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## Determinants of children's exposure to pyrethroid insecticides in western France.

Philippe Glorennec<sup>1,2</sup>, Tania Serrano<sup>1,2</sup>, Morgane Fravallo<sup>2</sup>, Charline Warembourg<sup>2,3</sup>, Christine Monfort<sup>2,3</sup>, Sylvaine Cordier<sup>2,3</sup>, Jean-François Viel<sup>2,4</sup>, Florent Le Gléau<sup>5</sup>, Barbara Le Bot<sup>1,2</sup>, Cécile Chevrier<sup>2,3</sup>.

<sup>1</sup>EHESP-School of Public Health, Rennes, Sorbonne Paris Cité, France

<sup>2</sup>Irset INSERM-UMR1085, -Research Institute for Environmental and Occupational Health, France

<sup>3</sup>Rennes 1 University, France.

<sup>4</sup>Department of Epidemiology and Public Health, University Hospital, Rennes, France

<sup>5</sup>Labocéa, Plouzané, France.

Corresponding author: Philippe Glorennec, EHESP School of Public Health, Avenue du Pr Léon Bernard, 35043 Rennes Cédex – [philippe.glorennec@ehesp.fr](mailto:philippe.glorennec@ehesp.fr)

### Abstract

Pyrethroids are insecticides frequently used in agriculture and in the home; exposure occurs through dietary and non-dietary pathways, including indoor and outdoor environmental contamination. Our objective was to study the potential determinants of pyrethroid metabolite concentrations measured in children's urine samples and in the dust of their homes. Specifically, we measured urinary metabolites from morning spot samples of 245 six-year-old children living in Brittany (France) in 2009-2012 and from dust vacuumed from the floor of their homes. Mothers reported home insecticide use, dietary habits, sociodemographic data; residential and school proximity to agricultural crops was assessed with spatialized data. The metabolites *cis*-DBCA, *trans*-DCCA, *cis*-DCCA, 3-PBA, and F-PBA were detected in 84, 95, 64, 63, and 16% of the urine samples, respectively. Permethrin, cypermethrin, cyfluthrin, deltamethrin, and tetramethrin pyrethroids were detected in 100, 56, 9, 15, and 26% of the dust samples, respectively. Multiple regression analysis suggested diet plays a role in children's exposure, in particular, the food groups "pasta, rice or semolina" (for *cis*-DCCA and F-PBA), fruit (3-PBA), and "breakfast cereals and whole grain bread" (*cis*-DBCA), and the global proportion of organic food in diet (for *cis*-DBCA, *trans*-DCCA). Children with a parent occupationally exposed to pesticides were about 3-times more likely to have higher urinary concentrations of 3-PBA (OR=2.8, 95%CI [1.2; 6.5]). Dust content was correlated mainly with household insecticide use: higher mean concentrations of permethrin ( $\beta$ =0.8 [0.3; 1.3], in  $\mu\text{g/g}$ ) and an increased risk of a detectable level of cyfluthrin (OR=4.7 [1.7; 12.9]) were

observed in home dust, for indoor use of at least twice a year. Outdoor insecticide use at least once a year was associated with detection in dust of cypermethrin (OR=3.0 [1.3; 6.7]) and tetramethrin (OR=3.7 [1.6; 8.3]). Three positive and one negative correlations (out of 11) between urinary metabolite concentrations and home dust contents of their possible corresponding parent compounds were observed. The strength of this study lies in its concurrent use of biomarkers, environmental measurements, and potential sources of exposure. Its limitations include the use of a single urine sample and imprecise data about pyrethroid use in local agriculture.

## Highlights

- Determinants of pyrethroid exposure of 245 six-year-old children were assessed
- Urinary metabolites were mainly associated with dietary habits
- Household dust contents were mainly associated with household insecticide use

## Keywords

Dietary exposure, environmental exposure, pesticide, biomarker, dust

## 1. Introduction

Pyrethroids are among the most commonly used insecticides in agriculture; they are also widely used indoors in pet shampoo, lice treatment, and even insect repellent (Saillenfait et al 2015). They are therefore frequently present both in food and in the air and dust of dwellings and thus can lead to both dietary and non-dietary exposure (Morgan 2012). With a half-life of less than 24 hours, they are rapidly metabolized once absorbed to polar metabolites, eliminated primarily in urine (Leng et al 1997). Urinary metabolite concentrations thus reflect recent exposure. The five urinary metabolites usually measured may reflect different patterns of pyrethroid exposure. The non-specific metabolite 3-phenoxybenzoic acid (3-PBA) results from exposure to cypermethrin, deltamethrin, and/or permethrin, as well as lambda-cyhalothrin, cyphenothrin, fenpropathrin, fenvalerate, fluvalinate-tau, phenothrin, and tralomethrin. The *cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (*cis*-DCCA) and the *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (*trans*-DCCA) result from cyfluthrin, cypermethrin, or permethrin, and the 4-fluoro-3-phenoxybenzoic acid (F-PBA) from cyfluthrin and flumethrin. Finally, the *cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid (*cis*-DBCA) is a specific metabolite of deltamethrin. A recent review noted that the frequent detection of pyrethroid metabolites, especially 3-PBA and *cis*- and *trans*-DCCA, in urine samples from non-occupationally exposed populations is evidence of widespread exposure, notably of children (Saillenfait et al. 2015). In

particular, 3-PBA, *cis*-DCCA, *trans*-DCCA, *cis*-DBCA, and F-PBA have been detected in urine of French adults (Frery et al. 2013) and German children (Becker et al. 2006).

Dietary determinants of the pyrethroid urinary metabolite concentrations include fruit and vegetables (Morgan 2012), fruit juice (Morgan and Jones 2013), and poultry (Morgan and Jones 2013) for children, and seafood, dairy products, and cereals (Frery et al. 2013) for adults. Potential non-dietary determinants include household use — indoors and outdoors — of products containing pyrethroids as insecticides or for pets (Becker et al. 2006; Lu et al. 2006), tobacco use (Frery et al. 2013; Riederer et al. 2008), agricultural use of pyrethroids on nearby crops, and dust contamination (Becker et al. 2006).

Pyrethroid pesticides disrupt the nervous system of insects and, to a lesser degree, of mammals, and thus raise human health concerns. Although the potential risks of low levels of exposure to pyrethroids in children have not yet been adequately examined, recent studies in the general population report adverse associations between urinary concentrations of pyrethroid metabolites and neurodevelopmental outcomes among children (Oulhote and Bouchard 2013; Viel et al. 2015).

The objective of this study was to improve our understanding of children's exposure to these insecticides by identifying the major determinants of their pyrethroid urinary metabolites, including their dietary habits and the use of products in and around the home. We also sought to assess the determinants of indoor pyrethroid levels in the home by measuring it in floor dust. We focused on urinary metabolites commonly measured and detected in Europe (Saillenfait et al. 2015), on substances that have been detected in French house dust (Blanchard et al. 2014a), and on cyfluthrin and deltamethrin because of their low volatility and common use (Saillenfait et al. 2015). These findings should help to provide guidance on developing policies to reduce and even prevent this widespread exposure among children.

## **2. Material and methods**

### **2.1 Study population**

The study population is a group of 245 children aged 6 years between 2009 and 2012 who participated in a neuropsychological follow-up as part of the Pélagie mother-child cohort in Brittany, France (Cartier et al. 2016; Viel et al. 2015), a region with both rural and urban areas. During this follow-up, a home visit allowed investigators to collect a first-morning-void urine sample and dust from the household vacuum cleaner. The children's parents completed a questionnaire about their dietary habits and insecticide use in and around the home. The initial population comprised 287 children, but 36 did not provide enough or

any dust due to empty vacuum cleaner bags, and questionnaire data were missing for 6 more. Table 1 summarizes the population characteristics.

## 2.2 Selection of potential determinants of exposure

Potential determinants of pyrethroid concentrations in both urinary metabolites and dust were chosen *a priori* on the basis of a literature review. For diet, we selected the consumption of fruit and vegetables (Morgan 2012), fruit juices (Morgan and Jones 2013), chicken or turkey more than three times a week (Morgan and Jones 2013), seafood, butter, cheese, yoghurt, and cereals (Frery et al. 2013). The potential non-dietary determinants selected were indoor or nearby outdoor insecticide use (Becker et al. 2006; Lu et al. 2006), exposure to environmental tobacco smoke (given the likelihood that pyrethroids are contained in tobacco leaves (Stewart and McClure 2013) and thus present in tobacco smoke), and use of pyrethroids on local agricultural crops (provided by the Brittany Regional Agriculture Council, personal communication).

## 2.3 Data collection

First-morning-void urine samples were collected during the home visit and frozen at  $-20^{\circ}\text{C}$  in the laboratory until analysis of 3-PBA, *cis*-DCCA, *trans*-DCCA, F-PBA, and *cis*-DBCA. The details of the analytic methods have been described elsewhere (Viel et al. 2015). Briefly, 3-PBA and F-PBA metabolites in 1-mL urine samples were extracted by solid-phase extraction followed by ultra-performance liquid chromatography and triple quadrupole mass spectrometry. *Cis*-DCCA, *trans*-DCCA, and *cis*-DBCA metabolites in 2-mL urine samples were extracted, derivatized, and then analyzed by gas chromatography and then triple quadrupole spectrometry. Average recoveries were 100% +/- 20%. Limits of detection (LOD) in urine were defined as the concentration with a signal to noise ratio of 3 and ranged from 0.003  $\mu\text{g/L}$  for F-PBA to 0.008  $\mu\text{g/L}$  for 3-PBA, whereas limits of quantification (LOQ) were defined with a signal to noise ratio of 10. The calibration curves showed good linearity with a correlation coefficient  $>0.997$ . Regarding precision, coefficients of variations were lower or equal to 25%. For quality control, a blank (mix of pesticide-free urine) and a control sample at three concentration levels were included every 10 samples. The calibration was performed every 120 samples, and the concentration of the LOQ control level (lowest control concentration) was verified every 20 samples.

Urinary creatinine was also assessed, as was urinary cotinine ( $\geq 6\mu\text{g/L}$ ) (Galanti 2008) as an indicator of environmental tobacco smoke exposure.

Household vacuum bags were collected in each home, then frozen at  $-18^{\circ}\text{C}$  until analysis to ensure preservation of the compounds (Blanchard et. al 2014b). Dust samples were analyzed after sieving to  $< 100\ \mu\text{m}$ . Cyfluthrin, cypermethrin, deltamethrin, permethrin, and tetramethrin were then extracted from dust by pressurized liquid extraction with dichloromethane, followed by gas chromatography coupled to mass spectrometry, as described by (Mercier et. al 2014). For quality assurance and quality control, fenprothrin and methoprotryn were used as surrogate standards to monitor recoveries. Positive values in each sample were confirmed by comparing retention times and MRM transition (GC/MS/MS) ratios between calibration solutions and samples. Analytical methods were previously validated concerning LOQ, LOD, and relative standard deviation (RSD) of replicate injections of our reference dust extract in each sample series. LOQs were defined as the lowest concentration of a substance in a calibration solution for which the RSD of replicate injections was lower than 20%. This estimate took into account the concentration levels in procedural blank samples. The LOD and LOQ were respectively 26.5 ng/g and 65.8 ng/g for all pyrethroids. The average recoveries varied between 90-102%, and the RSD was estimated at less than or equal to 20% except for deltamethrin (RSD around 44%). The concentrations for the five pyrethroids in blank samples were lower than the LOD. Parents were asked if the vacuum cleaner was ever used outdoors or in a car, chimney, or barbecue grill.

Sociodemographic data, home insecticide use (indoors/outdoors), and housekeeping and dietary habits (based on typical weekly consumption) were collected by a questionnaire completed by a parent. Sociodemographic data included the child's gender, body mass index (BMI), and home and school addresses, as well as the mother's educational level at study inclusion. Parents were also asked about occupational pesticide use (agriculture, horticulture, green spaces, or road network maintenance) since the child's birth, the frequency of insecticide use (against ant, lice, ticks, etc.) inside and outside the dwelling, and whether products were stored in rooms used in common by the household (kitchen, bathroom, utility room, toilets, and entrance). The questionnaire also inquired about the number of cigarettes smoked indoors, the frequency of floor washing (wet cleaning), the food the child usually ate weekly, as well as the proportions of home-grown products and organic food consumed.

Agricultural crops grown around the home and schools were identified with a geographic information system (GIS). The addresses of schools and children's residences, obtained by questionnaire, were geocoded with the free batchgeocoder (<http://www.batchgeocodeur.mapjnz.com/>). The quality of the geocoding was manually verified. Using the Agricultural Parcel Registry (RPG) database, we identified crop types in a 500-m radius buffer around children's homes and schools and calculated their acreage.

The RPG is a national database updated yearly since 2006 by farmers seeking financial support from the European Union. The RPG database used for each child's analysis was that of the year of his or her sixth birthday. Experts from the Regional Agricultural Council provided information about the use of pyrethroids on growing crops (but not seed treatment). Next we categorized crops in five groups: grain crops excluding corn, together with colza (oilseed rape), protein peas, fruit trees, and vegetables and flowers. To study the potential determinants of the urinary concentrations, we assessed agriculture proximity by a weighted score that assumed that children spend 2/3 of their time at home and 1/3 at school. Only home proximity to crops was considered to study the potential determinants of dust concentrations.

## 2.4 Data handling and modeling

Missing data (all < 3.5% except for outdoor vacuum cleaner use: 7%) were replaced by the median value of the respective distributions. Variables were categorized with a minimum of 20 observations per modality. After performing normality tests and using log-scale when needed (cis-DBCA, trans-DCCA), we ran regression models separately for each urinary metabolite and for each dust pyrethroid. Potential sources identified in the literature were all included, then removed from multiple models with a backward selection strategy at  $p < 0.20$ . For urinary metabolites, the following adjustment variables were forced into the models: gender, BMI (<14.4 kg, between 14.4 and 15.3 kg, between 15.4 and 16.2 kg, > 16.2 kg), creatinine (continuous), and mother's educational level (no high school diploma, high school diploma/baccalaureate, at least two years postsecondary education). For dust, the following adjustment variables were forced: mother's educational levels (same categories), and outdoor vacuum cleaner use (yes, no). The left censorship rate governed the choice of statistical models: linear regression when this rate was less than 1% (2 subjects excluded), Tobit regression (Little and Rubin 2002) from 1 to 30%, polytomous logistic regression (Hosmer and Lemeshow 2000) from 30 to 50% (with three ordered categories of concentrations when the proportional odds ratio hypothesis was not rejected), and finally logistic regression (detected or not detected) (Hosmer and Lemeshow 2000) when the censorship rate was greater than 50% and when the proportional odds ratio hypothesis was rejected in the polytomous logistic regression. Beta coefficients for linear and Tobit regression models correspond to the difference between the mean urinary or dust concentration for a covariate category vs. its reference category. The odds ratio indicates how the odds, or likelihood, of the event (i.e., higher concentrations for ordinal polytomous regression, or detected concentrations for logistic regression) changed between a covariate category and its reference category. Relations between urinary metabolite concentrations and the dust

levels of their corresponding parent pyrethroids were then assessed with similar models, minimally adjusted for gender, creatinine, and BMI.

### **3. Results**

The characteristics of the 245 children are presented in Table 1, as well as the parental occupational exposure, the presence of diverse agricultural crops close to children's homes, insecticide use at home, pesticide storage, and floor cleaning. Girls accounted for 52% of the population sample. Most mothers (71%) had at least 2 years of postsecondary education. In all, 84% of school and residence addresses were correctly geocoded at the street level; 16% were less accurate, mainly due to their location in small villages in rural areas. Most (88%) children lived in a residence located less than 500 m from a grain crop (other than corn) field. Overall, 11% of parents reported occupational exposure to pesticide; and 32% reported its home use indoors and 16% outdoors. More than half (53%) the children ate pasta, rice, or semolina more than 3 times a week, and 63% whole bread or grains daily, while 83% ate poultry at least weekly and 36% seafood at least monthly. Daily fruit intake was reported for 42% of children and daily vegetables for 56%; 15% ate fresh home-grown fruit or vegetables every day. Organic food accounted for half of total food intake for 18%, and 11% ate organic fruit, vegetables, or grains daily.



**Table 1. Population characteristics and potential sources of exposure (n=245).**

Characteristic	n	%
<b>Gender</b>		
Female	127	52
Male	118	48
<b>Mother's educational level <sup>a</sup></b>		
No high school diploma	32	13
Completed high school (baccalaureate)	39	16
At least 2 years postsecondary education	173	71
<b>Body mass index (kg.m<sup>-2</sup>)</b>		
<14.4	61	25
14.4-15.3	57	23
15.4-16.2	67	27
>16.2	60	24
<b>Home; Home and school near crops (less than 500 m)</b>		
Grain crops (other than corn)	216;226	88;92
Colza	74;90	30;37
Protein peas	37;57	15;-23
Fruit trees	25;32	10;13
Vegetables or flowers	37;54	15;22
<b>Urinary cotinine <math>\geq</math> 6<math>\mu</math>g/L in child's urine sample <sup>d</sup></b>	14	6
<b>Mother smokes <sup>c</sup></b>	54	22
<b>One parent occupationally exposed to pesticide <sup>d</sup></b>	26	11
<b>Use of anti-insect products at home at least once a year</b>		
Outdoors <sup>b</sup>	39	16
Indoors <sup>d</sup>	79	33
<b>Pesticides stored in room used in common by household</b>	53	22
<b>Wet floor cleaning &gt; 2/week</b>	70	29

Missing data: a: n=1; b: n=2; c: n=3; d: n=6.

The creatinine concentrations were 978 +/- 23 mg/L. The concentrations of pyrethroids in urinary metabolites and dust are presented in Table 2. All the pyrethroid metabolites except F-PBA were detected in more than half the urine samples; the detectable as well as the highest concentrations were most frequently those of *cis*-DBCA and *trans*-DCCA. In dust, permethrin (100%) and cypermethrin (56%) were detected most frequently, with the highest (at least seven-fold) median concentration for permethrin (770 ng/g).

**Table 2. Urinary metabolites and house dust concentrations of pyrethroid insecticides (n=245 six-year-olds, France).**

Urinary metabolites (µg/L)	Missing data	LOD	>LOD	Percentile 50	Percentile 75	Percentile 90	Percentile 95
<i>Cis</i> -DBCA	1	0.067	84%	0.20	0.42	0.88	1.12
<i>Trans</i> -DCCA	1	0.01	95%	0.22	0.58	1.14	1.75
<i>Cis</i> -DCCA	1	0.067	64%	0.09	0.19	0.32	0.49
3-PBA	0	0.008	63%	0.02	0.05	0.08	0.20
F-PBA	0	0.003	16%	<LoD	<LoD	0.008	0.02
Floor dust concentration (ng/g)	Missing data	LOD	>LOD	Percentile 50	Percentile 75	Percentile 90	Percentile 95
Permethrin	2	26.5	100%	770	4361	14848	26333
Cypermethrin	0	26.5	56%	138	548	1388	3079
Cyfluthrin	0	26.5	9%	<LoD	<LoD	<LoD	65
Deltamethrin	0	26.5	15%	<LoD	<LoD	38.5	74.5
Tetramethrin	0	26.5	26%	<LoD	31.5	451	1392

LOD: Limit of detection. *Cis*-DBCA: cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid; *trans*-DCCA: trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid; *cis*-DCCA: cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid; 3-PBA:3-phenoxybenzoic acid; F-PBA: 4-fluoro-3-phenoxybenzoic acid.

The associations between urinary metabolites and their potential determinants are presented in Table 3.

**Table 3. Associations between urinary metabolites of pyrethroid insecticides and potential exposure sources according to multiple models with a backward selection strategy (n=245 6-year-old children, France).**

	<i>Cis</i> -DBCA (log-scale, µg/L)	<i>Trans</i> -DCCA (log-scale, µg/L)	<i>Cis</i> -DCCA	3-PBA	F-PBA
Regression model type	Tobit	Tobit	Polytomous ordered	Polytomous ordered	Logistic
	β [95% CI]	β [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
<b>Crop surfaces in close proximity (&lt;500 m) to children's homes and schools</b>					
<b>Grain crops (except corn)</b>					
between 4.86 and 11.25 ha vs < 4.86 ha	0.18 [-0.12; 0.48]		0.93 [0.51; 1.70]		
> 11.25 ha vs < 4.86 ha	<b>0.31 [0; 0.61]</b>		1.69 [0.91; 3.14]		
<b>Vegetables and flowers &gt;0 ha vs 0 ha</b>				<b>2.17 [1.20; 3.93]</b>	
<b>One parent occupationally exposed to pesticide Yes vs No</b>				<b>2.81 [1.21; 6.54]</b>	
<b>Pesticides stored in common rooms Yes vs no</b>	-0.24 [-0.55; 0.07]				
<b>Wet floor cleaning at least twice a week Yes vs no</b>		<b>0.49 [0.14; 0.84]</b>	<b>2.07 [1.17; 3.65]</b>		
<b>Dietary habits (weekly consumption frequency)</b>					
<b>Pasta, rice, semolina</b>					
4-6 times vs 3 or fewer times			0.98 [0.57; 1.67]		1.55 [0.72; 3.35]
every day vs 3 or fewer times			<b>2.89 [1.12; 7.42]</b>		<b>3.36 [1.06; 10.65]</b>
<b>Poultry</b>					
Between 1 and 6 per week vs less than 3 per month		-0.38 [-0.81; 0.03]		0.52 [0.27; 1.02]	
<b>Fruits</b>					
4-6 vs 3 or less				<b>2.58 [1.33; 5.02]</b>	
Every day vs 3 or less				<b>2.54 [1.36; 4.74]</b>	
<b>Breakfast cereals and whole grain bread</b>					
At least twice a day vs less than once a day	<b>0.66 [0.24; 1.08]</b>		1.64 [0.68; 3.97]		
Every day vs less than once a day	0.22 [-0.08; 0.52]		0.77 [0.43; 1.39]		
<b>Organic fruits, vegetables, or cereal foods</b>					
Less than several times a week vs never		0.34 [-0.07; 0.75]	1.53 [0.79; 2.94]	0.84 [0.46; 1.56]	
Several times a week vs never		<b>0.83 [0.25; 1.41]</b>	<b>2.62 [1.03; 6.67]</b>	0.96 [0.49; 1.86]	
Every day vs never		0.47 [-0.40; 1.33]	<b>4.14 [1.02; 16.75]</b>	<b>0.19 [0.07; 0.50]</b>	
<b>Proportion of organic food</b>					
Between 30 and 50% vs between 0 and 20%	-0.21 [-0.51; 0.09]	<b>-0.52 [-1.02; -0.02]</b>	0.70 [0.32; 1.56]		
50% and more vs between 0 and 20%	<b>-0.41 [-0.74; -0.07]</b>	<b>-0.89 [-1.58; -0.20]</b>	0.34 [0.11; 1.05]		
<b>Daily consumption of fresh homegrown fruits or vegetables</b>					
Yes vs no		-0.43 [-0.89; 0.02]	0.54 [0.25; 1.14]		
<b>Child cotinine urinary level Detected vs not detected</b>					

Variables forced into the models: gender, BMI, creatinine, and mother's educational level. Bold font mean association with  $p$ -value < 0.05, non-bold means association with  $p$ -value > 0.05 and < 0.2.

Children living in proximity to grain crops (3<sup>rd</sup> tertile: >11.5 ha in a 500-m radius circle around home and school) had on average higher urinary concentration of *cis*-DBCA ( $\beta=0.3$  [0; 0.6]), in log-scale,  $\mu\text{g/L}$ , than those living in proximity to lower grain crop activity (1<sup>st</sup> tertile: <4.7 ha). Children living in proximity to crops of vegetables or flowers were more likely to have higher urinary 3-PBA concentrations (OR=2.3 [1.3; 4.3]) than other children. Children were more likely to have higher urinary 3-PBA concentrations (OR=2.6 [1.1; 6.0]) when parents were occupationally exposed to pesticides compared to no occupational exposure. This association was not observed for the other urinary metabolites. Wet floor cleaning at least twice a week was associated with higher mean urinary concentrations of *trans*-DCCA among children ( $\beta=0.5$  [0.1; 0.8], in log-scale,  $\mu\text{g/L}$ ), and with higher risk of increased urinary concentrations of *cis*-DCCA (OR=2.1 [1.2; 3.6]). Children with daily consumption of pasta, rice, or semolina (vs. 3 per week or less) were more likely to have higher urinary concentrations of *cis*-DCCA (OR=2.9 [1.1; 7.4]) and detectable urinary concentrations of F-PBA (OR=3.4 [1.1;10.6]). Fruit consumption was associated with higher urinary concentrations of 3-PBA (OR=2.6 [1.4; 4.9] for daily consumption vs. 3 per week or less), and cereal and whole grain bread consumption with higher mean urinary concentrations of *cis*-DBCA ( $\beta=0.6$  [0.2; 1.1] for twice vs. once a day). The frequency of organic fruit, vegetable, or cereal consumption was associated with lower urinary concentrations of 3-PBA (OR=0.2 [0.1; 0.5]) but higher urinary concentrations of *trans*-DCCA and *cis*-DCCA, while the proportion of organic food in children's diets was associated with lower concentrations of *cis*-DBCA ( $\beta=-0.4$  [-0.7; -0.1] for 50% and more) and *trans*-DCCA ( $\beta=-0.9$  [-1.6; -0.2] for 50% and more).

Table 4 reports the associations between house dust concentrations of pyrethroids, insecticide use, and home characteristics. Homes in proximity to grain crops (OR=6.0 [2.3; 15.7] for between 4.7 and 11.5 ha in a 500-m radius circle vs. less than 4.7, and OR=5.0 [1.9; 13.0] for higher than 11.5 vs. 4.7), and homes in proximity to protein peas (OR=2.7 [1.2; 5.8]) were more likely to have dust concentrations of tetramethrin detected. Outdoor insecticide use at least once a year was associated with a higher risk that both cypermethrin (OR=3.0 [1.3; 6.7]) and tetramethrin (OR=3.7 [1.6; 8.3]) would be detected in dust. Homes with indoor insecticide-product use at least twice a year had higher mean concentrations of permethrin ( $\beta=0.8$  [0.3; 1.3], in  $\mu\text{g/g}$ ) in dust and were more likely to contain detected dust-concentrations of cyfluthrin (OR=4.7 [1.7; 12.9]). Finally, tobacco smoke was associated with higher mean concentrations of permethrin in home dust ( $\beta=0.7$  [0.0; 1.3], in  $\mu\text{g/g}$ ).

Lower urinary concentrations of *cis*-DBCA were observed among children living in houses in which concentrations of deltamethrin were detected in home dust (vs. non-detected deltamethrin in home

dust;  $\beta=-0.5$  [-0.8; -0.2], in log-scale,  $\mu\text{g/g}$ ) (Table 5). Higher urinary *trans*-DCCA concentrations in children were associated with increasing dust levels of permethrin in homes ( $\beta=0.2$  [0.1; 0.3], in log-scale,  $\mu\text{g/g}$ ); no association was observed with dust concentrations of cyfluthrin or cypermethrin. Children living in homes with the highest dust concentrations of cypermethrin (>419 ng/g vs not detected) were more likely to have higher urinary concentrations of *cis*-DCCA (OR=2.5 [1.3; 4.6]) and of 3-PBA (OR=1.9 [1.0; 3.5]). No other association was observed between urinary concentrations of *cis*-DCCA, 3-PBA, or F-PBA and the home dust contents for the possible parent compounds (respectively, cyfluthrin and permethrin, deltamethrin and permethrin, and cyfluthrin).

**Table 4. Associations between house dust concentrations of pyrethroid insecticides, household insecticide use, and home characteristics according to multiple models with a backward selection strategy.**

	Permethrin (in µg/g)	Cypermethrin	Cyfluthrin	Deltamethrin	Tetramethrin
Regression type	Linear	Logistic	Logistic	Logistic	Logistic
	β [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
<b>Crop surfaces in close proximity (&lt;500 m) to children's home</b>					
<b>Grain crops (except corn)</b>					
Between 4.73 and 11.49 ha vs <4.73 ha	0.40 [-0.08; 0.88]				<b>5.97 [2.27; 15.72]</b>
>=11.49 ha vs <4.73 ha	-0.18 [-0.67; 0.30]				<b>4.96 [1.90; 12.97]</b>
<b>Colza</b>					
<2.52 ha vs 0 ha		1.29 [0.61; 2.70]	0.58 [0.11; 2.94]	0.33 [0.08; 1.47]	
>=2,52 ha vs 0 ha		2.13 [0.94; 4.82]	2.72 [0.90; 8.24]	1.85 [0.78; 4.39]	
<b>Protein peas &gt;0 ha vs 0 ha</b>		1.90 [0.85; 4.26]	2.87 [0.98; 8.41]		<b>2.67 [1.22; 5.85]</b>
<b>Fruit trees &gt;0 ha vs 0 ha</b>					
<b>Vegetables and flowers &gt;0 ha vs 0 ha</b>					2.11 [0.95; 4.68]
<b>Home insecticide use per year</b>					
<b>outdoor</b> Yes vs no	0.53 [-0.02; 1.08]	<b>3.00 [1.34; 6.71]</b>	2.26 [0.74; 6.93]		<b>3.69 [1.65; 8.27]</b>
<b>indoor</b>					
1 or 2 vs 0	-0.02 [-0.61; 0.56]		0.93 [0.18; 4.77]		
> 2 vs 0	<b>0.80 [0.27; 1.32]</b>		<b>4.67 [1.69; 12.90]</b>		
<b>Pesticides stored in living rooms</b> Yes vs no					
<b>Wet floor cleaning twice a week</b> Yes vs no					1.77 [0.89; 3.54]
<b>Daily no. of cigarettes smoked by mother</b>					
between 0 and 5 vs 0	<b>0.68 [0.03; 1.34]</b>				1.85 [0.67; 5.13]
> 5 vs 0	0.48 [-0.14; 1.09]				2.13 [0.83; 5.48]

Variables forced into the models: mother's educational level, and use of vacuum cleaner outdoor. Bold font means association with  $p$ -value < 0.05, non-bold font means association with  $p$ -value > 0.05 and < 0.2.

**Table 5. Associations between urinary metabolites of pyrethroid insecticides and house dust concentrations for the corresponding possible parent compounds (n=245 6-year-old children, France).**

	<i>Cis</i> -DBCA (log-scale, µg/L)	<i>Trans</i> -DCCA (log-scale, µg/L)	<i>Cis</i> -DCCA	3-PBA	F-PBA
Regression model type	Tobit	Tobit	Polytomous ordered	Polytomous ordered	Logistic
	β [95% CI]	β [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
<b>Pyrethroid compounds in home dust</b>					
<b>Permethrin (in continuous, µg/g)</b>		<b>0.25 [0.15; 0.34]</b>	1.15 [0.98; 1.34]	1.01 [0.86; 1.17]	
<b>Cyfluthrin Detected vs Not detected</b>		-0.37 [-0.92; 0.18]	1.02 [0.42; 2.45]		0.24 [0.03; 1.85]
<b>Deltamethrin Detected vs Not detected</b>	<b>-0.47 [-0.79; -0.15]</b>			0.55 [0.28; 1.11]	
<b>Tetramethrin Detected vs Not detected</b>					
<b>Cypermethrin</b>					
<419 ng/g vs Not detected		0.09 [-0.30; 0.47]	1.02 [0.56; 1.83]	0.80 [0.45; 1.42]	
>419 ng/g vs Not detected		-0.18 [-0.56; 0.19]	<b>2.46 [1.33; 4.56]</b>	<b>1.90 [1.05; 3.46]</b>	

Variables forced into the models: gender, BMI, creatinine, and mother's educational level. Bold font mean association with  $p$ -value < 0.05, non-bold means association with  $p$ -value > 0.05 and < 0.2.

## 4. Discussion

This study showed that dietary habits were the variables most consistently associated with urinary concentrations of pyrethroid metabolites, followed by para-occupational exposures and agricultural activities closely surrounding homes and schools. Household use of anti-insect products was the variable most consistently associated with pyrethroid concentrations in dust (except for deltamethrin), followed by proximity to fields of grain crops (except corn) and colza for tetramethrin. Few correlations between urinary metabolite concentrations and home dust contents of their possible corresponding parent compounds were observed.

We measured concentrations of five free pyrethroid urinary metabolites in children living in urban and rural areas of western France (Brittany region). Comparison of our results to those of recent studies conducted among children in Europe and North America (Saillenfait et al. 2015), and specifically to Germany where (Becker et al. 2006) measured free metabolites in children, shows lower levels of 3-PBA, a nonspecific indicator of pyrethroid exposure, in our study and suggests lower global exposure to pyrethroids in our population. We found levels of *cis*-DCCA similar to those observed in Germany (Becker et al. 2006). Trans-DCCA urinary concentrations were similar to those observed in Germany (Becker et al. 2006). F-PBA has rarely been detected in any study, including this one; the 95<sup>th</sup> percentile F-PBA level in our study was lower than those in the few studies reporting values over the LOD (Saillenfait et al. 2015). The levels of *cis*-DBCA observed here, higher than those reported elsewhere (Saillenfait et al. 2015), suggest higher exposure to deltamethrin, since *cis*-DBCA is specific for this pyrethroid. Finally the differences among urinary metabolites may be due to variety in agriculture practices related to different types of crops and climate in the vicinity, different dietary habits, or even differing proportions of time spent inside and immediately outside the home from household to household, which may also modify the relative importance of different exposure pathways.

The use of insecticides at home, reported by parents in a self-administered questionnaire, appeared quite frequent in this study. In the previous year, 16% of households had used insecticides outdoors and 32% indoors, compared with around 10% outdoor use in the U.S. in 1999-2002 (Riederer et al. 2008), 47% for use, indoors or outdoors, against flies, ants, or roaches in California in 2003-2005 (Deziel et al. 2013), and 30% indoors or out in Seattle in 2003-2004 (Lu et al. 2006). This frequent use is consistent with previous findings in France. In a study in 2003-2004 (Auburtin 2003), for example, at least one pesticide was used in 93% of the 2190 dwellings surveyed, with cypermethrin one of the most common.



Another French study reported that among 30 families living in rural areas, pyrethroid-based products were present in 87% of dwellings (Bouvier 2005). We note however that our study population was significantly more educated and more rural than the overall French population.

Despite the lack of precise data about dietary exposure, which came from a food frequency questionnaire completed by a parent, most urinary metabolites were associated with several dietary habits: fruit for 3-PBA, pasta, rice, and semolina for *cis*-DCCA and F-PBA, and cereals for *cis*-DBCA. This correlation of 3-PBA with fruit was not observed in an Italian adult population (Fortes et. al 2013); that study found instead a correlation with vegetables, as also reported in a general Canadian population for total pyrethroid urinary metabolites (Ye et. al 2015). Associations with the weekly intake frequency of organic fruits, vegetables, and cereals were variable in our study, while results using the global proportion of organic food in diet were in the expected direction. Lu et al. noted that an organic diet reduced pyrethroid exposure (Lu et. al 2009), as Bradman et al. also saw in a urban community, but not in an agricultural one (Bradman et. al 2015). Concentrations of urinary metabolites in our study did not appear to be consistently associated with either household insecticide use or proximity to agricultural crops, despite the associations of 3-PBA concentrations with flower and vegetable crops and of *cis*-DBCA with grain crops. Nonetheless, given the long interval possible between pest treatment (within the last year) and the urine sampling, this exposure indicator may well fail to show pyrethroid use. Wet floor cleaning more than twice a week was significantly associated with an increase of *cis* and *trans*-DCCA concentrations, which was unexpected and is not readily explainable. Urinary 3-PBA was associated with occupational exposure of a parent, which may suggest that substances tracked in from the workplace explain the household contamination.

The dust levels of all pyrethroids except deltamethrin were associated with household use of anti-insect products; for permethrin and cyfluthrin, indoor use at least twice a year was the strongest of the determinants studied. Cypermethrin and tetramethrin concentrations were associated with outdoor use. As we did not collect information about the formulations or names of the insecticides used in the homes, we cannot examine the consistency between the associations we found and the household use of pyrethroid insecticides. This association between dust contamination and household use of pyrethroids has previously been observed (Deziel et. al 2015; Trunnelle et. al 2013). We also found that dust concentrations of pyrethroids, especially tetramethrin, were associated with proximity to some agricultural crops, as observed elsewhere (Harnly et. al 2009). Tobacco use also appeared to be

associated with higher permethrin concentrations, possibly due to treatment of tobacco leaves (Stewart and McClure 2013).

When studying correlations between dust pyrethroid concentrations and their corresponding urinary metabolite concentrations, we observed three positive and one negative statistically significant correlations among the 11 of interest. The single spot nature of urine samples may be inadequate for considering episodic environmental contamination, whereas a single spot dust measurement may reflect a longer period and might possibly catch repeated occasional contamination, although this has been studied less. It may also indicate that dust contributes less to exposure than food does. A few studies have addressed this issue of the relative contributions of dietary and residential exposures. The Children's Pesticide Exposure Study in Washington state (US) applied a longitudinal approach, collected several urine samples throughout the year, and concluded that dietary exposure was predominant and chronic, periodically supplemented by high residential exposures (Lu et al. 2009). One of its limitations, however, is that the diet hypothesis was essentially a default hypothesis and crop-related exposures were not studied. A study modeling permethrin exposure found that diet was predominant for most children, but non-dietary ingestion (including dust and absorption of skin residues) played a greater role for those living in households that used permethrin (Zartarian et. al 2012). Similarly dietary exposure was found to be twice as high as residential exposure in North Carolina between 2000 and 2001 (Morgan et. al 2014).

The limitations of this study include, as already mentioned, the single-spot nature of the urine and dust samples, although dietary habits, insecticide use, and agricultural use are estimated on a long-term basis. These different time lags may have affected our ability to detect an association between exposure indicators. On the basis of repeated measurements of 3-PBA and *trans*-DCCA in children's urine, Attfield (Attfield et. al 2014) showed that within-subject variance is about twice between-subject variance. This finding illustrates the limitation of a single urine sample to describe an exposure that is not constant. Furthermore, the urinary metabolites were not deconjugated before analysis. Consequently, if we assume the conjugation factors are independent of the exposure determinants, our procedure might have introduced a random misclassification of exposure that has the potential to underestimate the strength of the associations we found compared to consideration of total metabolites. Another limitation is the lack of detailed information about household use of the substances we studied. Important strengths of our study are that urine and dust samples were collected from the same population,

together with diet habits, and that we were able to estimate exposure to agricultural insecticides based on accurate spatial and temporal databases.

Because of the relatively high socioeconomic status of the population we studied and due to the close relation between insecticide use and climate and land use, no inference that these results can be extended to other populations is possible.

To conclude, although the contribution of the different pathways of children's exposure to pyrethroid compounds is not yet fully understood, our study adds to the evidence that dietary exposure is predominant for pyrethroids. It would however be useful to conduct a study based on urinary metabolites, with several samples over time, coupled with detailed assessment of dietary habits, occupational exposure, and residential and agricultural use. This issue might be further addressed by obtaining more specific data about pesticide quantities used in agriculture and conducting an intervention study to assess the benefit of avoiding sources of exposure.

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