Temporal Association of Children's Pesticide Exposure and Agricultural Spraying: Report of a Longitudinal Biological Monitoring Study

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We measured organophosphorus (OP) pesticide exposures of young children living in an agricultural community over an entire year and evaluated the impact of agricultural spraying on exposure. We also examined the roles of age, sex, parental occupation, and residential proximity to fields. We recruited 44 children (2–5 years old) through a Women, Infants, and Children clinic. We collected urine samples on a biweekly basis over a 21-month period. Each child provided at least 16 urine samples, and most provided 26. We analyzed samples for the dialkylphosphate (DAP) metabolites common to the OP pesticides. DAP concentrations were elevated in months when OP pesticides were sprayed in the region's orchards. The geometric means of dimethyl and diethyl DAPs during spray months were higher than those during nonspray months ($p = 0.009$ for dimethyl; $p = 0.018$ for diethyl). Dimethyl DAP geometric means were 0.1 and 0.07 µmol/L for spray months and nonspray months, respectively (57% difference); diethyl DAP geometric means were 0.49 and 0.35, respectively (40% difference). We also observed differences for sex of the child, with male levels higher than female levels ($p = 0.005$ for dimethyl; $p = 0.046$ for diethyl). We observed no differences due to age, parental occupation, or residential proximity to fields. This study reports for the first time the temporal pattern of pesticide exposures over the course of a full year and indicates that pesticide spraying in an agricultural region can increase children's exposure in the absence of parental work contact with pesticides or residential proximity to pesticide-treated farmland. *Key words*: agricultural spraying, biological monitoring, children, dialkylphosphate compounds, exposure, longitudinal study, organophosphorus pesticides, urine. *Environ Health Perspect* 110:829–833 (2002). [Online 9 July 2002]
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Concerns about quantitative and qualitative differences in the toxicity of and the exposure to pesticides between children and adults were raised by the National Research Council's 1993 report, *Pesticides in the Diets of Infants and Children* (*1*). This report recognized that although dietary intake of pesticides may represent the major source of exposure for children, nondietary intake of pesticides should also be accounted for in the analysis of total or aggregate exposure. As a result, the Food Quality Protection Act of 1996 (FQPA) (*2*) calls for analysis of exposure from all sources and pathways in the setting of pesticide tolerances, with special emphasis on children, and new methods have been proposed for such analyses (*3,4*). Recent studies have demonstrated that children living in agricultural communities can have elevated pesticide exposures because of their proximity to pesticide-treated farmlands and because their parents can transmit pesticides from the workplace to the home (*5,6*).

Because of behavioral, dietary, and physiologic characteristics associated with development, children may be particularly susceptible to the effects of pesticides (*7*), and to organophosphorus (OP) pesticides in particular (*8*). OP pesticides represent the first group of chemicals to be regulated as a class under FQPA because of their wide use in both agricultural and residential settings, and

because they exhibit a common mechanism of action—the inhibition of cholinesterase, an important neurologic enzyme in humans (*9*). Several studies have focused on monitoring children's exposure to OP pesticides by measuring dialkylphosphate (DAP) compounds in the urine (*6,10–13*). A recent study by the U.S. Centers for Disease Control and Prevention analyzed these same metabolites in 703 people 6 to 59 years old (*14*). All of these studies were conducted cross-sectionally, so their results represent exposures over relatively short time periods. Only one study to date has examined pesticide exposure with a longitudinal study design, but the study population did not include young children (*15*).

Our primary objectives in this study were to develop a temporal profile of OP pesticide exposure in a cohort of children living in an agricultural community and to examine the relationship between agricultural pesticide use and exposure. We also examined the temporal pattern of exposure regarding age, sex, residential proximity to orchards, and parental occupation using urinary DAP metabolite concentrations as exposure biomarkers.

Methods

Recruitment. Recruitment of participants took place in a Women, Infants, and Children (WIC) clinic in a central Washington State

community located in the tree fruit production region. WIC clinics provide health and social services to expectant parents or parents with young children. Recruitment of participants through the WIC clinic allowed us to efficiently enroll young children. Each day the study staff obtained a list of the WIC clinic's appointments before the patients' visit, to know how many families to expect. The study staff attempted to talk to every family that came into the office waiting room before their appointments. We considered families with children 2–5 years old eligible for the study, regardless of parental occupation or residential location. We asked parents if they would be willing to assist in the collection of biweekly urine samples from their child over the course of 1 year. We asked parents who chose to enroll their children in the study to sign a consent form and to provide contact information. These procedures took approximately 5 min and did not disrupt the normal operations of the clinic.

Initial recruitment took place in December 1997. Some attrition occurred during the winter months, so we recruited additional families in April 1998. We interviewed each family four times: one interview at enrollment, two interim interviews, and an exit interview. Information collected through this interview process included date of birth of study children, weight, parental occupations, household pesticide use, and children's activities. All procedures that involved adult or child participants were reviewed and approved by the University of

Washington Division of Human Subjects before we started data collection.

Field sample collection. We hired local bilingual residents to facilitate the routine collection of urine samples and to conduct the interviews. Staff members picked up the urine samples at a convenient time chosen by the family and provided the families with a new urine collection cup or commode insert (Specipan; Baxter Scientific, McGaw Park, IL) for the next collection. We labeled the collection cup with the family identification number and the time of sample collection and placed it in a cooler with ice packs. We also placed a blank (a urine or surrogate solution that did not have any OP pesticide urinary metabolites) in the sample cooler on alternating weeks to monitor for cross-contamination.

We then transported samples to a field laboratory for processing. We measured and recorded the total volume of each urine sample and aliquoted each sample into three 15-mL polypropylene screw-cap centrifuge tubes, discarding any remaining urine. Along with the field samples, we froze quality control samples that consisted of blank urine samples to evaluate potential cross-contamination, internal standard samples fortified with tributyl phosphate, and field spike samples to determine possible OP metabolite degradation before analysis. We stored all samples at –10°C in the field laboratory until we transferred them on dry ice to the University of Washington's Environmental Health Laboratory (Seattle, WA), where we stored them at –20°C before analysis.

Sample analysis. We analyzed urine samples for six DAP metabolites common to most OP pesticides: dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). We performed analysis according to the method described by Moate et al. (*16*): HP 5890 gas chromatograph (Hewlett Packard, Palo Alto, CA) with a flame photometric detector, a Supelco SPB-20 column (Supelco, Bellefonte, PA), and a splitless injector. Sample preparation included solid-phase extraction, azeotropic distillation, and pentafluoro(methyl)benzylbromide derivatization.

We performed method validation by fortification of blank urine samples with the six DAPs at three levels (2, 4, and 10 µg/L) and analysis for recovery accuracy and precision across the fortification levels. Mean recoveries for the six DAPs ranged from 85% to 137%, and coefficients of variation ranged from 9% to 24%. We found no significant differences of recoveries of DAPs across the three fortification levels (analysis of variance, $p > 0.05$). We determined the limit of detection (LOD)

for each DAP compound based on the mean recovery of the lowest fortification level minus 3 standard deviations: 7.4 (µg/L) for DMP, 1.1 for DMTP, 0.7 for DMDTP, 6.6 for DEP, 1.2 for DETP, and 1.1 for DEDTP. We also measured urine samples for creatinine concentration by the Jaffe colorimetric method (Sigma Diagnostics, St. Louis, MO). We report results as milligrams creatinine per liter of urine.

Residential proximity to farmland. We determined the proximity of each participant's residence to orchards with a global position system (GPS) unit (Enertech, Campbell, CA) and digital aerial photographs for the study region (*17*). We placed the GPS unit in front of the house and recorded data for 2 min (~20 readings). We later downloaded data from the GPS unit and superimposed them onto the digital aerial photographs in which orchard locations had been plotted as polygons. We assumed an area of land to be an orchard if orderly rows of trees were visible in the aerial photograph. We measured the distances between the homes (points) and orchards (polygons) with a function in ArcView 3.2 (ESRI, Redlands, CA), a spatial analysis software application that links mapping with databases of geographic and feature information.

Data analysis. We identified metabolite residues that were < LOD and assigned them values of 0.5 LOD for statistical analysis. DMTP and DETP were the DAP compounds most frequently detected in urine samples (73% for DMTP and 53% for DETP). This finding is consistent with a previous study in which spot urine samples were collected from children living in this same agricultural community (*6*) and with a study in which spot urine samples were collected from children living in a metropolitan area (*13*).

We converted each of the dimethyl and diethyl DAP metabolite concentrations to their molar concentrations (micromoles per liter) and summed them to produce a single dimethyl or diethyl DAP concentration for each sample:

$$OP_{DM} = (C_{DMP}/MW_{DMP} \\ + C_{DMTP}/MW_{DMTP} \\ + C_{DMDTP}/MW_{DMDTP}),$$

where OP_{DM} is the total dimethyl OP pesticide metabolite concentration (micromoles per liter), C is the concentration of the respective metabolite (micrograms per liter), and MW is the molecular weight of the respective metabolite (grams per mole). We used a similar equation for the diethyl metabolites.

We established two criteria for children to be included in the final data analysis: *a*) contribution of at least one urine sample

every 3 months for three consecutive seasons and *b*) a sampling period that spanned the OP pesticide spray months (March–August). The distributions for the dimethyl and diethyl DAP molar concentrations were skewed and fit a log-normal distribution. We used SAS software (SAS, Inc., Cary, NC) to conduct a general linear model procedure (*proc glm*). We treated child and month as main effects, and we fit the model to the log of the metabolite concentration. We tested the primary hypothesis of the study—that agricultural spraying increased OP pesticide metabolite concentrations in children's urine—by designating certain months as spray months and all other months as nonspray months. Spray month designation was based on interviews with the region's cooperative extension agents and records of the Washington Tree Fruit Research Commission's laboratory and field station.

Results

Recruitment efforts yielded a total of 57 children in 52 families, and we included 44 children (one child per family) in the final data set based on the selection criteria described above. Most of the families that participated in this study were Latino. A child's age was defined as age at the midpoint of his or her participation in the study. Two children were 2 years old, and 14 children each were 3, 4, and 5 years old. There were 28 girls (64%) and 16 boys (36%), and their mean ages were 3.7 and 4.3 years, respectively. Parents of 27 children worked in field agriculture as farm workers (none were pesticide applicators), and the parents of 17 children were employed as packing shed workers, truck drivers, or salespeople. Five families lived < 60 m (200 ft) from an orchard, 9 families lived between 60 and 400 m (200 ft and 0.25 mile), and 30 families lived ≥ 400 m (> 0.25 mile) from an orchard.

The original study goal was to collect biweekly samples from each child until 26 samples had been collected. However, individual children gave anywhere from 16 to 26 urine samples over a 21-month period. We collected 998 urine samples from the 44 children, of which we did not analyze 26 (3%) because of spillage, loss, or insufficient volume for analysis. We analyzed the remaining 972 samples for DAP metabolites and creatinine concentrations.

Table 1 presents the overall distributions of dimethyl and diethyl DAP concentrations for the 44 children that we sampled over a 21-month sampling period. In general, dimethyl DAP concentrations (geometric mean = 0.08 µmol/L; geometric SD = 2.5) were higher and more variable than were diethyl DAP concentrations (geometric mean = 0.036 µmol/L; geometric SD = 1.6).

Temporal variation of metabolite concentrations. We analyzed DAP concentration data to determine whether the children's exposure to OP pesticides had a temporal variation. Figures 1 and 2 show the geometric means and the 95% confidence intervals of dimethyl and diethyl DAP concentrations, respectively, by months. The arrows indicate the months that either dimethyl OP pesticides (e.g., azinphos-methyl or phosmet) or diethyl OP pesticides (e.g., chlorpyrifos or diazinon) were sprayed in the region's orchards. Dimethyl DAP concentrations in urine were elevated in the months of June, July, and August of 1998 and 1999, with a decrease across the fall and the winter. An increase in diethyl DAP concentrations was clearly evident in the March and April 1998 spraying period and gradually decreased during the rest of the study period. Concentrations in 1999 were low compared with 1998, and no apparent increase coincident with spraying was apparent in that year.

Results from the general linear model procedure (Table 2) demonstrated that the between-month ($p < 0.001$) and between-child ($p < 0.001$) variations were significant for both dimethyl and diethyl DAP concentrations. The large error terms shown in Table 2 indicate no substantial variability for a child within a single month. Because we discovered month-to-month variation, we compared the geometric means of both dimethyl and diethyl DAP levels for months when respective groups of OP pesticides were sprayed in the field with those months when there was no spraying (Table 1). The geometric means of both dimethyl and diethyl DAP were significantly higher during spray months than during nonspray months ($p = 0.009$ for dimethyl and $p = 0.018$ for diethyl DAP). Table 1 also provides percentiles for dimethyl and diethyl DAP concentrations during the spray versus the nonspray months between December 1998 and August 1999.

Effects of age and sex. We treated age and sex as categorical variables to account for nonlinear patterns in their effects on the DAP levels. Results from the general linear model procedure showed that a child's sex did affect the DAP levels in the urine (Table 2). The geometric means of both dimethyl and diethyl DAP metabolite concentrations (Table 1) were significantly higher in boys than in girls ($p = 0.005$ for dimethyl and $p = 0.046$ for diethyl DAP). Table 1 also shows the percentiles of dimethyl and diethyl DAP concentrations for boys and girls. We did not find child age to be a significant factor in this analysis.

Proximity and parental occupation. We analyzed data for the entire 21-month sampling period and for the 1998 spray months, as indicated in Table 3. We found no significant differences between DAP levels and parental occupation (farm workers vs. all others) or residential proximity to fields (< 60 m vs. > 60 m). The geometric means of dimethyl and diethyl DAP concentrations of all five children who lived within 60 m (200 ft) of an orchard were above the 50th percentile of the overall concentrations over the 21-month sampling period. However, their DAP levels during the months when agricultural spraying was conducted were not significantly different from those of the other 39 children.

Discussion

Our current understanding of children's exposure to pesticides is limited to measurements collected in cross-sectional studies (6,-10–13), and estimates derived from mathematical models (18,19). The longitudinal data presented in this article provide a first opportunity to examine temporal variability in year-long exposures and to explore factors that might lead to elevated exposures in young children.

The principal finding of this study—the elevation of children's OP pesticide metabolite levels during agricultural spraying—is plausible from a temporal perspective. That is, DAP levels in children's urine rose during the spray months, and because of the relatively short biological half-lives of most OP pesticides, the levels subsequently decreased as agricultural applications ended. This pattern is also consistent with the general theory that children are exposed continuously to a low level of these pesticides through their diet and that this chronic exposure is punctuated by episodes of relatively higher exposure

Table 1. Geometric mean and percentile of dimethyl and diethyl DAP concentrations (μmol/L) in urine samples of 44 children collected over a 21-month period, compared by sex and by months when OP pesticides were sprayed in orchards.

	Mean[a]	SD[a]	No.	5%	25%	50%	75%	95%
Dimethyl DAP concentration								
Overall	0.080	2.51	972	0.04	0.04	0.06	0.13	0.51
Boys	0.085[b]	2.45	351	0.04	0.04	0.06	0.13	0.44
Girls	0.078[b]	2.29	621	0.04	0.04	0.06	0.13	0.53
Spray months	0.096[c]	2.72	275	0.04	0.05	0.07	0.16	0.79
Nonspray months	0.072[c]	2.52	697	0.04	0.04	0.06	0.11	0.44
Diethyl DAP concentration								
Overall	0.036	1.56	972	0.03	0.03	0.03	0.04	0.1
Boys	0.037[d]	1.59	351	0.03	0.03	0.03	0.04	0.1
Girls	0.036[d]	1.47	621	0.03	0.03	0.03	0.04	0.1
Spray months	0.049[e]	1.98	119	0.03	0.03	0.04	0.08	0.18
Nonspray months	0.035[e]	1.54	853	0.03	0.03	0.04	0.04	0.08

[a]Geometric mean and SD. [b]Significantly different, $p = 0.005$. [c]Significantly different, $p = 0.009$. [d]Significantly different, $p = 0.046$. [e]Significantly different, $p = 0.018$.
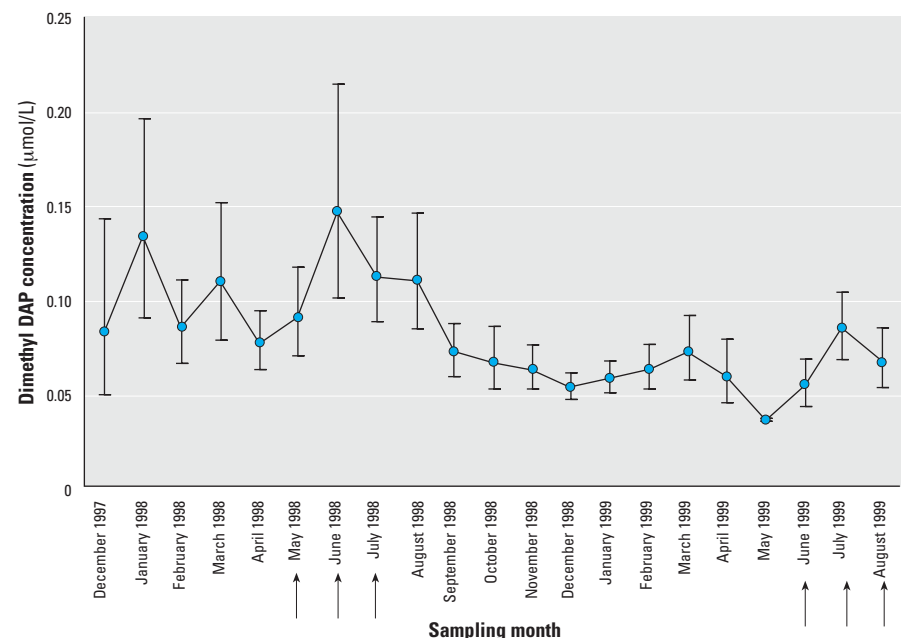

Figure 1. Geometric mean and 95% confidence interval for dimethyl DAP concentrations by sampling months. Arrows indicate months when dimethyl OP compounds were applied to tree fruit orchards.

from additional sources and pathways, such as residential pesticide use (*20*). In this agricultural community, pesticide applications on crops appear to serve as multiple-point sources for those residing in the region, and exposures rise and fall accordingly.

This conclusion is supported by earlier findings of measurable levels of the OP pesticide azinphos-methyl in every home sampled in this same community, regardless of distance from farmland (*5,6*). Azinphos-methyl is the most frequently applied insecticide in

the region's agriculture and is not registered for residential use. Unlike these previous studies, parental occupation and residential proximity did not contribute significantly to the pattern observed in this study. Earlier studies found that the homes of workers who mixed or applied pesticides and homes very near treated farmland had higher levels of agricultural pesticides in residential soil and house dust. In this study, however, these risk factors were not present. None of the workers was a pesticide mixer or applicator, and only five of the 44 study homes were within 60 m (200 ft) of farmland.

The specific exposure pathways for children in this community cannot be discerned from the data presented. Children may be exposed to spray drift directly by inhalation or indirectly by contacting contaminated surfaces both indoors and outdoors. Investigators with the Agricultural Health Pilot Study (*21*) have reported that food eaten by farmers and their families during pesticide application events is a potential source of exposure, but this finding may be of limited relevance for this study population, because none were farmers. Identification of exposure pathways will require simultaneous biological monitoring and environmental sampling.

Children were exposed to higher levels of OP pesticides in 1998 than in 1999 (Figures 1 and 2). According to the communications with field scientists from the Washington State Tree Fruit Research Commission (*22*), the temperature readings for the spring of 1999 were much lower (18–22°C; 10–12°F lower) than normal, a phenomenon attributed to El Niño. Orchard growers were therefore advised to either postpone or cancel the first several sprayings for the season. The decreased use of OP pesticides during the 1999 spraying season was actually reflected in the lower DAPs levels that we measured longitudinally in children's urine.

We found a significant difference in the levels of both dimethyl and diethyl DAPs measured in boys and girls. This finding is not consistent with results reported in previous cross-sectional studies (*6,10,13*). The causes of this sex disparity are unknown, but we speculate that substantial and consistent differences in behavioral and/or activity patterns between boys and girls may contribute to this difference. If young boys tend to have higher frequency of hand-to-mouth activity or perform more frequent strenuous physical activities than do young girls, they might receive higher exposures. Such activity differences have been reported previously (*23,24*). In this study, 64% (9 of 14) of boys reported having frequent hand-to-mouth activity, whereas 41% (11 of 27) of girls had such behavior (data not shown). Three families did not answer this question in the interview.
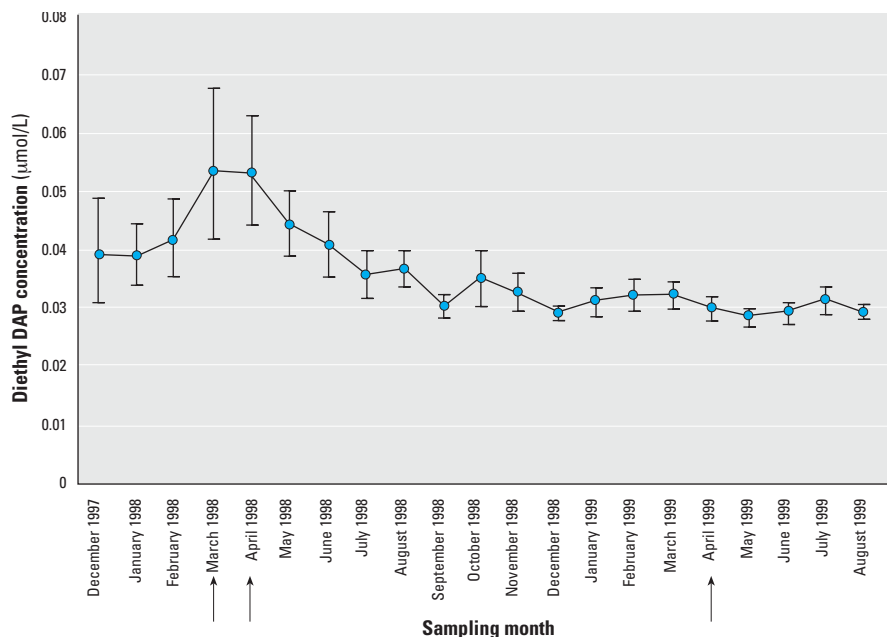

Figure 2. Geometric mean and 95% confidence interval for diethyl DAP concentrations by sampling months. Arrows indicate months when dimethyl OP compounds were applied to tree fruit orchards.

Table 2. Selected SAS outputs of general linear model results for dimethyl and diethyl DAP concentrations in 44 children's urine samples collected over a 21-month period.

Model	Source	Degrees of freedom	Dimethyl DAP (µmol/L)			Diethyl DAP (µmol/L)		
			Sum of squares	Mean square	F-value (Pr > F)[a]	Sum of squares	Mean square	F-value (Pr > F)[a]
1	Child	43	88.7	2.1	2.88 (0.0001)[a]	12.5	0.3	1.73 (0.0029)[a]
	Month	20	76.7	3.8	5.35 (0.0001)[a]	28.2	1.4	8.35 (0.0001)[a]
	Error	971	816.1			193.7		
2[b]	Sex	1	5.8	5.8	8.09 (0.005)[a]	0.7	0.7	3.98 (0.046)[a]
	Age	4	4.8	1.2	1.66 (0.16)	0.9	0.2	1.29 (0.27)
	Error	946	748			186		

[a]Pr, probability. [b]Sex and age data obtained from model 2, which is adjusted for variables including residential pesticide use, proximity, and parental occupation. These variables may act as possible confounders.

Table 3. Dimethyl and diethyl DAP concentrations in urine samples of 44 children over a 21-month period, compared by residential proximity to a pesticide-treated orchard and parental occupation.

	Dimethyl DAP (µmol/L)			Diethyl DAP (µmol/L)		
	Mean[a]	SD[a]	Children/samples[b]	Mean[a]	SD[a]	Children/samples[b]
Proximity during 21-month study period						
≤ 200 ft	0.079	2.45	5/104	0.033	1.44	5/104
> 200 ft	0.080	2.51	39/868	0.036	1.57	39/868
Proximity during spray months in 1998						
≤ 200 ft	0.137	3.56	5/21	0.035	1.46	3/8
> 200 ft	0.110	2.97	39/152	0.051	2.01	35/109
Parental occupation during 21-month study period						
Agricultural	0.079	2.49	27/621	0.036	1.57	27/621
Nonagricultural	0.081	2.51	17/351	0.036	1.55	17/351
Parental occupation during spray months in 1998						
Agricultural	0.108	2.98	27/117	0.052	1.95	24/74
Nonagricultural	0.124	3.15	17/56	0.051	1.95	13/33

[a]Geometric mean and SD. [b]Number.

We did not include the frequency of strenuous physical activities in the interview.

This study had several limitations. First, subject attrition occurred and was perhaps inevitable because of the longitudinal nature of this study. Families decided to withdraw from the study for a variety of reasons, such as movement out of the area or the burden of repeated urine collections. We recruited 15 additional families from the same WIC clinic office in April 1998 to offset subject attrition, and therefore the study period was not uniform across subjects. Second, we did not always collect samples on the biweekly schedule outlined in the original study design. Most of the families were not long-term residents of the addresses that were provided during the recruitment phase. We made efforts regularly to keep track of where the families moved, but gaps between two consecutive urine sample collections sometimes were longer than 2 weeks. Third, we drew the study population from the office of a federal program that has income eligibility requirements, so all participants were from households on the lower end of the income scale. For this reason, they are not representative of the population of children in the region. Finally, we used the DAP metabolites of OP pesticides as biomarkers of exposure rather than more compound-specific metabolites. The measurement of DAPs in children's urine is a useful technique that integrates exposure across this chemical class. However, it does not allow characterization of exposure to specific OP pesticides. At the time of this study, analytical methods were available for only a few of the OP pesticide metabolites, and in current assays metabolites for only approximately six of the 40 or so commercial OP pesticides can be analyzed (25). Ideally future studies will include both types of assays, providing a richer source of information for exposure assessment.

In conclusion, this study provides useful new information regarding the temporal pattern of young children's pesticide exposure in an agricultural community. This study found elevated levels of OP pesticide metabolite levels associated with agricultural spraying of OP pesticides in the region. The pattern was consistent for both dimethyl and diethyl compounds. Additional studies that couple biological and environmental monitoring could assist in determining specific exposure pathways for such populations.

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