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Urinary levels of pyrethroid pesticides and determinants in pregnant French women from the Elfe cohort

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ABSTRACT

Pyrethroids are insecticides which are widely used for agricultural and domestic purposes. The general population can be exposed to them. Given the suspected effects of pesticides on the development of the foetus, exposure to pyrethroids during pregnancy is a major public health concern. The objective of this paper is to describe the urinary levels of the following five pyrethroid metabolites and their associated determinants among pregnant French women in 2011 enrolled in the Elfe cohort (n = 1077): a) 3-phenoxy benzoic (3-PBA), b) 4-fluoro-3-phenoxy benzoic acid (4-F-3-PBA), c) Cis-3-(2,2dibromovinyl)-2,2-dimethyl cyclopropane-carboxylic acid (Cis-DBCA); d) Cis-3-(2,2dichlorovinyl)-2,2-dimethyl cyclopropane-carboxylic acid (Cis-DCCA) and e) Trans-3-(2,2dichlorovinyl)-2,2-dimethyl cyclopropane-carboxylic acid (Trans-DCCA). The distribution levels were estimated for each pyrethroid metabolite. Multivariable analyses helped determine the predictors of these levels. All metabolites except 4-F-3-PBA were detected in all the urine samples. The mean urinary concentration of the sum of the metabolites (3-PBA, Cis-DBCA, Cis-DCCA, Trans-DCCA) was 1.18 µg/L, with the highest concentrations observed for 3-PBA. A comparison of these levels with other studies showed that pregnant French women tend to be more exposed to pyrethroids than their American counterparts, less exposed than Chinese and Caribbean mothers, and have similar exposure to Japanese mothers. In our study, urinary levels of pyrethroid metabolites were positively related to smoking during pregnancy, consuming fish and alcohol, domestic pesticide use and living in the vicinity of crops during pregnancy. These findings highlight the importance of non-dietary pathways when evaluating exposure to pyrethroids.

1. Introduction

Pesticides are extensively used in France, the leading country within the European Union, both in terms of Utilized Agricultural Land (approximatively 29 million hectares) and turnover from agriculture (69 billion euros in 2011). In 2011, 77,000 tons of pesticides (mainly fungicides and herbicides) were sold for agricultural use in France (www.statistiques.developpement-durable.gouv.fr). Pesticides are also widely used by French people for domestic use (insecticides, lice, fleas, etc.). Pyrethroids are one of the most common pesticide families used as agricultural and domestic insecticides (Saillenfait et al., 2015). They are increasingly replacing restricted or banned insecticides, such as organochlorine and organophosphorus pesticides (Horton et al., 2011; Williams et al., 2008).

There is growing concern about the effects of exposure to pesticides on fetuses during pregnancy. Some studies suggest that environmental exposure to pyrethroids have adverse effects on pregnancy outcomes and infant health, including birth size (Zhang et al., 2014), immune systems and neurodevelopment (Hisada et al., 2017; Neta et al., 2011; Shelton et al., 2014; Xue et al., 2013).

Pyrethroid urinary levels among pregnant women have been assessed in studies in the US (Castorina et al., 2010), in Mexico (Watkins et al., 2016), in the Brittany region in France (Viel et al., 2015), in Japan (Zhang et al., 2014), in China (Qi et al., 2012) and in Caribbean countries (Dewailly et al., 2014; Lewis et al., 2014). Despite this, little is known about the determinants of pyrethroid exposure in this population. Few studies have evaluated both dietary and non-dietary sources of exposure. Determinants of pyrethroid urinary metabolite concentrations have been studied among children (Glorennec et al., 2017; Morgan and Jones, 2013) and adults in the general population in France and North America (Frery et al., 2012; Frery et al., 2013; McKelvey et al., 2013; Morgan et al., 2016a).

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Table 1
Metabolites of pyrethroids measured in the study, possible precursors and analytical performances.

Metabolite	Possible precursor pyrethroid	Acronym	LOD (µg/L)	LOQ (µg/L)	Intra-day precision (%)
3-phenoxybenzoic	Lambda-cyhalothrin, cypermethrin, deltamethrin, fenvalerate[a], flumetrhina, permethrin, tau-fluvanilate, phenotrin[a], tralomethrin[a]	3-PBA	0.004 µg/L	0.014 µg/L	3.5%
4-fluoro-3-phenoxybenzoic acid	Cyfluthrin[a], flumetrhin[a]	F-BPA	0.005 µg/L	0.015 µg/L	4.9%
Cis-3-(2,2dibromovinyl)-2,2-dimethylcyclopropane-carboxylic acid	Cyfluthrin[a], cypermethrin, permethrin	Cis-DBCA	0.005 µg/L	0.016 µg/L	4.0%
Cis-3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid	Cyfluthrin[a], cypermethrin, permethrin	Cis-DCCA	0.003 µg/L	0.011 µg/L	3.9%
Trans-3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid	Deltamethrin	Trans-DCCA	0.006 µg/L	0.019 µg/L	4.9%

LOD: limit of detection; LOQ: limit of quantification.
[a] Not approved in France in 2011.

This paper describes pyrethroid metabolite urinary levels among pregnant French women in 2011 and associated determinants of these levels. The results come from the perinatal component of the French human biomonitoring (HBM) program which uses data from the Elfe cohort study (the French Longitudinal Study since Childhood). The study protocol and the main descriptive results are described elsewhere (Dereumeaux et al., 2016; Dereumeaux et al., 2017).

2. Material and methods

2.1. Study design

The French HBM program was implemented by Santé publique France, the French national public health agency in 2010. It comprises two studies: a perinatal study based on a sub-sample of 4145 pregnant women, and a cross-sectional study called Esteban (*Etude de SanTé sur l'Environnement, la Biosurveillance, l'Activité physique et la Nutrition* [Health Study on the Environment, Biomonitoring, Physical Activity and Nutrition]) which focuses on the general population, and is based on a sample of 4000 adults (18–74 years) and 1000 children (6–17 years). The program was designed to provide a national representative estimation of the general population's exposure levels to environmental pollutants, and to study variations in exposure levels by comparing results with those from previous studies conducted both in France and internationally, and finally to investigate the determinants of exposure (Dereumeaux et al., 2017). The perinatal component of the French HBM program uses data from the Elfe cohort study, which follows 18,000 children over 20 years in order to characterize the relationship between the environment and the development, health and socialization of the children (Charles et al., 2011; Vandentorren et al., 2009). More details on the Elfe cohort are available from the study website: http://www.elfe-france.fr/index.php/en/.

The protocol for the Elfe cohort was approved by several national bodies, including the National Commission for Data Protection and Liberties, the National Council for Statistical Information, and the national committee for the Protection of Persons.

The study design of the perinatal component of the French HBM program is described in detail elsewhere (Dereumeaux et al., 2016). Briefly, the study population was based on the random selection of pregnant women (> 18 years) who gave birth in 2011 in mainland France (i.e., excluding Corsica and French overseas regions) and who were enrolled in the Elfe cohort. These women had to provide consent for the collection of biological samples and had to provide at least one spot urine sample.

A two-stage probability sample design was used. In the first stage, the primary sampling units (PSU) were maternity hospitals. In the second stage, pregnant women were exhaustively included. The sampling frame of maternity hospitals is described in a previous article (Dereumeaux et al., 2016).

For the analysis of pyrethroid metabolites, a subsample of participants was randomly drawn from the list of pregnant women included in the perinatal component of the program. The number of participants per maternity stratum was chosen in order to preserve the original distribution according to the type of maternity unit institution (i.e., private/public), the authorization type (depending on the number of births per institute per year), and the geographical area (5 regional clusters). A total of 1077 pregnant women were included in the descriptive statistical analyses of pyrethroid metabolite levels. Thirteen percent (n = 145) of this sample were subsequently excluded from multivariable statistical analyses because of missing questionnaires and the absence of comprehensive data for women who although agreeing to provide biological samples, refused to participate in the 20-year follow-up outlined in the Elfe cohort.

2.2. Urine collection and analysis

Spot urine samples were collected just after the mother's admission at the maternity unit. Sampling, aliquoting and storing conditions, as well as analytical methods and quality controls are described in detail elsewhere (Dereumeaux et al., 2016). The analyses of pyrethroids were performed by the Toxicology Center of the National Institute of Public Health of Québec, Canada. Briefly, the concentrations of pyrethroids were quantified by gas chromatography–mass spectrometry using single ion monitoring mode, after an acid extraction and an enzymatic hydrolysis (beta-glucuronidase) (INSPQ, 2009). The biological analyses included five urinary metabolites of pyrethroids (Table 1): 3-phenoxy benzoic (3-PBA; PubChem CID 19539), 4-fluoro-3-phenoxy benzoic acid (F-BPA; PubChem CID 157032), Cis-3-(2,2dibromovinyl)-2,2-dimethyl cyclopropane-carboxylic acid (Cis-DBCA; PubChem CID 181248), Cis-3-(2,2dichlorovinyl)-2,2-dimethyl cyclopropane-carboxylic acid (Cis-DCCA; PubChem CID 91658) and Trans-3-(2,2dichlorovinyl)-2,2-dimethyl cyclopropane-carboxylic acid (Trans-DCCA; PubChem CID 91658). Limits of detection (LOD) and quantification (LOQ) were lower than 0.006 µg/L and 0.019 µg/L, respectively. Pyrethroid metabolite concentrations were measured in µg/L, and in µg/g of creatinine. Calibration standards, blanks and quality control (QC) samples (spiked urine samples) were introduced into each batch of samples to verify the calibration at the LOQ levels (every 20 samples), and both the accuracy and the precision of the measurements (every 10 samples) at three concentration levels: low levels (between 0.07 and 0.14 µg/L, depending of the metabolite), medium levels (between 0.14 and 0.42 µg/L) and high levels (between 0.77 and 1.62 µg/L). Coefficients of variation (CVs) at medium levels ranged between 3.5% and 6.1% for repeatability, and between 3.2% and 8% for reproducibility. The analyses of creatinine were performed using the kinetic Jaffe method (Moss et al., 1975).

2.3. Construction of potential predictors

Retrospective data about lifestyle (e.g. smoking and alcohol),