though the magnitude of effect varies among all these studies, a consistent negative effect of pesticide exposure on lung ventilatory function was observed.

Modelling the spirometric outcome of percent reference FEV_1 categories, our results yielded a non-significant odds ratio of 1.14 in our final model. After categorizing TCPy in our models we still did not observe a significant relationship between urinary TCPy levels and spirometric measures. While results were non-significant, we did observe worse lung function for the highest exposure level. Prior studies, CHAMACOS and Ugandan studies, evaluating spirometric measurements and pesticide exposure have observed a negative association in adults and children. Hansen et al. observed that smallholder farmers in Uganda (n = 364) who were exposed to carbamate and organophosphate insecticides displayed a significant association between high exposure (AChE/Hb 24.50 U/g) and a lower mean FEV_1(14). Raanan et al. found that childhood exposure to organophosphates displayed an adverse association with spirometric measures in children of age 7 with their coefficient estimates through regression modelling showing a decrease in FEV_1 $\beta = -0.16$ (95% CI: −0.30 – −0.02) and FVC $\beta = -0.17$ (95% CI: −0.34 – 0.01) per tenfold increase in pesticide concentrations(5).

The findings of human lung ventilatory function impacted by CPF exposure are also supported by studies utilizing rats to model the effects of organophosphate pesticide exposure. Inhibition of AChE activity and deleterious effects on enzyme activity were found in the lungs of adult rats when exposed specifically to chlorpyrifos(24). CPF was also found to alter the respiratory function in rats that manifested in symptoms such as bradypnea when injected with the pesticide(25). A potential mechanism by which CPF may impact

lung ventilator function is the induction of neuronal M2 muscarinic receptor dysfunction and airway hyperactivity based on studies using animal models(26, 27).

Our study had some limitations. Due to the variability within CPF exposure categories, the impact of exposure on spirometry could vary within the categories of exposure in our statistical models. We expect this exposure classification would bias results towards the null. Assessing wheeze was only through self-reported measures. However, the assessment was uniformly applied to all adolescents in the study cohort independent of pesticide exposure. Inclusion of non-applicators had the potential to bias the relationship of CPF and lung ventilatory function based on unmeasured confounding and selection bias from self-selection into the applicator population. Further, non-applicators had fewer spirometry visits than applicators. To explore this bias, non-applicators were excluded in sensitivity analysis that yielded similar results to the models including the full population. Within the applicator only population residual confounding may still exist. We observed the applicator population to have little variability across the measured covariates, so we believe the potential of residual confounding or unmeasured confounding to bias our results to be low. We were unable to complete non-applicator only sensitivity analysis to evaluate if higher levels of residential exposure to pesticides impaired lung ventilatory function in low-level exposed individuals. Our results should not be generalized to these lower exposed populations. Finally, there is also a limitation in attributing physiological impacts solely to the active ingredient in pesticides as many often are combined with inert ingredients (e.g. solvents and adjuvants) to assist in the absorption(28). A systematic review found that a majority of pesticide formulations had increased toxicity compared to the active ingredient alone(29). Analyzing how the mixture or independent inert ingredients impact our outcomes of interest (wheezing and spirometry) will be important in understanding associations between pesticide exposure and lung function.

Conclusion

The results of this study and analysis provide further evidence of the impact pesticide exposure can have on human health. Specifically, CPF exposure in young adolescent agricultural workers increased wheezing. Additional studies focused on occupational exposure in this vulnerable population will be crucial to develop our understanding of both acute and chronic health effects. Additionally, the development and implementation of controls to reduce or prevent exposure will be crucial in preventative measures to protect not only workers, but their communities as well. Future studies would benefit from a larger sample with fully completed measurements of lung ventilator function for both applicators and their referent group.

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Table 1.

Characteristics of EGAD study participants by applicator status 2016.

	Applicators ***(n = 206)***	**Non-Applicators** ***(n = 72)***
	Mean (SD)	
Age (years)	15.2 (2.0)	14.8 (2.3)
Education (years)	9.6 (1.9)	9.4 (2.2)
Body Mass Index (kg/m^2)	22.0 (3.2)	21.7 (2.7)
Time spent working (Hours)	3.3 (1.2)	N/A
	Number (%)	
Smoking Household (Yes)	103 (50.0)	37 (51.4)
	Field Station	
	Number (%)	
Qwesna	72 (35.0)	15 (20.8)
Shohada	53 (25.7)	23 (31.9)
Tala	41 (19.9)	21 (29.2)
Berket El-Saba	40 (19.4)	13 (18.1)
Wears while applying pesticide, Number (%)		
Shoes (yes)	123 (59.7)	
Head cover/cap (yes)	84 (40.8)	
Goggles (yes)	62 (30.1)	
Glasses (yes)	11 (5.3)	
Mask over mouth (yes)	5 (2.4)	
Mask over mouth and nose (yes)	41 (19.9)	
Respirator (yes)	2 (1.0)	

Notes: Abbreviations: SD, standard deviation; %, percent of total recorded responses.

Table 2.

Spirometry and CPF exposure measures of EGAD study participants by applicator status 2016.

	Applicators ***(n = 206)***	**Non-Applicators** ***(n = 72)***
Participation per Urinary Collection Session		
	Number (%)	
Session:		
APR	138 (67.0)	50 (69.4)
MAY	18 (8.7)	N/A
AUG	133 (64.6)	49 (68.1)
DEC	17 (8.3)	N/A
Urinary TCPy (μg/g creatinine)		
	Mean (SD)	
Session:		
APR	18.1 (17.8)	15.6 (13.1)
MAY	18.8 (17.2)	N/A
AUG	28.2 (44.4)	13.3 (7.8)
DEC	7.8 (4.4)	N/A
Spirometric measurements		
	Mean (SD)	
APR FEV_1	3.0 (1.0)	3.1 (1.0)
MAY FEV_1	2.6 (0.7)	2.7 (0.8)
AUG FEV_1	2.5 (0.8)	2.5 (0.7)
DEC FEV_1	2.4 (0.9)	2.5 (0.7)
%Ref APR FEV_1	88.1% (26.1)	93.7% (24.6)
%Ref MAY FEV_1	73.7% (20.2)	77.1% (16.5)
%Ref AUG FEV_1	71.5% (20.2)	75.6% (17.0)
%Ref DEC FEV_1	70.3% (22.6)	76.8% (18.9)

Notes: Abbreviations: SD, standard deviation; FEV_1, forced expiratory volume in one second; %Ref, percent reference for FEV_1 calculated by dividing the recorded FEV_1 value of the participant by their reference value for FEV_1.

Table 3.

Odds ratios and 95% confidence levels for wheezing based on log urinary TCPy concentration and category.

	N	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	N	Applicators Only Adj. OR (95% CI)
One unit increase in log TCPy	370	1.64 (1.26 – 2.15)	1.74 (1.32 – 2.31)	271	1.38 (1.07 – 1.78)
TCPy Category (μg/g creatinine)	**N**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**N**	**Applicators Only Adj. OR (95% CI)**
<7.77	91	Referent	Referent	66	Referent
7.77–12.18	89	0.94 (0.47 – 1.86)	0.92 (0.45 – 1.89)	56	1.36 (0.70 – 2.67)
12.30–20.70	91	1.41 (0.76 – 2.63)	1.42 (0.74 – 2.74)	68	1.42 (0.76 – 2.67)
>20.91	99	2.46 (1.36 – 4.44)	2.77 (1.49 – 5.15)	81	2.10 (1.14 – 3.86)

Notes: Abbreviations: OR, odds ratio; CI, confidence interval. Adjusted model controlled for age and smoking in the household. N includes measures at times in April and August.

Table 4.

Ordinal Model Odds ratios and 95% confidence levels for reference FEV_1 categories based on applicator status and urinary TCPy concentration.

	N	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	N	Applicators Only Adj. OR (95% CI)
One unit increase in log TCPy	313	1.09 (0.85 – 1.39)	1.14 (0.87 – 1.48)	228	1.23 (0.92 – 1.64)
TCPy Category (μg/g creatinine)	**N**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**N**	**Applicators Only Adj. OR (95% CI)**
<7.77	78	Referent	Referent	57	Referent
7.77–12.18	71	0.70 (0.39 – 1.26)	0.74 (0.41 – 1.33)	44	0.80 (0.38 – 1.68)
12.30–20.70	81	0.74 (0.41 – 1.33)	0.84 (0.47 – 1.51)	59	1.21 (0.60 – 2.42)
>20.91	83	0.98 (0.56 – 1.73)	1.11 (0.61 – 2.00)	68	1.33 (0.67 – 2.67)

Notes: Abbreviations: OR, odds ratio; CI, confidence interval. Adjusted model controlled for age and smoking in the household. N includes measures at times in April and August.