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## Exposure of the general French population to herbicides, pyrethroids, organophosphates, organochlorines, and carbamate pesticides in 2014–2016: Results from the Esteban study

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## ABSTRACT

Esteban is a nationwide cross-sectional study conducted in France in 2014–2016, including 2503 adults aged 18–74 years old and 1104 children aged 6–17 years old, as part of the French Human Biomonitoring programme. The present paper describes the biological levels of five families of pesticides analysed on random sub-samples of 900 adults and 500 children for urine concentrations, and 759 adults and 255 children for serum concentrations, and the determinants of exposure. Organophosphates, carbamates and herbicides were measured in urine by UPLC-MS/MS; chlorophenols and pyrethroids were measured in urine by GC-MS/MS; specific organochlorines were measured in serum by GC-HRMS. Multivariate analyses were performed to identify the determinants of exposure using a generalized linear model. Pyrethroid metabolites were quantified in 99% of adults and children, with the exception of F-PBA, which was quantified in 31% of adults and 27% of children, respectively. Carbamates and some specific organophosphates were barely or not quantified. DMTP was quantified in 82% of adults and 93% of children, and  $\gamma$ -HCH (lindane) was quantified in almost 50% of adults and children. Concentration levels of pesticide biomarkers were consistent with comparable international studies, except for  $\beta$ -HCH, DMTP, and the deltamethrin metabolite Br2CA, whose levels were sometimes higher in France. Household insecticide use and smoking were also associated with higher levels of pyrethroids. All pyrethroids concentration levels were below existing health-based HBM guidance values, HBM-GVs<sub>GenPop</sub>, except for 3-PBA, for which approximately 1% and 10% of children were above the lower and upper urine threshold values of 22  $\mu$ g/L and 6.4  $\mu$ g/L, respectively. Esteban provides a French nationwide description of 70 pesticide biomarkers for the first time in children. It also describes some pesticide biomarkers for the first time in adults, including glyphosate and AMPA. For the latter, urine concentration levels were overall higher in children than in adults. Our results highlight a possible beneficial impact of existing regulations on adult exposure to organochlorine and organophosphate pesticides between 2006 and 2016, as concentration levels decreased over this period.

### 1. Introduction

A pesticide is any substance or combination of chemical or biological substances intended to repel, destroy or control harmful organisms, or to be used as a plant growth regulator (FAO, 2021). The term 'pesticides'

also refers to a broad classification of plant protection products, which includes various categories of chemical substances according to their main targets (insecticides and acaricides, herbicides, fungicides, nematocides, rodenticides). France is one of the world's largest users of plant protection products, with approximately 83,983 tonnes of pesticides

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being sold there in 2018, the largest user over the period in the European Union (Eurostat data<sup>1</sup>). Approximately 90% of total pesticide consumption in France is used in agriculture (Aubertot et al., 2005); this facilitates the ubiquitous presence of pesticides in the human environment (in particular through pesticide spreading) and widespread contamination of the whole food chain. People come into contact with pesticides in several ways, including their use in food, in the community or household environment, in and around homes and gardens, on pets, and at work (NPIC, 2022).

Many pesticides have been associated with health and environmental issues (Nicolopoulou-Stamati et al., 2016). Exposure can be overt or subacute, and effects range from acute to chronic (Roberts et al., 2012). Health effects depend on the type of pesticide. Some, such as organophosphates and carbamates, affect the nervous system. Others can irritate the skin or eyes. Some are carcinogenic while others can affect the body's hormonal or endocrine system. The risk of pesticide exposure to human health depends on both the toxicity or hazard of the pesticide and the likelihood of exposure (EPA, 2022). Epidemiological studies have shown the strong likelihood that exposure to certain pesticides is associated with the occurrence of certain diseases, such as non-Hodgkin's lymphoma, multiple myeloma, prostate cancer, and Parkinson's disease in adults (INSERM, 2022). This is especially true for people most exposed to pesticides because of their regular use in their occupational activities. In addition, studies have also shown the strong likelihood that acute leukemia in children is associated with the domestic use of pesticides by mothers during pregnancy (INSERM, 2022). Repetitive low-level and combined non-acute exposure to pesticides is also a cause for concern. In children, the health effects associated with chronic exposure to pesticides are diverse, reflecting the diversity of the toxicological properties of this broad group of different chemicals (Roberts et al., 2012).

Human biomonitoring (HBM) is a valuable and practical tool for assessing human exposure to chemicals, including toxicants (Angerer et al., 2007). It integrates all routes of uptake and all sources of exposure through different pathways, such as the living or working environment, diet, and the use of consumer products (Gilles et al., 2021). It allows scientists and public health actors to identify new chemical exposures, trends and changes in exposure, vulnerable groups and populations with higher exposure, and environmental risks at specific contaminated sites with relatively low expenditure. It also allows them to establish exposure distribution in the general population (Ougier et al., 2021). For several years, national HBM programmes in several countries have continuously assessed and monitored population exposure to various chemical substances (Seifert et al., 2000; Becker et al., 2006; Schoeters et al., 2017; Health Canada and Health, 2020; CDC, 2021a; b; Schoeters et al., 2022). The French national HBM programme was established in 2010 to provide a national representative estimation of the French population's exposure to various environmental chemicals, and to better investigate the determinants of exposure (Dereumeaux et al., 2017). The Esteban survey, conducted in 2014–2016, was one component of this programme. It targeted the general population of adults and children living in mainland France. In addition, Esteban will also make it possible, for certain chemical substances, to assess changes in exposure over time compared with the previous French national representative study ENNS (Fréry et al., 2013). Previous bans on certain pesticides does not automatically eliminate exposure, especially for the most persistent chemical substances in the environment. The pesticides measured in Esteban were all selected as part of the French national HBM programme, depending on their biomonitoring feasibility, exposure relevance, existing regulations, and priorities in terms of health effects (Fillol et al., 2014).

The aim of this article was to describe the biomonitoring

concentration levels of 70 biomarkers of pesticides in the general French population, as well as the determinants of exposure levels. Five families of pesticides were studied, covering regulated and unregulated chemical substances which were in use at the time of Esteban, namely organochlorines, organophosphates, carbamates, pyrethroids, and herbicides.

## 2. Material and methods

### 2.1. Study design and individual data collection

Esteban is a cross-sectional study based on a representative sample of the general population living in mainland France during the period 2014–2016. The survey protocol was approved by an Ethical Committee and the French Data Protection Authority (authorization no 2012-A00456-34). The study design is described in detail elsewhere (Balicco et al., 2017). Briefly, 2503 adults and 1104 children were included between April 2014 and March 2016. Three-stage sampling was implemented as follows: a sample of municipalities was first selected; then a sample of households was selected from each selected municipality; finally, a sample of individuals was selected from each selected household (one eligible individual per household). Two independent samples were formed, one including children 6–17 years old, and the other including adults 18–74 years old. Data were collected using socio-demographic, behavioral and environmental questionnaires, food questionnaires, and a health examination comprising anthropometric measurements and biological samples. The latter were collected either at a National Health Insurance examination centre or at participants' homes. Participants collected a first morning urine sample at home in a polypropylene container. A nurse collected fasting blood samples by venous catheter. Once in the laboratory, after centrifugation, urine and serum samples were aliquoted in polypropylene cryotubes (10 mL, 5 mL, 2 mL and 1 mL), before being stored at  $-80^{\circ}\text{C}$  in the biobank for long-term conservation.

A sub-sample of participant health examinations was randomly selected to measure a range of pesticides (organophosphates, organochlorines included chlorophenols, pyrethroids, carbamates, and herbicides). Laboratory analyses were performed on random sub-samples of all the children and adults who had a sufficient quantity of serum or urine in the biobank, specifically 900 adults and 500 children for urine, and 759 adults and 255 children for serum.

### 2.2. Pesticide biomarker measurements

Seventy pesticide biomarkers were selected in Esteban after a prioritization process which took into account their importance in terms of public health (Fillol et al., 2014). The laboratories that performed the biomarker measurements were selected by *Santé publique France* (the French Public Health Agency) in a call for tenders based on price, quality, performance, delivery, suitability, and experience in HBM studies (Fillol et al., 2021). Each laboratory was provided either a volume of urine or serum to determine all the metabolites of a specific family of pesticide biomarkers. The limits of detection (LOD) of analytical methods in France are determined according to the European Directive 2002/657/EC, which specifies the number of identification points for each different method. Laboratories must define the limit of quantification (LOQ) by performing repeated measurements ( $n = 10$ ) in the assay matrix (serum, urine). They must also evaluate the accuracy and intermediate precision of the analytical method at this concentration level. This corresponds to the limit of the method used in these conditions and not to the instrumental limit. For each pesticide biomarker measured, the LOD and LOQ were constant for all subsamples analysed. The process followed by the laboratories to validate certain analytical methods is covered in Supplementary Information.

Labocea (Plouzané, France) performed the analyses of organophosphates, pyrethroids, chlorophenols, and carbamates. Urinary concentrations of organophosphates and carbamates were quantified using

<sup>1</sup> [https://ec.europa.eu/eurostat/databrowser/view/aei\\_fm\\_salpest09/default/table?lang=en](https://ec.europa.eu/eurostat/databrowser/view/aei_fm_salpest09/default/table?lang=en).

Acquity ultra-high-performance liquid chromatography H-Class system with tandem mass spectrometry Xevo TQ-S (UPLC-MS/MS) (Waters, Milford, USA). Data analysis was performed using TargetLynx software from Waters. Analyses were performed using multiple reaction monitoring (MRM) in positive/negative electrospray ionization (ESI) mode measuring at least two specific transitions. Urinary concentrations of pyrethroids and chlorophenols were quantified using gas chromatography (Agilent 700B, USA) with tandem mass spectrometry (GC-MS/MS) (with the MRM mode measuring at least three specific transitions). Data analysis was performed using MassHunter software from Agilent. Labocea's characterisations are carried out in accordance with standards NF T90-210 and SH GTA 14. Labocea is also participating in EQUAS for pentachlorophenol (the only compound in the chlorophenol family proposed by G-EQUAS). A quality control was analysed every ten samples and a blank every twenty samples.

The analyses of specific organochlorines were performed by Laberca/Oniris (Nantes, France). Serum concentrations were quantified using gas chromatography (Agilent 7890A) coupled with high resolution mass spectrometry (GC-HRMS) on electromagnetic sector instruments (JEOL MS 700D or 800D), operating at 10,000 resolution and in the single ion monitoring (SIM) acquisition mode. Laberca ensures the performance of the method used and the maintenance of its skills by taking part in inter-laboratory tests at national and international level. This participation also makes it possible to check and the following points: data quality and validity, laboratory performance (robustness, accuracy), the competence of its staff, and possible sources of error and ways of for improvement. For specific organochlorines, Laberca participates every year in at least two proficiency tests on food and feed organized by the European Reference Laboratory POPs and in several tests on human serum samples organised by the QUEBEC Toxicology Centre.

Labéo (Saint-Contest, France) performed the analyses of herbicides. Urinary concentrations were quantified using ultra-high-performance liquid chromatography (Agilent 6495) with tandem mass spectrometry (UPLC-MS/MS) with at least two specific MRM transitions for each compound. The standard solutions used for internal calibration were prepared in synthetic urine with same protocol than samples. The control quality procedure was performed with analysis of negative, and 3 positive control urine samples (low-medium and high level) every ten samples in each batch of analysed samples. The control quality samples followed all the analytical process. The laboratory performance (LOD, LOQ, robustness, accuracy) were determined for each method according to NF AFNOR T90-210. LABEO participates every year in proficiency testing program OSEQAS (Organic Substances in urine Quality Assessment Scheme) for Glyphosate and AMPA in urine organized by the QUEBEC Toxicology Centre/INSPQ.

**Analytical methods:** i) The extraction of **organophosphates** (chlorpyrifos, chlorpyrifos-methyl, chlorpyrifos methyl-oxon, chlorpyrifos-oxon, TCPy, parathion, parathion-methyl and para-nitrophenol) was performed with Solid Phase Extraction-off line, Oasis HLB well Plate, 30 µm, 2 mg, Waters (Milford, Massachusetts, USA). Five internal standards were used for extraction and detection control: Chlorpyrifos D<sub>10</sub>, chlorpyrifos-methyl D<sub>6</sub>, parathion-methyl D<sub>6</sub>, parathion D<sub>10</sub> and para-nitrophenol D<sub>4</sub>. The sample volume used was 300 µl, diluted by 300 µl of water 4% formic acid. The elution was done using a methanol-acetonitrile solution. A volume of 10 µl was injected in a column Acquity UPLC® BEH C18 1.7 µm 2.1 × 50 mm (Waters, Milford, USA). The eluents used were water/acetonitrile +0.01% formic acid with a gradient from 95 to 5% water 0.01% formic acid, in an oven at 40 °C temperature with a flow rate of 0.4 ml/min ii) The extraction method of **dialkyl phosphate metabolites** (DMP, DMTP, DMDTP, DEP, DETP, DEDTP) was 96-well µElution Solid Phase Extraction-off line, Oasis Wax well Plate, 30 µm, 2 mg, Waters (Milford, Massachusetts, USA) for purification and concentration purposes. Two internal standards were used for extraction and detection control: DETP D10 and DMTP D6. The sample volume used was 200 µl, diluted by 200 µl of water 4% formic

acid. The compounds were eluted using a 5% ammonium hydroxide solution in acetonitrile. Volume of 15 µl was injected in a column Acquity UPLC® BEH amide 1.7 µm 2.1 × 100 mm (Waters, Milford, USA) in an oven at 40 °C. The eluents used were water 50 mM ammonium acetate/acetonitrile with a gradient from 90% to 20% acetonitrile, with a flow rate of 0.3 ml/min iii) **Pyrethroids** (3-PBA, F-PBA, cis-DBCA, cis-DCCA, trans-DCCA) were simultaneously extracted with dichloromethane and derivatized with PFBBr (PentaFluoroBenzyl Bromide) in the presence of TBHAS buffer (tetrabutylammonium hydrogenated sulphate). The internal standard (cis-DCCA – D6) was added directly to 5 mL of sample at the start of the analysis for extraction and detection controls. A purification phase on a Florisil column was carried out, then analytes were eluted and concentrated. iv) The extraction of **chlorophenols** (4-MCP; 2,4-DCP; 2,5-DCP; 2,6-DCP; 2,3,4-TCP; 2,4,5-TCP; 2,4,6-TCP; 2,3,4,6-TeCP; PCP) was performed with liquid-liquid extraction in acid conditions. The internal standards (pentachlorophenol 13C6 and 2,4 Dichlorophenol D3) were added directly to 5 mL of sample at the start of the analysis for extraction and detection controls. A purification phase on a Florisil column was carried out, then analytes were eluted, concentrated and a derivatization with acetic anhydride was realized. v) The extraction of **carbamates** (Propoxur, 2-IPP, Carbofuranphenol) was performed with Solid Phase Extraction-off line, Oasis HLB well Plate, 30 µm, 2 mg, Waters (Milford, Massachusetts, USA). Two internal standards were used for extraction and detection control: propoxur D7, carbofuran D3. The sample volume used was 300 µl, diluted by 300 µl of water 4% formic acid. The elution was done using a methanol-acetonitrile solution. A volume of 10 µl was injected in a column Acquity UPLC® BEH C18 1.7 µm 2.1 × 100 mm (Waters, Milford, USA). The eluents used were water/acetonitrile with a gradient from 90% to 10% water in an oven at 40 °C temperature with a flow rate of 0.3 ml/min vi) The methodology applied to isolate, detect, and quantify **specific organochlorines** is that described earlier by other authors (Ploteau et al., 2016). Briefly, 13C-labeled congeners were added to each sample for quantification according to the isotopic dilution method. Serum (4–6 mL) samples were first submitted to an acidic degradation with formic acid during 15 min. The reaction was stopped using water. The extraction of specific organochlorines was then performed on a C18 Solid Phase Extraction (SPE) column followed by a Florisil SPE column. All internal exposure data were generated blindly among the different collected samples whatever the status of individuals. QA/QC procedures included systematic analysis of negative blank following the entire process, and 3 positive control samples (low-medium and high level) in each batch of analysed samples. All the analyses were conducted in an ISO 17025:2017 accredited laboratory. Recoveries were in the 70–120% range, and the method's extended uncertainty was calculated at low, medium and high level in serum for each compound. vii) Two methods were used for the analysis of **herbicides**. Atrazine, atrazine-desethyl, atrazine-desethyl-2-hydroxy, atrazine-desisopropyl, atrazine-desethyl-desisopropyl, atrazine-2-hydroxy, atrazine mercapturate, 2,4-Dichlorophenoxyacetic acid, alachlor, alachlore mercapturate, 2,6-Diethylaniline, simazine, simazine-2-hydroxy, simazine mercapturate, Isoproturon-monodemethyl (IPPMU), diuron, chlortoluron, isoproturon, and dimetachlor were extracted with Solid Phase Extraction (SPE) online. The urine sample used was 100 µl. 7 internal standards were added and the sample was diluted with water until 1 ml. A volume of 450 µl was introduced in analytic system for SPE extraction using Oasis HLB (2,1 mm × 20 mm × 25 µm), then the chromatographic separation was performed on a BEH C18 1.7 µm 2.1 × 150mm column). The column temperature was kept at 40 °C during the analysis and a gradient elution with flow rate of 0.35 ml/min was used with ultrapure water and acetonitrile with both 0.005% of formic acid. The analysis of glyphosate and its metabolite AMPA required derivatization with fluorenylmethoxycarbonyl chloride (FMOCCL) in order to reduce the polarity and increase the retention of the molecules during separation on a reversed phase polarity chromatography column. This was followed by purification. 200 µl urine sample

were diluted with 700 µl of water and 100 µl of internal standard solution (glyphosate 13C215N and AMPA 13C15N). The derivatization was done during the night with 1 ml FMOC-cl and 1 ml Borate buffer (pH 9.5). This step was stopped by adding 2 ml of dichloromethane and the mixture was shaken. This extract was centrifugated and 500 µl of supernatant was purified and concentrated with online SPE using Oasis HLB (2,1 mm × 20 mm × 25 µm). The analysis was performed on Acquity UPLC BEH C18 1.7 µm 2.1 × 150mm column (Waters, Milford, USA) kept at 60 °C with an elution gradient using acetonitrile and water 2 mM ammonium bicarbonate with a 0.4 ml/min flow rate.

Table 1 describes the type and volume of biological matrix, as well as the analytical method used and associated limits of detection (LOD) and of quantification (LOQ) for each pesticide biomarker analysed in the Esteban study.

### 2.3. Urinary creatinine and serum lipids measurements

Analyses of creatinine were performed by Chemtox, France, using the kinetic Jaffe method (JAFJE, 1886). Cholesterol and triglycerides levels were determined by Laberca using the ISO-17025 accredited enzymatic-colorimetric method, on serum obtained at the same time as the serum used for the analyses of persistent organic pollutants. Total lipid (TL) concentration was calculated using the following formula:  $TL = 1.677 * (TC - FC) + FC + TG + PL$  (all expressed in grammes per litre), where TC is the total cholesterol, FC is free cholesterol, TG is triglycerides and PL is phospholipids (Akins et al., 1989). Urinary concentrations of pesticide biomarkers were expressed as volume-weighted concentrations - specifically microgrammes per litre - and adjusted for urine creatinine by including creatinine in the results (Barr et al., 2005). Serum concentrations of specific organochlorines were expressed on a wet-weight basis - specifically nanogrammes per litre -, and were adjusted for serum lipids as nanogrammes per gramme of total serum lipids, to take their lipophilic nature into account (Mussalo-Rauhamaa, 1991).

### 2.4. Statistical analysis

The statistical analysis method used was broadly similar to that previously described by Fillol et al. (2021) (i.e., first published results from the Esteban survey). All statistical analyses were performed separately for children and for adults (Balicco et al., 2017). All statistical analyses (descriptives and multivariates) were weighted except for the sample of children measured in serum due to the small sample size (255 children). The geometric mean, median, and 25th, 75th, 90th and 95th percentiles were estimated for each biomarker. When the proportion of values below the LOQ was greater than 40%, geometric means were not estimated.

Factors influencing pesticide biomarker levels were identified through a multivariate analysis using a generalized linear model (GLM). Pesticide level values were log-transformed to ensure that the residuals were normally distributed. Some factors were included in the model *a priori* after a literature search on the relationship between these factors and the specified biomarker. Other factors were selected during the modelling process based on statistical criteria, including the Akaike Information Criterion (AIC). To take into account the possible nonlinear relationship between a given biomarker and continuous factors, a natural cubic spline function was fitted. Models were not run when the subsample was small (i.e., included few individuals, for example as was the case with children).

Four different types of factors were considered as follows: i) individual and dietary factors: tobacco consumption; eating and drinking habits; consumption of various products from one's own garden or livestock; consumption of various products from organic farming; ii) domestic parameters and do-it-yourself activities: machining, manipulation of treated wood; working in old houses; wood renovation; domestic use of pesticides; time spent in house; home ventilation

frequency; iii) housing and environmental parameters: type of habitat; characteristics of the dwelling; place of residence; housing nearby a railway line, a cultivation area, a public garden, an incinerator or a waste dump; iv) occupational factors: current or past professional activities in agriculture, arboriculture, cereal crops, working as a florist, gardening, nursery plants, market gardening; professional activities with possible exposure to pesticides; certain exposures in current workplace. Confounding variables were: age and sex of participants, body mass index (BMI), educational level, marital status of head of the child's household (in child models only), number of children in the household (in adult models only), and urinary creatinine (for urine biomarkers only). Results are presented either as percentage changes of pesticide biomarker concentrations, associated with an interquartile increase of quantitative variables, or compared to reference groups for the qualitative variables.

Missing data in a questionnaire and left-censored data (i.e., missing data due to chemical levels below the LOD or LOQ) were imputed using multiple imputations (ICE: STATA module) (Little and Rubin, 2002; Royston and White, 2011).

The concentration levels of urinary biomarkers expressed per gram of creatinine allow to take into account the effects of urinary dilution among participants, as well as certain physiological differences (renal function, lean body mass) (Barr et al., 2005; Pearson et al., 2009). Creatinine excretion may vary depending on the age, sex and race/ethnicity. It is not advisable to compare creatinine-corrected levels of different demographic groups (e.g. adults – children, men – women) (Barr et al., 2005). In Esteban, the detection rate of urine creatinine was 100%. The proportion of adults with urine creatinine concentrations below 0.3 g/L was 12.9% and the proportion above 3 g/L was 0.3%. In children, these proportions were 3.1% and 0.5%, respectively. In this study, individuals with creatinine concentrations <0.3 g/L and >3 g/L were all included in the various analyses. In addition, creatinine (log-transformed) was systematically included in the models as a covariate.

The statistical analyses were conducted using Stata software (ICE module) for data imputation and R software (package 'survey') to take into account the sample design (StataCorp.; Team.).

## 3. Results

### 3.1. Concentrations of pesticide biomarkers

Table 2 summarises descriptive statistics for pesticide biomarkers measured in urine samples of adults (n = 900) and children (n = 500), only for the chemical substances quantified to at least 10% (cf. Table 1).

#### 3.1.1. Pyrethroid biomarkers

Pyrethroid metabolites were quantified in 99% of urine samples from the Esteban population, except for F-PBA which was quantified in 31% and 27% of the samples from children and adults, respectively. Globally, distribution levels of pyrethroid metabolite concentrations found in children were higher than those measured in adults, except for trans-Cl2CA, which were similar for both groups.

#### 3.1.2. Organophosphate biomarkers

All specific organophosphate biomarkers measured in children and adults were barely or not quantified in urine samples (0–1% for chlorpyrifos, chlorpyrifos methyl-oxon, chlorpyrifos-methyl, chlorpyrifos-oxon, parathion, and parathion-methyl; 2–4% for TCPy and par-nitrophenol). DMTP was the most quantified dialkylphosphate metabolite in urine samples both in children and in adults (93% and 82%, respectively). DMP, DEP and DETP were quantified in 22%–46% of the urine samples (children and adults), whereas DMDTP and DEDTP were barely or not quantified (0–2%). Distribution levels of DMP, DMTP, and DETP urinary concentrations in children were all higher than those found in adults; the opposite was true for DEP.

**Table 1**  
Analytical performance of pesticide biomarkers analysed in the Esteban study, 2014–2016.

| Chemical substance (abbreviation)                                      | Biomarker measured          | Biological matrix | Volume needed (mL) | Analytical method | LOD ( $\mu\text{g}\cdot\text{L}^{-1}$ ) | LOQ ( $\mu\text{g}\cdot\text{L}^{-1}$ ) | % $\geq$ LOQ (children) | % $\geq$ LOQ (adults) |
|--|-----------------------------|-------------------|--------------------|-------------------|---|---|-------------------------|-----------------------|
| <b>Pyrethroid pesticides</b>   |                             |                   |                    |                   |   |   |                         |                       |
| Pyrethroid metabolites   |                             |                   |                    |                   |   |   |                         |                       |
| 3-phenoxybenzoic acid  | 3-PBA                       | urine             | 5 <sup>c</sup>     | GC-MS/MS          | 0.005                                   | 0.015                                   | 99.6                    | 100                   |
| 4-fluoro-3-phenoxybenzoic acid   | 4-F-3-PBA (or F-PBA)        | urine             |                    | GC-MS/MS          | 0.005                                   | 0.015                                   | 31.0                    | 27.0                  |
| cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid    | cis-BR2CA (or cis-DBCA)     | urine             |                    | GC-MS/MS          | 0.005                                   | 0.015                                   | 99.6                    | 99.4                  |
| cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid   | cis-Cl2CA (or cis DCCA)     | urine             |                    | GC-MS/MS          | 0.005                                   | 0.015                                   | 99.4                    | 99.8                  |
| trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid | trans-Cl2CA (or trans DCCA) | urine             |                    | GC-MS/MS          | 0.005                                   | 0.015                                   | 98.6                    | 98.6                  |
| <b>Organophosphate pesticides</b>                                      |                             |                   |                    |                   |   |   |                         |                       |
| <i>Specific organophosphate compounds and metabolites</i>              |                             |                   |                    |                   |   |   |                         |                       |
| Chlorpyrifos   | Chlorpyrifos                | urine             | 10 <sup>a</sup>    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 0                       | 0.66                  |
| Chlorpyrifos-methyl-oxon   | Chlorpyrifos-methyl-oxon    | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 0                       | 0                     |
| Chlorpyrifos-methyl  | Chlorpyrifos-methyl         | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 0.4                     | 1.59                  |
| Chlorpyrifos-oxon  | Chlorpyrifos-oxon           | urine             |                    | UPLC-MS/MS        | 0.002                                   | 0.005                                   | 0.4                     | 1.72                  |
| 3,5,6-trichloro-2-pyridinol (TCPy)                                     | TCPy                        | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 2.04                    | 3.05                  |
| Parathion  | Parathion                   | urine             |                    | UPLC-MS/MS        | 0.2                                     | 0.5                                     | 0                       | 0                     |
| Parathion-methyl   | Parathion-methyl            | urine             |                    | UPLC-MS/MS        | 0.2                                     | 0.5                                     | 0                       | 0                     |
| Para-nitrophenol   | Para-nitrophenol            | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 2.04                    | 4.38                  |
| <i>Common dialkyl phosphate metabolites</i>                            |                             |                   |                    |                   |   |   |                         |                       |
| Dimethylphosphate (DMP)  | DMP                         | urine             | 2 <sup>b</sup>     | UPLC-MS/MS        | 0.8                                     | 2.0                                     | 39.2                    | 35.5                  |
| Dimethylthiophosphate (DMTP)   | DMTP                        | urine             |                    | UPLC-MS/MS        | 0.3                                     | 0.6                                     | 92.6                    | 82.5                  |
| Dimethyldithiophosphate (DMDTP)  | DMDTP                       | urine             |                    | UPLC-MS/MS        | 0.3                                     | 0.6                                     | 0.2                     | 2.2                   |
| Diethylphosphate (DEP)   | DEP                         | urine             |                    | UPLC-MS/MS        | 0.3                                     | 0.6                                     | 21.6                    | 46.0                  |
| Diethylthiophosphate (DETP)  | DETP                        | urine             |                    | UPLC-MS/MS        | 0.3                                     | 0.6                                     | 36.4                    | 36.4                  |
| Diethyldithiophosphate (DEDTP)   | DEDTP                       | urine             |                    | UPLC-MS/MS        | 0.3                                     | 0.6                                     | 0                       | 0.33                  |
| <b>Organochlorine pesticides</b>                                       |                             |                   |                    |                   |   |   |                         |                       |
| <i>Dichlorodiphenyltrichloroethanes and metabolites</i>                |                             |                   |                    |                   |   |   |                         |                       |
| Dichlorodiphenyltrichloroethane (DDT)                                  | p,p'-DDT                    | serum             | 5 <sup>c</sup>     | GC-HRMS           | 0.002                                   | 0.01                                    | 14.5                    | 50.86                 |
|  | o,p'-DDT                    | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 2.35                    | 2.37                  |
| Dichlorodiphenyldichloroethylene (DDE)                                 | p,p'-DDE                    | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 100                     | 100                   |
|  | o,p'-DDE                    | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0                       | 0                     |
| <i>Hexachlorocyclohexanes</i>  |                             |                   |                    |                   |   |   |                         |                       |
| $\alpha$ -Hexachlorocyclohexane ( $\alpha$ -HCH)                       | $\alpha$ -HCH               | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 1.18                    | 2.63                  |
| $\beta$ -Hexachlorocyclohexane ( $\beta$ -HCH)                         | $\beta$ -HCH                | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 82.0                    | 99.74                 |
| $\gamma$ -Hexachlorocyclohexane ( $\gamma$ -HCH)                       | $\gamma$ -HCH (lindane)     | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 50.2                    | 49.28                 |
| <i>Cyclodienes</i>   |                             |                   |                    |                   |   |   |                         |                       |
| cis-chlordane  | cis-chlordane               | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0                       | 0                     |
| trans-chlordane  | trans-chlordane             | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0                       | 0                     |
| Oxychlordane   | Oxychlordane                | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 19.6                    | 91.8                  |
| cis-nonachlor  | cis-nonachlor               | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0                       | 13.3                  |
| trans-nonachlor  | trans-nonachlor             | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 15.7                    | 88.7                  |
| cis-heptachlor epoxide   | cis-heptachlor epoxide      | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 31.0                    | 89.5                  |
| trans-heptachlor epoxide   | trans-heptachlor epoxide    | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0                       | 0                     |
| Aldrin   | Aldrin                      | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0                       | 0                     |
| Dieldrin   | Dieldrin                    | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 58.0                    | 94.9                  |
| Endrin   | Endrin                      | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0                       | 0                     |
| Mirex  | Mirex                       | serum             |                    | GC-HRMS           | 0.002                                   | 0.01                                    | 0.39                    | 19.4                  |
| <i>Chlorophenols</i>   |                             |                   |                    |                   |   |   |                         |                       |
| Monochlorophenols (MCP)  | 4-MCP                       | urine             | 5 <sup>d</sup>     | GC-MS/MS          | 0.05                                    | 0.15                                    | 1.8                     | 11.6                  |
| Dichlorophenols (DCP)  | 2,4-DCP                     | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 4                       | 7.6                   |
|  | 2,5-DCP                     | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 4.8                     | 9.7                   |
|  | 2,6-DCP                     | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 0                       | 0.11                  |
| Trichlorophenols (TCP)   | 2,3,4-TCP                   | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 0                       | 0.11                  |
|  | 2,4,5-TCP                   | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 0                       | 0.56                  |
|  | 2,4,6-TCP                   | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 0                       | 0.56                  |
| Tetrachlorophenols (TeCP)  | 2,3,4,6-TeCP                | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 1.6                     | 3.9                   |

(continued on next page)

Table 1 (continued)

| Chemical substance (abbreviation)   | Biomarker measured            | Biological matrix | Volume needed (mL) | Analytical method | LOD ( $\mu\text{g}\cdot\text{L}^{-1}$ ) | LOQ ( $\mu\text{g}\cdot\text{L}^{-1}$ ) | % $\geq$ LOQ (children) | % $\geq$ LOQ (adults) |
|---|-------------------------------|-------------------|--------------------|-------------------|---|---|-------------------------|-----------------------|
| Pentachlorophenols (PCP)  | PCP                           | urine             |                    | GC-MS/MS          | 0.05                                    | 0.15                                    | 14.6                    | 17.7                  |
| <b>Carbamate pesticides</b><br><i>Carbamate compounds and metabolites</i> |                               |                   |                    |                   |   |   |                         |                       |
| Carbofuranphenol  | Carbofuranphenol              | urine             | 10 <sup>f</sup>    | UPLC-MS/MS        | 1                                       | 5                                       | 2.2                     | 1.7                   |
| Propoxur  | Propoxur                      | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 6.0                     | 6.0                   |
| 2-Isopropoxyphenol  | 2-IPP                         | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 11.6                    | 8.5                   |
| <b>Herbicides</b><br><i>Herbicide compounds and metabolites</i>           |                               |                   |                    |                   |   |   |                         |                       |
| Atrazine  | Atrazine                      | urine             | 10 <sup>g</sup>    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0                       | 0                     |
| Atrazine-desethyl   | Deethylatrazin                | urine             |                    | UPLC-MS/MS        | 0.002                                   | 0.005                                   | 0.2                     | 3.0                   |
| Atrazine-desethyl-2-hydroxy   | Deethylhydroxyatrazine        | urine             |                    | UPLC-MS/MS        | 0.05                                    | 0.2                                     | 0.2                     | 0.1                   |
| Atrazine-desisopropyl   | Desisopropylatrazine          | urine             |                    | UPLC-MS/MS        | 0.05                                    | 0.2                                     | 0.2                     | 0.2                   |
| Atrazine-desethyl-desisopropyl  | Desethyl-desisopropylatrazine | urine             |                    | UPLC-MS/MS        | 0.05                                    | 0.2                                     | 0                       | 0.3                   |
| Atrazine-2-hydroxy  | 2-hydroxyatrazine             | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 0                       | 0.7                   |
| Atrazine mercapturate   | Atrazine mercapturate         | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0.2                     | 1.5                   |
| 2,4-Dichlorophenoxyacetic acid  | 2,4-D                         | urine             |                    | UPLC-MS/MS        | 0.03                                    | 0.1                                     | 55.8                    | 40.4                  |
| Alachlor  | Alachlor                      | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0                       | 0.1                   |
| Alachlore mercapturate  | Alachlor mercapturate         | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0.4                     | 0.1                   |
| 2,6-Diethylaniline  | 2,6-Diethylaniline            | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 0.4                     | 0.6                   |
| Simazine  | Simazine                      | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0                       | 0.6                   |
| Simazine-2-hydroxy  | 2-Hydroxysimazine             | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0                       | 0.3                   |
| Simazine mercapturate   | Simazine mercapturate         | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 1.4                     | 0.7                   |
| Isoproturon-monodemethyl (IPPMU)  | IPPMU                         | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0.2                     | 0.8                   |
| Diuron  | Diuron                        | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0                       | 0.8                   |
| Chlortoluron  | Chlortoluron                  | urine             |                    | UPLC-MS/MS        | 0.03                                    | 0.1                                     | 0                       | 0.1                   |
| Isoproturon   | Isoproturon                   | urine             |                    | UPLC-MS/MS        | 0.01                                    | 0.02                                    | 0                       | 0.7                   |
| Dimetachlor   | Dimetachlor                   | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 0                       | 0                     |
| Glyphosate  | Glyphosate                    | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 14.3                    | 16.6                  |
| Aminomethylphosphonic acid (AMPA)   | AMPA                          | urine             |                    | UPLC-MS/MS        | 0.02                                    | 0.05                                    | 93.4                    | 74.0                  |

Volume needed for the analysis of a family of chemical substances:

<sup>a</sup> Specific organophosphate compounds and metabolites;

<sup>b</sup> Common metabolites of organophosphate pesticides,

<sup>c</sup> Specific organochlorine compounds and metabolites;

<sup>d</sup> Chlorophenol compounds;

<sup>e</sup> Pyrethroid metabolites;

<sup>f</sup> Carbamate compounds and metabolites;

<sup>g</sup> Herbicide compounds and metabolites.

### 3.1.3. Carbamate biomarkers

The three biomarkers of carbamate pesticides selected were also quantified in very few urine samples in Esteban. Specifically, carbofuranphenol, propoxur and its metabolite 2-isopropoxyphenol (2-IPP) were quantified in 2%, 6%, and 12% of child samples, respectively, and in 2%, 6%, and 8% of adult samples, respectively.

### 3.1.4. Herbicide biomarkers

Most of the herbicide biomarkers studied were barely or not quantified (0–3%), except for 2,4-D, glyphosate and its metabolite AMPA, which were quantified in 56%, 14%, and 93% of child urine samples, respectively, and in 40%, 17%, and 74% of the urine samples in adults, respectively. The distributions of both glyphosate and AMPA urinary concentrations were overall higher in children than those in adults, with respectively, P95 values of 0.57  $\mu\text{g}/\text{L}$  (0.53  $\mu\text{g}/\text{g}$  creatinine) and 0.45

**Table 2**Description of urinary concentrations ( $\mu\text{g/L}$  and  $\mu\text{g/g}$  creatinine) of organophosphates, chlorophenols, pyrethroids, carbamates, and herbicide biomarkers in adults and children living in mainland France, Esteban study, 2014–2016.

| Biomarker  | Population | N   | % $\geq$ LOQ | P25   | P50   | P75   | P90   | P95   | GM [95% CI] <sup>a</sup> |
|--|------------|-----|--------------|-------|-------|-------|-------|-------|--------------------------|
| <b>volume-based (in <math>\mu\text{g/L}</math>)</b>                |            |     |              |       |       |       |       |       |                          |
| <b>Pyrethroid compounds</b>  |            |     |              |       |       |       |       |       |                          |
| 3-PBA  | Children   | 499 | 99.6         | 0.59  | 1.03  | 1.97  | 4.28  | 7.30  | 1.10 [0.93; 1.29]        |
|  | Adults     | 900 | 100          | 0.37  | 0.72  | 1.28  | 2.42  | 3.23  | 0.72 [0.66; 0.79]        |
| 4-F-3-PBA (or F-PBA)   | Children   | 499 | 31.0         | < LOQ | < LOQ | 0.023 | 0.048 | 0.085 | nc                       |
|  | Adults     | 900 | 27.0         | < LOQ | < LOQ | 0.018 | 0.037 | 0.068 | nc                       |
| BR2CA (or DBCA)  | Children   | 499 | 99.6         | 0.53  | 1.16  | 2.41  | 4.47  | 5.70  | 1.09 [0.92; 1.28]        |
|  | Adults     | 900 | 99.4         | 0.31  | 0.69  | 1.30  | 2.89  | 4.43  | 0.64 [0.58; 0.71]        |
| cis-Cl2CA (or cis DCCA)  | Children   | 499 | 99.4         | 0.18  | 0.32  | 0.57  | 1.18  | 1.89  | 0.32 [0.27; 0.38]        |
|  | Adults     | 900 | 99.8         | 0.12  | 0.25  | 0.48  | 1.05  | 1.53  | 0.24 [0.22; 0.27]        |
| trans-Cl2CA (or trans DCCA)  | Children   | 499 | 98.6         | 0.10  | 0.18  | 0.40  | 0.79  | 1.14  | 0.19 [0.16; 0.22]        |
|  | Adults     | 900 | 98.6         | 0.08  | 0.17  | 0.35  | 0.79  | 1.46  | 0.18 [0.16; 0.20]        |
| <b>Chlorophenol compounds</b>                                      |            |     |              |       |       |       |       |       |                          |
| 4-MCP  | Adults     | 900 | 11.6         | < LOQ | < LOQ | < LOQ | < LOQ | 0.21  | nc                       |
| PCP  | Children   | 500 | 14.6         | < LOQ | < LOQ | < LOQ | 0.18  | 0.34  | nc                       |
|  | Adults     | 900 | 17.7         | < LOQ | < LOQ | < LOQ | 0.16  | 0.23  | nc                       |
| <b>Common organophosphates metabolites</b>                         |            |     |              |       |       |       |       |       |                          |
| DMP  | Children   | 500 | 39.2         | <LOQ  | <LOQ  | 3.93  | 10.98 | 16.00 | nc                       |
|  | Adults     | 899 | 35.5         | <LOQ  | <LOQ  | 3.07  | 8.31  | 14.08 | nc                       |
| DMTP   | Children   | 500 | 92.6         | 1.96  | 4.63  | 9.24  | 16.33 | 26.48 | 4.01 [3.38; 4.75]        |
|  | Adults     | 899 | 82.5         | 0.90  | 2.16  | 4.69  | 10.32 | 14.77 | 2.00 [1.74; 2.30]        |
| DEP  | Children   | 500 | 21.6         | <LOQ  | <LOQ  | <LOQ  | 3.24  | 6.48  | nc                       |
|  | Adults     | 899 | 46.0         | <LOQ  | <LOQ  | 2.64  | 9.18  | 16.34 | nc                       |
| DETP   | Children   | 500 | 36.4         | <LOQ  | <LOQ  | 1.09  | 3.38  | 5.64  | nc                       |
|  | Adults     | 899 | 36.4         | <LOQ  | <LOQ  | 0.98  | 2.83  | 4.44  | nc                       |
| <b>Carbamate compounds</b>   |            |     |              |       |       |       |       |       |                          |
| 2-IPP  | Children   | 500 | 11.6         | < LOQ | < LOQ | < LOQ | 0.12  | 0.30  | nc                       |
|  | Adults     | 899 | 8.5          | < LOQ | < LOQ | < LOQ | < LOQ | 0.11  | nc                       |
| <b>Herbicide compounds</b>   |            |     |              |       |       |       |       |       |                          |
| 2,4-D  | Children   | 498 | 55.8         | <LOQ  | 0.11  | 0.18  | 0.28  | 0.41  | nc                       |
|  | Adults     | 891 | 40.4         | <LOQ  | <LOQ  | 0.15  | 0.28  | 0.40  | nc                       |
| Glyphosate   | Children   | 498 | 14.3         | <LOQ  | <LOQ  | <LOQ  | 0.20  | 0.57  | nc                       |
|  | Adults     | 891 | 16.6         | <LOQ  | <LOQ  | <LOQ  | 0.15  | 0.36  | nc                       |
| AMPA   | Children   | 498 | 93.4         | 0.10  | 0.17  | 0.25  | 0.36  | 0.45  | 0.16 [0.14; 0.18]        |
|  | Adults     | 891 | 74.0         | <LOQ  | 0.09  | 0.16  | 0.26  | 0.34  | 0.08 [0.08; 0.09]        |
| <b>creatinine-adjusted (<math>\mu\text{g/g}</math> creatinine)</b> |            |     |              |       |       |       |       |       |                          |
| <b>Pyrethroid compounds</b>  |            |     |              |       |       |       |       |       |                          |
| 3-PBA  | Children   | 499 | -            | 0.56  | 1.07  | 2.21  | 4.50  | 7.34  | 1.11 [0.95; 1.30]        |
|  | Adults     | 900 | -            | 0.56  | 0.96  | 1.71  | 3.08  | 4.45  | 1.00 [0.93; 1.08]        |
| 4-F-3-PBA (or F-PBA)   | Children   | 499 | -            | < LOQ | < LOQ | 0.02  | 0.06  | 0.09  | nc                       |
|  | Adults     | 900 | -            | < LOQ | < LOQ | 0.025 | 0.057 | 0.093 | nc                       |
| BR2CA (or DBCA)  | Children   | 499 | -            | 0.55  | 1.21  | 2.49  | 4.75  | 6.86  | 1.10 [0.93; 1.30]        |
|  | Adults     | 900 | -            | 0.42  | 0.90  | 2.01  | 4.01  | 5.46  | 0.89 [0.80; 0.99]        |
| cis-Cl2CA (or cis DCCA)  | Children   | 499 | -            | 0.18  | 0.32  | 0.64  | 1.12  | 1.59  | 0.33 [0.28; 0.38]        |
|  | Adults     | 900 | -            | 0.18  | 0.32  | 0.65  | 1.21  | 1.97  | 0.34 [0.31; 0.37]        |
| trans-Cl2CA (or trans DCCA)  | Children   | 499 | -            | 0.10  | 0.21  | 0.41  | 0.78  | 1.15  | 0.19 [0.16; 0.22]        |
|  | Adults     | 900 | -            | 0.12  | 0.24  | 0.46  | 0.96  | 1.90  | 0.25 [0.22; 0.27]        |
| <b>Chlorophenol compounds</b>                                      |            |     |              |       |       |       |       |       |                          |
| 4-MCP  | Adults     | 900 | -            | < LOQ | < LOQ | < LOQ | < LOQ | 0.35  | nc                       |
| PCP  | Children   | 500 | -            | < LOQ | < LOQ | < LOQ | 0.40  | 0.40  | nc                       |
|  | Adults     | 900 | -            | < LOQ | < LOQ | < LOQ | 0.27  | 0.39  | nc                       |
| <b>Common organophosphates metabolites</b>                         |            |     |              |       |       |       |       |       |                          |
| DMP  | Children   | 500 | -            | <LOQ  | <LOQ  | 4.48  | 13.02 | 19.72 | nc                       |
|  | Adults     | 899 | -            | <LOQ  | <LOQ  | 4.62  | 13.05 | 25.21 | nc                       |
| DMTP   | Children   | 500 | -            | 1.80  | 4.09  | 9.67  | 18.82 | 30.76 | 4.06 [3.37; 4.87]        |
|  | Adults     | 899 | -            | 1.20  | 2.71  | 6.72  | 13.39 | 24.37 | 2.78 [2.43; 3.17]        |
| DEP  | Children   | 500 | -            | <LOQ  | <LOQ  | <LOQ  | 3.49  | 11.39 | nc                       |
|  | Adults     | 899 | -            | <LOQ  | <LOQ  | 3.72  | 13.15 | 26.65 | nc                       |
| DETP   | Children   | 500 | -            | <LOQ  | <LOQ  | 1.31  | 3.62  | 5.23  | nc                       |
|  | Adults     | 899 | -            | <LOQ  | <LOQ  | 1.51  | 3.72  | 6.58  | nc                       |
| <b>Carbamate compounds</b>   |            |     |              |       |       |       |       |       |                          |
| 2-IPP  | Children   | 500 | -            | < LOQ | < LOQ | < LOQ | 0.12  | 0.26  | nc                       |
|  | Adults     | 899 | -            | < LOQ | < LOQ | < LOQ | < LOQ | 0.19  | nc                       |
| <b>Herbicide compounds</b>   |            |     |              |       |       |       |       |       |                          |
| 2,4-D  | Children   | 498 | -            | <LOQ  | 0.10  | 0.18  | 0.31  | 0.39  | nc                       |
|  | Adults     | 891 | -            | <LOQ  | <LOQ  | 0.20  | 0.41  | 0.66  | nc                       |
| Glyphosate   | Children   | 498 | -            | <LOQ  | <LOQ  | <LOQ  | 0.23  | 0.53  | nc                       |
|  | Adults     | 891 | -            | <LOQ  | <LOQ  | <LOQ  | 0.18  | 0.45  | nc                       |
| AMPA   | Children   | 498 | -            | 0.11  | 0.16  | 0.27  | 0.39  | 0.52  | 0.16 [0.14; 0.18]        |
|  | Adults     | 891 | -            | 0.07  | 0.12  | 0.21  | 0.30  | 0.42  | 0.11 [0.10; 0.13]        |

<sup>a</sup> For each biomarker, if more than 40% of samples were below the LOQ, the percentile distribution is reported but the geometric mean was not calculated (nc).

µg/L (0.52 µg/g creatinine) in children, and 0.36 µg/L (0.45 µg/g creatinine) and 0.34 µg/L (0.42 µg/g creatinine) in adults.

### 3.1.5. Chlorophenol biomarkers

Among the nine chlorophenols measured in Esteban, PCP was the biomarker with the highest quantification rate both in children (14.6%) and in adults (17.7%), with P95 values of 0.34 µg/L (0.40 µg/g creatinine) and 0.23 µg/L (0.39 µg/g creatinine), respectively. Four chlorophenols, 4-MCP, 2,4-DCP, 2,5-DCP, and TeCP, were quantified in 1.6%–4.8% of child urine samples, and in 3.9%–11.6% of adult urine samples, respectively. Four other chlorophenols, 2,6-DCP, 2,3,4-TCP, 2,4,5-TCP, and 2,4,6-TCP, were not quantified in children and in less than 1% of adult samples.

### 3.1.6. Specific organochlorine biomarkers

Table 3 summarises descriptive statistics for pesticide biomarkers measured in serum in adults (n = 759) and children (n = 255), only for the chemical substances quantified to at least 10% (cf. Table 1).

The following specific organochlorine biomarkers were barely quantified (<3%) in children and adult serum samples: o,p'-DDT, o,p'-DDE, α-HCH, cis-chlordane (both 0%), trans-chlordane (both 0%), cis-nonachlor (0% in children), trans-heptachlor epoxide (both 0%),

Aldrin (both 0%), endrin (both 0%), and mirex (0.4% in children). Other organochlorine biomarkers were quantified between 13% and 40% of serum samples in adults (mirex (19.4%)) or in children ((p,p'-DDT (14.5%), trans-nonachlor (15.7%), oxychlordane (19.6%), and cis-heptachlor epoxide (39%)).

The remaining organochlorine biomarkers studied were quantified in at least half of the populations of children and adults: p,p'-DDE (both 100%), β-HCH (82.0% and 99.7%, respectively), γ-HCH (50.2% and 49.3%, respectively); or only in adults: p,p'-DDT (50.9%), oxychlordane (91.8%), trans-nonachlor (88.7%), cis-heptachlor epoxide (89.5%), and dieldrin (94.9%).

Overall, the distributions of concentration levels (geometric means) of the studied specific organochlorine biomarkers (dichlorodiphenyltrichloroethanes, hexachlorocyclohexanes, and cyclodienes) measured in adult serum samples were all higher than the distributions observed in children.

## 3.2. Factors influencing exposure levels to pesticide biomarkers

### 3.2.1. Pyrethroid biomarkers

Results of the multivariate analyses for pyrethroid biomarkers in adults are detailed in Supplementary Tables A1 and A2, for quantitative

**Table 3**

Description of the concentrations in serum (in ng/L and in ng/g lipids) of specific organochlorine pesticide compounds and metabolites in the population of adults and children living in mainland France, Esteban study, 2014–2016.

| Biomarker   | Population <sup>a</sup> | N   | % ≥ LOQ <sup>b</sup> | P25   | P50    | P75   | P90    | P95    | GM [95% CI]          |
|---|-------------------------|-----|----------------------|-------|--------|-------|--------|--------|----------------------|
| <b>volume-based (in ng/L)</b>                           |                         |     |                      |       |        |       |        |        |                      |
| <b>Dichlorodiphenyltrichloroethanes and metabolites</b> |                         |     |                      |       |        |       |        |        |                      |
| p,p'-DDT  | Children                | 255 | 14.5                 | <LOQ  | <LOQ   | <LOQ  | 12.32  | 20.06  | nc                   |
|   | Adults                  | 759 | 50.9                 | <LOQ  | 9.25   | 15.00 | 25.02  | 38.44  | nc                   |
| p,p'-DDE  | Children                | 255 | 100                  | 67.25 | 102.04 | 166.3 | 279.8  | 444.7  | 113.0 [112.9; 113.1] |
|   | Adults                  | 759 | 100                  | 179.0 | 355.7  | 760.1 | 1583.9 | 2540.8 | 393.1 [350.6; 440.8] |
| <b>Hexachlorocyclohexanes</b>                           |                         |     |                      |       |        |       |        |        |                      |
| β-HCH   | Children                | 255 | 82.0                 | 11.81 | 17.8   | 24.23 | 43.05  | 55.68  | 18.10 [18.02; 18.17] |
|   | Adults                  | 759 | 99.7                 | 34.37 | 70.96  | 164.4 | 402.7  | 596.5  | 79.23 [69.97; 89.73] |
| γ-HCH (lindane)   | Children                | 255 | 50.2                 | <LOQ  | 10.02  | 12.35 | 17.09  | 20.14  | nc                   |
|   | Adults                  | 759 | 49.3                 | <LOQ  | 9.75   | 12.41 | 17.13  | 26.74  | nc                   |
| <b>Cyclodienes</b>                                      |                         |     |                      |       |        |       |        |        |                      |
| Oxychlordane  | Children                | 255 | 19.6                 | <LOQ  | <LOQ   | <LOQ  | 13.08  | 16.43  | nc                   |
|   | Adults                  | 759 | 91.8                 | 12.2  | 22.1   | 37.47 | 55.81  | 73.60  | 21.55 [19.67; 23.60] |
| cis-nonachlor   | Children                | 255 | 13.3                 | <LOQ  | <LOQ   | <LOQ  | 9.99   | 13.36  | nc                   |
|   | Adults                  | 759 | 15.7                 | <LOQ  | <LOQ   | <LOQ  | 12.08  | 15.45  | nc                   |
| trans-nonachlor   | Children                | 255 | 15.7                 | <LOQ  | <LOQ   | <LOQ  | 12.08  | 15.45  | nc                   |
|   | Adults                  | 759 | 88.7                 | 11.28 | 19.70  | 34.52 | 52.83  | 62.08  | 19.15 [17.38; 21.09] |
| cis-heptachlor epoxide                                  | Children                | 255 | 31.0                 | <LOQ  | <LOQ   | 10.90 | 14.59  | 16.33  | nc                   |
|   | Adults                  | 759 | 89.5                 | 11.68 | 17.4   | 27.33 | 43.64  | 58.47  | 18.10 [16.75; 19.56] |
| Dieldrin  | Children                | 255 | 58.0                 | <LOQ  | 10.96  | 15.11 | 20.84  | 25.84  | nc                   |
|   | Adults                  | 759 | 94.9                 | 14.69 | 23.34  | 36.46 | 58.05  | 80.78  | 23.78 [21.87; 25.87] |
| Mirex   | Adults                  | 759 | 19.4                 | <LOQ  | <LOQ   | <LOQ  | 11.45  | 14.28  | nc                   |
| <b>lipid-adjusted (ng/g lipids)</b>                     |                         |     |                      |       |        |       |        |        |                      |
| <b>Dichlorodiphenyltrichloroethanes and metabolites</b> |                         |     |                      |       |        |       |        |        |                      |
| p,p'-DDT  | Children                | 255 | -                    | <LOQ  | <LOQ   | <LOQ  | 2.36   | 3.73   | nc                   |
|   | Adults                  | 759 | -                    | <LOQ  | 1.57   | 2.36  | 4.00   | 5.93   | nc                   |
| p,p'-DDE  | Children                | 255 | -                    | 13.65 | 20.35  | 33.8  | 56.84  | 82.15  | 22.70 [22.62; 22.80] |
|   | Adults                  | 759 | -                    | 30.18 | 57.76  | 126.1 | 242.4  | 422.2  | 64.85 [57.97; 72.55] |
| <b>Hexachlorocyclohexanes</b>                           |                         |     |                      |       |        |       |        |        |                      |
| β-HCH   | Children                | 255 | -                    | 2.41  | 3.40   | 5.07  | 8.14   | 11.88  | 3.64 [3.56; 3.71]    |
|   | Adults                  | 759 | -                    | 5.94  | 11.14  | 24.99 | 62.74  | 94.2   | 13.07 [11.58; 14.76] |
| γ-HCH (lindane)   | Children                | 255 | -                    | <LOQ  | 2.04   | 2.56  | 3.21   | 4.10   | nc                   |
|   | Adults                  | 759 | -                    | <LOQ  | 1.65   | 2.15  | 2.92   | 4.01   | nc                   |
| <b>Cyclodienes</b>                                      |                         |     |                      |       |        |       |        |        |                      |
| Oxychlordane  | Children                | 255 | -                    | <LOQ  | <LOQ   | <LOQ  | 2.58   | 3.04   | nc                   |
|   | Adults                  | 759 | -                    | 2.14  | 3.48   | 5.96  | 8.56   | 10.53  | 3.55 [3.26; 3.87]    |
| cis-nonachlor   | Children                | 255 | -                    | <LOQ  | <LOQ   | <LOQ  | 2.00   | 2.00   | nc                   |
|   | Adults                  | 759 | -                    | <LOQ  | <LOQ   | <LOQ  | 2.41   | 2.93   | nc                   |
| trans-nonachlor   | Children                | 255 | -                    | <LOQ  | <LOQ   | <LOQ  | 2.41   | 2.93   | nc                   |
|   | Adults                  | 759 | -                    | 1.92  | 3.22   | 5.36  | 7.86   | 9.56   | 3.16 [2.89; 3.44]    |
| cis-heptachlor epoxide                                  | Children                | 255 | -                    | <LOQ  | <LOQ   | 2.09  | 2.74   | 3.25   | nc                   |
|   | Adults                  | 759 | -                    | 2.02  | 2.87   | 4.34  | 6.67   | 8.74   | 2.99 [1.38; 2.02]    |
| Dieldrin  | Children                | 255 | -                    | <LOQ  | 2.19   | 3.04  | 4.07   | 5.30   | nc                   |
|   | Adults                  | 759 | -                    | 2.52  | 3.89   | 5.78  | 8.86   | 12.37  | 3.92 [3.63; 4.24]    |
| Mirex   | Adults                  | 759 | -                    | <LOQ  | <LOQ   | <LOQ  | 2.00   | 2.62   | nc                   |

<sup>a</sup> Descriptive statistics not weighted for children due to the small sub-sample.

<sup>b</sup> For each biomarker, if more than 40% of samples were below the LOQ, the percentile distribution is reported but the geometric mean was not calculated (nc).

and qualitative variables, respectively. The following exposure factors were associated with the highest levels of the sum of urine pyrethroid metabolite concentrations ( $\sum$ pyrethroids = 3-PBA + F-PBA + Br2CA + cisCl2CA + transCl2CA) in adults (Table A2): tobacco consumption, the use of pest control on pets at least three times a year, exposure to plant or animal substances and dust at the workplace, and consumption of at least one product of animal origin from the participant's own garden or livestock (poultry, meat, milk and eggs). In addition, having one's home in a green area (e.g., forest, meadow, and scrubland) was associated with higher urine concentration levels of 3-PBA (Table A2). Moreover, beef consumption was associated with higher urine concentration levels of Br2CA (Table A1). In contrast, moderate consumption of vegetables from organic farming (1–3 times a week) was associated with lower urine concentration levels of 3-PBA, cisCl2CA, transCl2CA, and  $\sum$ pyrethroids (Table A2).

Results of the multivariate analyses for pyrethroid biomarkers in children are detailed in Supplementary Tables A3 and A4, for quantitative and qualitative variables, respectively. In children, the concentration levels of F-PBA, cisCl2CA and transCl2CA decreased with age (Table A3). The same trends were observed with 3-PBA, Br2CA, and  $\sum$ pyrethroids, but they were not significant (Table A3). Exposure factors associated with highest levels of the  $\sum$ pyrethroids in children were (Table A4): the use of pest control on pets at least once a year, and the frequent use of pesticides against dust mites in the home. In addition, living within 200 m of an agricultural area (e.g., cultivated fields, orchards, and greenhouses) was associated with higher urine concentration levels of F-PBA, and living within 200m of a garden was associated with higher urine concentration levels of transCl2CA (Table A4).

### 3.2.2. Organochlorine biomarkers

Results of the multivariate analyses in adults for the specific organochlorine biomarkers studied are presented in Supplementary Tables A5 and A6, for quantitative and qualitative variables, respectively.

The concentration levels of all the specific organochlorine biomarkers studied (p,p'-DDE,  $\beta$ -HCH, cis-heptachlor epoxide, oxychlordane, trans-nonachlor, and dieldrin) increased with age (Table A5); older adults had higher serum organochlorine concentration levels than younger adults. Serum concentration levels of these biomarkers also increased with body mass index (BMI), except for trans-nonachlor (Table A5).

There were significant differences in concentration levels of specific organochlorine biomarkers according to sex (Table A6). Levels of serum  $\beta$ -HCH and p,p'-DDE in women were 41.2% and 26.6% higher than in men, respectively. In contrast, levels in men were 27.2%, 21.9% and 16.0% higher than in women for dieldrin, cis-heptachlor epoxide, and trans-nonachlor, respectively.

Several dietary factors were associated with serum concentration levels for the studied specific organochlorines. Higher levels were observed for the following types of foodstuffs (Table A5): eggs (8.4% and 4.6% for p,p'-DDE and oxychlordane, respectively); fats (9.2%, 8.7% and 6.5%, for  $\beta$ -HCH, oxychlordane and dieldrin, respectively); fish and seafood (17.0% for trans-nonachlor); crustaceans, molluscs and shellfish (3.5% for oxychlordane); all vegetables (13.2% for p,p'-DDE and 9.5% for dieldrin); all fruits (18.3% for p,p'-DDE and 16.7% trans-nonachlor). Higher levels were also observed for the consumption of tap water (8.2% for oxychlordane), and alcoholic beverages (14.4%, 11.5% and 10.9%, for trans-nonachlor, dieldrin and cis-heptachlor epoxide, respectively) (Table A5). In contrast, beef consumption (bovine meat) were associated with lower serum concentration levels of both oxychlordane (−6.7%) and trans-nonachlor (−6.6%) (Table A5).

Serum concentration levels of trans-nonachlor, cis-heptachlor epoxide, and oxychlordane, were 22.5%, 20.4%, and 18.4% higher, respectively, in participants who moderately (i.e., 1–3 times a month) consumed eggs from their own garden or farm (Table A6). In contrast, the consumption of the following foodstuffs was associated with lower serum concentration levels of certain specific organochlorines

(Table A6): meat or poultry from one's own livestock with cis-heptachlor epoxide levels (−18.2%), organically farmed meat with p,p'-DDE levels (−22.3%), and of organic food products (dairy products, eggs, poultry and other meats, fruits and vegetables, cereals or wholemeal bread) with  $\beta$ -HCH levels (−10.2%), respectively.

With regard to domestic and environmental factors (Table A6), adults who reported using pesticides on their houseplants (indoor plants) had higher serum organochlorine biomarker concentration levels than those who reported not having indoor plants. Specifically, percentages were 25.8%, 23.4%, 21%, 15%, 10%, and 14% higher for p,p'-DDE,  $\beta$ -HCH, cis-heptachlor epoxide, oxychlordane, transnonachlor, and dieldrin in the former group. Moreover, the  $\beta$ -HCH serum concentration level was 17.8% higher in adults who reported using pesticides on the lawn at their house than in those with no lawn (Table A6). Furthermore, serum concentration levels of trans-nonachlor and dieldrin were 11.8% and 26.3% higher, respectively, in users of body repellents than in non-users (Table A6).

The serum concentration level of p,p'-DDE was 21.4% higher in adult participants living in suburban districts than in those living in city centres (Table A6). In addition, serum concentration levels of trans-nonachlor and cis-heptachlor epoxide were 18.8% and 13% higher, respectively, in adults who declared aerating their home (ventilation of housing during spring and summer) once or twice daily than in those who aerated their home more often (Table A6).

With regard to occupational exposure factors (Table A6), adult participants exposed to plant, animal, or topsoil dusts had serum concentration levels of  $\beta$ -HCH 30.8% higher than that in unexposed individuals. Similarly, serum concentration levels of dieldrin and cis-heptachlor epoxide were 43.1% and 16.6% higher, respectively, in adult participants who worked in occupational fields related to agriculture, plants, pesticides or wood than in those with other occupations.

### 3.2.3. Organophosphate biomarkers

In terms of exposure levels to organophosphate pesticides, multivariate analyses did not identify potential sources of exposure to DMTP in children. However, younger children had higher urine DMTP concentration levels than older children (Table A7). In adults, the consumption of food from organic farming (dairy products, eggs, poultry and other meats, fruits and vegetables, cereals or wholemeal bread) was associated with lower urine concentration levels of DMTP (Table A8).

### 3.2.4. Herbicide biomarkers

With respect to the exposure levels to the glyphosate metabolite AMPA, none of the potential exposure variables analysed was significantly associated with differences in urine concentration in children. However, children sampled in spring had higher urine concentration levels of AMPA than those in autumn or winter (Table A9). In adults, AMPA concentration levels in urine were higher in those who had an individual boiler for the main mode of heating (Table A10).

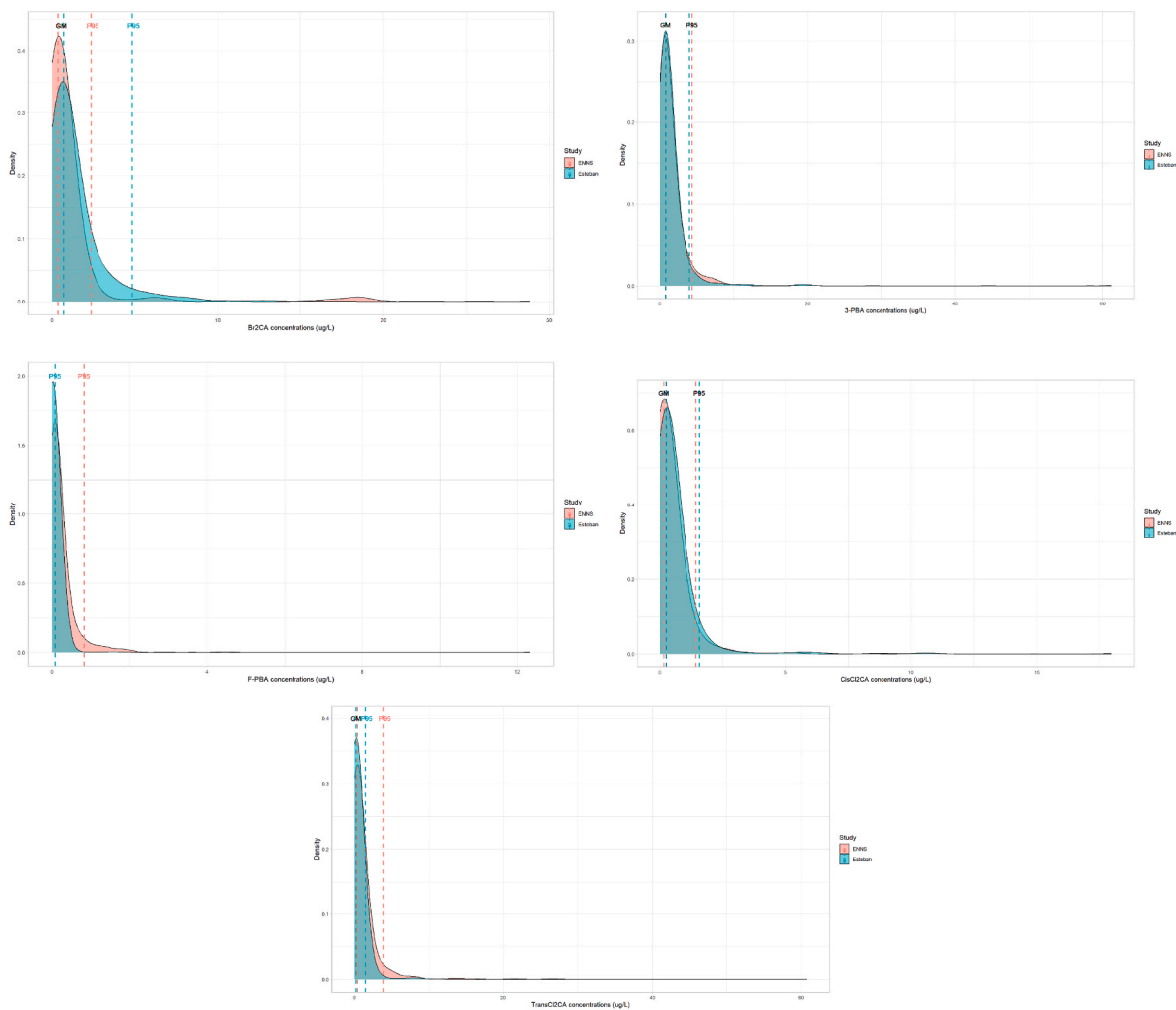
## 4. Discussion

### 4.1. Pesticide levels in France and comparison with international studies

#### 4.1.1. Pyrethroid concentrations

In 2006–2007, the ENNS study provided the first distributions of urine pyrethroid metabolite exposure levels in the adult population living in mainland France (Fréry et al., 2013). The present study showed that the average concentration levels of urine F-PBA and urine trans-Cl2CA slightly decreased between 2006–2007 and 2014–2016 (Fig. 1). The overall distribution of urine 3-PBA and urine cis-Cl2CA remained stable over the decade 2006–2016, while urine Br2CA concentration levels increased.

In Esteban, younger children had higher pyrethroid concentrations than older children and adults, reflecting other studies in Poland (Wielgomas and Piskunowicz, 2013), Spain (Fernandez et al., 2020),



**Fig. 1.** Comparison of the distribution of urine concentration levels of pyrethroid metabolites in French adults aged 18–74 years between the ENNS survey (2006–2007) and the Esteban survey (2014–2016).

Slovenia (Bravo et al., 2020) and the United States (CDC, 2021a). This could be explained by the fact that younger children have more frequent hand-to-mouth activity, and are also more in contact with indoor dust containing pyrethroids (Berger-Preiss et al., 2002; Mandin et al., 2016). In addition, their food intake is higher than adults, in terms of body weight (Dewalque et al., 2014; Zentai et al., 2016; Katsikantami et al., 2019).

The only metabolite of pyrethroids to show an increase in concentration levels between the ENNS and Esteban surveys was Br2CA. This may reflect greater use of deltamethrin in France compared to other pyrethroid pesticides over 2006–2016, and also greater use of deltamethrin in France between the two surveys, probably mainly in houses. Deltamethrin is used very rarely in France for veterinary purposes. Currently, only three authorized veterinary drugs are based on deltamethrin, and sales are low (according to the French national databank for pesticide sales (BNVD)). In addition, deltamethrin is rarely used as an insecticide in vector control (adulticidal treatments) in mainland France, and was not used at all in 2014–2016. A possible increase in agricultural uses of deltamethrin in France could also be a source of the increase observed in concentration levels. The ban on several families of insecticides between the ENNS and Esteban studies, in particular carbamates in 2008, may have led to increased use of deltamethrin. This hypothesis however needs greater investigation, as French data did not show any substantial increase in the sale of deltamethrin-based plant protection products by authorized distributors nationally (12,500 kg and 12,582 kg for 2008 and 2016, respectively, for various commercial

specialties). Finally, the lower concentration levels of transCl2CA in Esteban than in North American countries would suggest that related pesticides are used differently in France.

The results from the Esteban study would suggest that in 2014–2016, the French population did not have pyrethroid metabolite exposure levels different from those measured in international studies, except for Br2CA, a metabolite of deltamethrin. However, results from the ENNS survey in the general French population (2006–2007, see above) and from the French perinatal survey ELFE (2011) (Dereumeaux et al., 2018), showed that the adult population living in mainland France had higher exposure levels to pyrethroid metabolites than European and North American populations over the same period (i.e., 2006–2011). Furthermore, in France, the concentration levels of the different pyrethroid metabolites remained stable or declined between 2006–2007 and 2014–2016, while in Spain (Fernandez et al., 2020), Canada (Health Canada and Health, 2019) and in the United States (CDC, 2021a) they increased.

#### 4.1.2. Organochlorine concentrations

Esteban is the first survey to measure exposure levels to organochlorines and their metabolites in French children aged 6–17 years.

Average organochlorine concentration levels in serum in the youngest children were slightly higher than those in older children (p,p'-DDE,  $\beta$ -HCH and  $\gamma$ -HCH (lindane)) (see Table A11). This indicates greater exposure of young children to organochlorines, perhaps due to possible greater exposure to household dust and/or food contaminated.

Few international studies have evaluated exposure levels to organochlorines in children. In Europe, the GerES V study conducted in 2014–2017 on German children aged 3–17 years (Bandow et al., 2020) is the closest temporal study to Esteban. The organochlorine p,p'-DDE was 100% quantified in both German and French children. However, the average serum concentration of p,p'-DDE was higher in German children than in French children, at 158 ng/L and 113 ng/L, respectively. The organochlorines p,p'-DDT,  $\alpha$ -HCH,  $\beta$ -HCH and  $\gamma$ -HCH (lindane) were all quantified less in German children.

With regard to exposure to chlorophenolic compounds, 4-MCP, 2,4-MCP, 2,5-MCP, 2,4,5-TCP, 2,4,6-TCP and PCP were quantified in 59%–100% of adults in the French ENNS survey (Fréry et al., 2013), in contrast to only 0.6%–17.7% in Esteban; however, all LOQ were lower in Esteban.

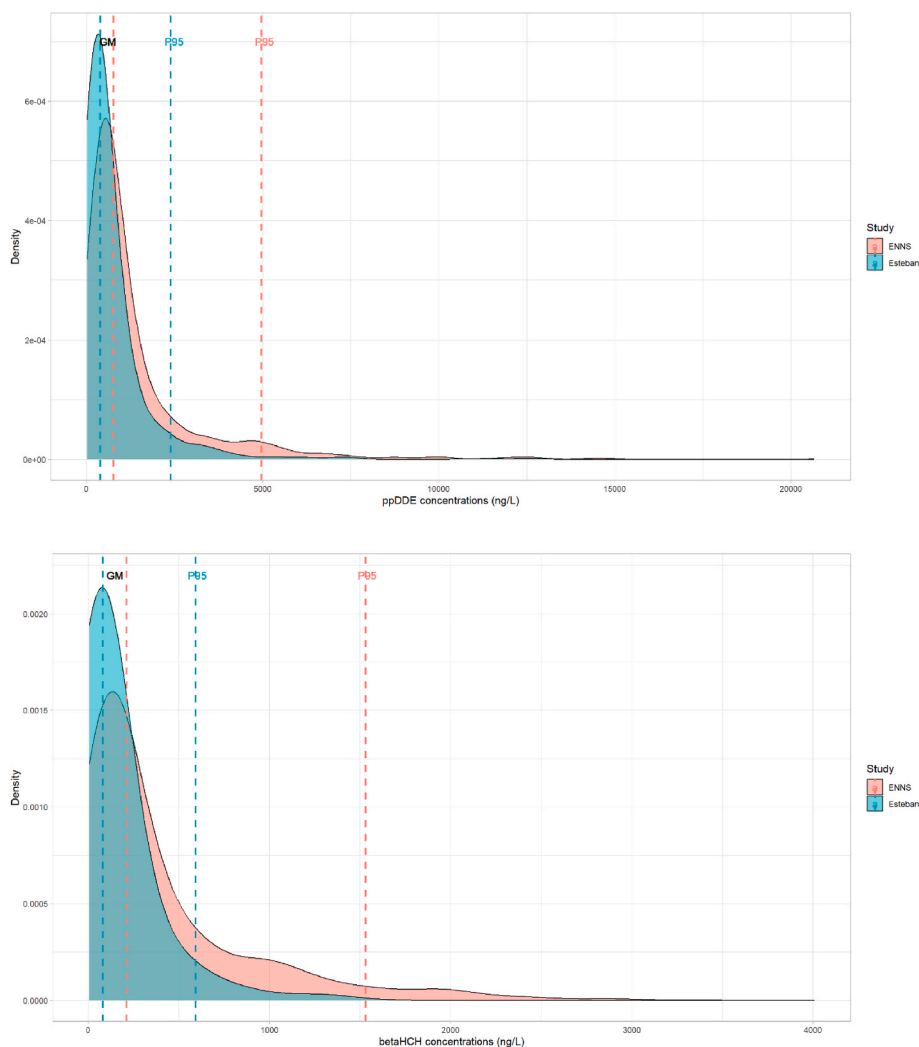
The organochlorines p,p'-DDE and  $\beta$ -HCH were nearly 100% quantified in both ENNS (Fréry et al., 2013) and Esteban, with serum geometric means of 760 ng/L and 210 ng/L in the former, and 393 ng/L and 79 ng/L in the latter, respectively. The very marked difference in serum concentration levels these two biomarkers between both surveys (Fig. 2), reflects the definitive ban on organochlorine pesticides in France in 2009.

The concentration levels of all the organochlorines studied, with the exception of hexachlorocyclohexanes ( $\beta$ -HCH and  $\gamma$ -HCH), were all lower in French adults in 2014–2016 (i.e., Esteban) than in Canadian

adults in 2007–2009 for p,p'-DDT, p,p'-DDE and cyclodiene compounds (oxychlorane, cis-nonachlor, trans-nonachlor, mirex) (Health Canada and Health, 2010). Although organochlorine-based pesticides were hardly used anymore in France at the time of Esteban, highest serum concentration levels were found for p,p'-DDE and  $\beta$ -HCH. This can be at least partly explained by the fact that these two chemical compounds are very persistent in the environment. For example, DDT, the parent substance of p,p'-DDE, has a reported half-life of 2–15 years in the environment (Blaylock, 2005) and 3–6 years in humans (Burr, 2014). In addition, DDT breaks down in the environment to more stable chemical forms, including p,p'-DDE and higher serum concentrations of p,p'-DDE than p,p'-DDT are usually found in human populations (Blaylock, 2005; Kang et al., 2008; Li et al., 2022). While French legislation has helped limit direct exposure to organochlorines, it cannot limit their long-term presence in the body.

#### 4.1.3. Organophosphate concentrations

The very high quantification of the dialkylphosphate metabolite DMTP in Esteban is an indicator of permanent exposure of the French population to organophosphate compounds in 2014–2016. The second most quantified dialkylphosphate metabolite in the study was DMP. Although measuring DMTP and DMP does not allow the specific identification of their parent organophosphate compounds, they are nevertheless the only dialkylphosphate metabolites of certain pesticides, such



**Fig. 2.** Comparison of the distribution of serum concentration levels of specific organochlorine metabolites in French adults 18–74 years old between the ENNS survey (2006–2007) and the Esteban survey (2014–2016).

as chlorpyrifos methyl, which were still widely used in France at the time of Esteban.

All of the common dialkylphosphate metabolites in urines were less quantified in French adults in Esteban than in adults from the ENNS survey (Fréry et al., 2013). The average DMTP concentration in Esteban adults was one third that in ENNS adults. These results reflect a clear decrease in the exposure to organophosphorus compounds in France between 2006–2007 and 2014–2016. At the time of the ENNS survey, several organophosphorus pesticides such as trichlorfon, dichlorvos, malathion and diazinon were still authorized and widely used in agriculture in France, before a gradual ban on their use was introduced, starting in 2008.

The mean level of urine DMTP concentration levels in Esteban were higher in France than those observed in both US (CDC, 2021a) and Canada (Health Canada and Health, 2019). Note that the Canadian sample was more recent (2016–2017), while the United States sample was older (2007–2008). Similarly in Europe, the average DMTP concentration level in young French children in Esteban was double that observed in 2011 in young Danish children in the Democophes study (Morck et al., 2016). Despite older regulations in Europe on the agricultural uses of organophosphorus pesticides, and their low persistence in the environment, the higher concentration levels of DMTP in the French population than in Western countries may be explained by non-agricultural factors, such as non-agricultural uses of organophosphorus compounds and exposure to non-pesticidal parent compounds of DMTP. In addition, the overexposure to DMTP in French children compared to Western children could also be explained by local differences in environmental exposure to organophosphorus compounds, coupled with local singularities in children's behaviors and habits (e.g., hand-to-mouth contact, presence of pets in housing, outdoor hobbies).

#### 4.1.4. Herbicide concentrations

Esteban is the first study to measure the concentration levels of several herbicides in both children and adults of the general population living in mainland France. In Esteban, only three herbicide biomarkers of all those measured (i.e., 2,4-D, and glyphosate and its metabolite AMPA) were quantified in urine samples in more than 2% of children and more than 5% of adults.

Glyphosate and AMPA were quantified, respectively, in 14% and 93% of child urine samples, and 17% and 74% of adult urine samples. AMPA exposure was therefore slightly higher in children than in adults. Urinary concentrations of 2,4-D measured in children and adults were generally lower than those in studies in North America (Nhanes in 2009–2010 (CDC, 2021a) and CHMS in 2009–2011 (Health Canada and Health, 2013)). In addition, urinary glyphosate concentration levels in the Nhanes survey 2013–2014 were also higher than those in Esteban (2014–2016) for both children and adults (Ospina et al., 2022). One of the most likely explanations for this is the greater use of herbicides in the United States and Canada (FAO, 2021), as these two countries rank second and fifth, respectively, in terms of herbicide-intensive countries in the world, while France ranks ninth (FAO, 2022).

In Europe, urine concentration levels to glyphosate and AMPA differ greatly between countries, e.g., when comparing upper percentiles of their distributions (Conrad et al., 2017; Connolly et al., 2018; Nova et al., 2020; Soukup et al., 2020; Stajniko et al., 2020; Lemke et al., 2021; Ruiz et al., 2021; Buekers et al., 2022a, 2022b; Schoeters et al., 2022). Comparison is difficult however because of particularities specific to each of the studies concerned (e.g., target population, study period, analytical method).

#### 4.1.5. Carbamate concentrations

Esteban is the first study to measure exposure levels of the French population to carbamate pesticides (carbofuranphenol and propoxur). Carbamates were barely quantified in Esteban, reflecting studies in the United States (CDC, 2021a), Canada (Haines et al., 2017), and the French ELFE cohort (see above) (Dereumeaux et al., 2016).

## 4.2. Factors influencing exposure levels to pesticides in the French population

### 4.2.1. Pyrethroid factors

Our analyses on pyrethroids exposure factors show that the domestic use of insecticides to control crawling insects, flying insects, fleas or lice was one of the main determinants of high urine pyrethroid concentrations in children and adults. This confirms results on the exposure to pyrethroids linked to the domestic use of insecticides in previous studies in France (Fréry et al., 2013; Dereumeaux et al., 2018).

No dietary factor was associated with pyrethroid concentration levels in children in Esteban. In Spain, higher urinary 3-PBA concentrations were observed in children with recent consumption of vegetables (Fernandez et al., 2020), but this was not the case for children from Belgium (Pirard et al., 2020).

In Esteban, we observed that adults who consumed organically grown vegetables had lower concentration levels of urine pyrethroid metabolites. On the contrary, higher levels were observed in adults who consumed their own livestock, and those who consumed beef (irrespective of its provenance). Using pyrethroids as antiparasitics for livestock could therefore be a source of contamination of related foods. In fact, several pyrethroid substances (in particular cyfluthrin, cypermethrin, deltamethrin and permethrin, for which a number of metabolites were measured in this study) are used in specific products designed for livestock breeding, in particular antiparasitic collars and ear tags. In other studies, the consumption of cereals and fruits or vegetables was associated with higher concentrations (Becker et al., 2006; Fortes et al., 2013; Ye et al., 2015; Glorennec et al., 2017).

Smoking was associated with higher pyrethroid concentration levels in adults in Esteban. This may be explained by direct exposure of smokers to pesticide residues used during tobacco growing, or indirect exposure through the ingestion of dust contaminated by pyrethroid residues. Exposure through the latter pathway would be higher in smokers than in non-smokers, due to more frequent hand-to-mouth contact (Cai et al., 2002).

Finally, residential proximity (i.e., within 200 m) to a garden or cropland or living in a green area also seemed to have an influence on urine concentration levels of pyrethroid metabolites in both adults and children. These observations deserve further investigation; in particular using geographical indicators would make it possible to explore this link in greater detail, especially proximity to specific agricultural crops.

### 4.2.2. Organochlorine factors

The present study shows an overall increase with age of serum concentration levels of the specific organochlorines studied. For example,  $\beta$ -HCH concentration levels in adults increased by almost two hundred percent between the first and third age quartiles. This positive relationship is consistent with findings observed in the French ENNS study (Fréry et al., 2013; Saoudi et al., 2014) and in international studies (Ibarluzea et al., 2011; Brauner et al., 2012). This age effect can be explained by the long half-lives of the specific organochlorines in the human body (6–9 years for DDE and 7 years for  $\beta$ -HCH), as well as their bioaccumulation in body tissue (Genuis et al., 2016). Furthermore, older participants were more likely to have had greater exposure to the specific organochlorines before regulatory measures were introduced.

With regard to dietary exposure factors, in adults in Esteban, the biggest consumers of fish and seafood (excluding crustaceans, molluscs and shellfish), and the biggest consumers of crustaceans, molluscs and shellfish had higher levels of exposure to, respectively trans-nonachlor and oxychlordane. This result is consistent with findings in the French ENNS study (Saoudi et al., 2014) and other European and international studies focusing on general populations (Brauner et al., 2012; Arrebola et al., 2018; Gonzalez-Alzaga et al., 2018; Harmouche-Karaki et al., 2019). There is also a positive association in Esteban between egg consumption and higher concentration levels of p,p'-DDE, cis-heptachlor epoxide, oxychlordane and trans-nonachlor. These results

reflect those in international studies on different populations (students and employees at a university (Harmouche-Karaki et al., 2019), pregnant women (Cao et al., 2011), persons living in the vicinity of a chemical plant (Narduzzi et al., 2020)).

In Esteban, the consumption of vegetables (all kinds) and of fruits (all kinds) was associated with higher serum concentration levels of p,p'-DDE, trans-nonachlor and dieldrin. In the French ENNS study, fruit consumption (all types) was also associated with higher concentration levels of serum p,p'-DDE (Saoudi et al., 2014). However, it is important to point out that in Esteban, the consumption of fruits from one's own garden was associated with lower concentration levels of serum oxy-chlordane. Similarly, the consumption of meat or poultry from one's own livestock was associated with lower cis-heptachlor epoxide; the consumption of organically-farmed meat was associated with lower p,p'-DDE; and the consumption of organic food products was associated with lower  $\beta$ -HCH. Few studies to date have investigated the agricultural origin of the food consumed in terms of exposure factors to specific organochlorines (i.e., food from all origins vs. homegrown food/livestock vs. food from organic products). However, in contrast to the Esteban results, a few studies focusing on specific populations have reported higher concentration levels of specific organochlorines associated with the consumption of products from one's own crops or livestock; these associations were probably due to local soil contamination and uncontrolled homegrown food/livestock production (Stehr-Green et al., 1988; Aerts et al., 2019; Narduzzi et al., 2020).

Finally, certain geographical and household environment factors, such as living in a suburban area or having a lawn at home (despite not using pesticides on lawn), were also associated with higher concentration levels of some of the organochlorines studied in Esteban. This could be also explained by higher contamination of organochlorine compounds in soil due to past agricultural uses and the proximity of housing to agricultural sites. In France, almost one third of the national agricultural area lies within 150 m of residential buildings (Guilpart et al., 2022).

#### 4.2.3. Organophosphate factors

In adults in Esteban, the consumption of organic food products were associated with lower urine concentration levels of DMTP. The potential protective effect of organic food consumption on exposure to organophosphorus pesticides is consistent with the fact that organic farming is, by definition, an agricultural production system that does not use synthetic pesticides. Accordingly, one can logically assume that people who report they regularly consume organic food products are less likely to be exposed to pesticide residues. However, it is important to note that when taken individually, the different organic foods we studied (dairy products, eggs, poultry and other meats, fruits and vegetables, cereals or wholemeal bread), did not show significant associations with urine DMTP concentration levels. This result needs future investigation.

#### 4.2.4. Herbicide factors

The investigation of exposure factors to herbicides in Esteban focused only on factors associated with the urinary concentrations of AMPA, which was the only metabolite quantified at levels high enough to permit researching exposure factors. No exposure factors were identified for children aged 6–17 years old. However, it would appear that children who had their health examinations in winter or autumn were less exposed than those who had them in the spring. This could be related to the greater amount of time spent outdoors in spring and summer, which would lead to greater exposure to outdoor sources of AMPA metabolites (and to their parent compounds).

A positive association was observed between urinary AMPA concentration levels in adults and using an independent boiler for home heating. AMPA exposure may have been linked to the use of phosphonates (exposure not related here to pesticide use), which are commonly used for descaling boilers, and which degrade into AMPA (Studnik et al., 2015; Grandcoin et al., 2017).

#### 4.3. Comparison with health guidance values

A new approach for the derivation of health-based HBM guidance values (HBM-GV) to assess health risks was recently derived as part of the European initiative HBM4EU (Nakayama et al., 2023). The HBM-GV derived for the general population (HBM-GV<sub>GenPop</sub>) represents the concentration of a specific chemical substance or its specific metabolite (s) in human biological matrices (e.g., urine, blood, hair) at and below which, according to current knowledge, there is no risk of health impairment anticipated, and consequently no need for action (Apel et al., 2020). HBM-GV<sub>GenPop</sub> are equivalent to the HBM-I values from the German Human Biomonitoring Commission (Angerer et al., 2011). They can also be derived for particularly vulnerable population groups and/or for certain phases of life by considering differences in physiology (e.g., women of child-bearing age, children, elderly persons) (Apel et al., 2020). The proposed HBM-GVs for biomarkers of pyrethroid exposure are still provisional and must obtain final approval (Tarazona et al., 2022). HBM-GVs are constructed according to specific critical effects. Therefore, for the same metabolite common to distinct active substances, different values can be proposed depending on the toxicological reference values used in the calculations. In France, the values for all the pyrethroid metabolites measured in Esteban in the general population were overall below existing HBM-GVs<sub>GenPop</sub>, guideline threshold values, except for 3-PBA, for which approximately 1% and 10% of children were above the urine lower and upper threshold values of 22  $\mu$ g/L and 6.4  $\mu$ g/L, respectively (according to tau-fluvalinate exposure assumptions) (Table 4). Tau-fluvalinate is a synthetic pyrethroid characterized by high lipid solubility and a more specific combat spectrum, insects and mites being its main targets. It is used as a spray on a wide variety of crops, but also in beekeeping through medicated strips. Based on the French BNVD (see above), the use of tau-fluvalinate slightly increased in France between 2008 and 2018, with 35,375 kg and 42,000 kg of various analogous chemical substances sold, respectively.

#### 4.4. Strengths and limitations

The results of the Esteban study described here are based on data collected according to rigorous standardized protocols and from a large sample of participants, representative of the population of mainland France. Certain limitations inherent in Esteban's design need to be considered in our present analyses.

First, there may have been selection bias arising from the process used to select households and non-response by households and individuals. More specifically, participation trends in Esteban were similar to those in previous related studies conducted in France (Falq et al., 2011; Saoudi et al., 2014) with less participation by young adults (18–35 years old), single adults, men and unemployed persons, and more participation by individuals with a high-school diploma and above, persons in a relationship, employed people, individuals close nearing retirement age, and those already retired. However, considering the weighting process used, it is reasonable to suppose that the potential impact of any selection bias was limited. This is why we consider the study population to be representative of the French population living in mainland France during 2014–2016.

Second, collecting a first voided urine specimen raises the question of the measurement variability of the chemical substances (Morgan et al., 2016). However, considering that the majority of pesticides included in the present study have short half-lives, ranging from a few hours to a few days (except for organochlorine compounds, with half-lives in years), the biomarker concentration levels measured reflected more recent and/or occasional exposure to parent compounds.

Third, the associations we highlighted should be interpreted with caution as cross-sectional studies alone do not allow causal links between the sources of exposure identified and the pesticide exposure levels, especially for exposure biomarkers with relatively short half-lives. In addition, due to the short half-lives of most pesticide

**Table 4**

Existing health-based HBM guidance values (HBM-GVs) in children and adults for the pyrethroid biomarkers measured in the Esteban study, 2014–2016.

| Pyrethroid metabolite                | Active Substance | Population | Percentile and maximum values in Esteban ( $\mu\text{g}$ Metabolite/L Urine) |       |       |       |      |      | Proposed HBM-GV <sub>GenPop</sub> <sup>a</sup> ( $\mu\text{g}$ Metabolite/L Urine) |
|--------------------------------------|------------------|------------|--|-------|-------|-------|------|------|--|
|                                      |                  |            | P50  | P75   | P90   | P95   | P99  | Max  |  |
| 3-PBA                                | Tau-fluvalinate  | Children   | 1.03   | 1.97  | 4.28  | 7.30  | 26.1 | 61.2 | 6.4–22 <sup>b</sup>  |
|                                      |                  | Adults     | 0.72   | 1.28  | 2.42  | 3.23  | 8.34 | 44.5 | 9.6–33 <sup>b</sup>  |
| 4-F-3-PBA (or F-PBA)                 | Cyfluthrin       | Children   | < LOQ  | 0.023 | 0.048 | 0.085 | 0.35 | 1.30 | 80   |
|                                      |                  | Adults     | < LOQ  | 0.018 | 0.037 | 0.068 | 0.18 | 1.83 | 130  |
| BR2CA (or DBCA)                      | Deltamethrin     | Children   | 1.16   | 2.41  | 4.47  | 5.70  | 12.5 | 22.8 | 90   |
|                                      |                  | Adults     | 0.69   | 1.30  | 2.89  | 4.43  | 8.08 | 25.8 | 130  |
| $\Sigma$ cis - trans Cl2CA (or DCCA) | Cypermethrin     | Children   | 0.50   | 0.97  | 1.97  | 3.03  | 11.2 | 17.9 | 30   |
|                                      |                  | Adults     | 0.42   | 0.83  | 1.84  | 2.99  | 8.82 | 14.9 | 45   |
| $\Sigma$ cis - trans Cl2CA (or DCCA) | Permethrin       | Children   | 0.50   | 0.97  | 1.97  | 3.03  | 11.2 | 17.9 | 320  |
|                                      |                  | Adults     | 0.42   | 0.83  | 1.84  | 2.99  | 8.82 | 14.9 | 480  |

<sup>a</sup> Reference: Tarazona et al. (2022).<sup>b</sup> Values based on the acceptable daily intake (ADI) of 0.005 mg/kg bw grounded on generic toxicity for the most conservative scenario and the most realistic scenario, respectively.

biomarkers of interest studied, the absence of any association between a potential source of exposure and the measured biomarker concentrations does not mean that this potential source of exposure must be totally excluded. Similarly, other potential exposure factors, in particular environmental factors, could not be analysed very accurately in the present study. For this, more adapted and targeted ad-hoc studies would be necessary. Furthermore, some differences in the comparisons of pesticide concentration levels observed between Esteban and international studies could also be explained by some methodological and temporal differences between the studies. Moreover, our study did not allow us to examine exposure to multiple chemicals among Esteban's participants; this would have provided a more accurate characterization of multi-chemical burden in the general population, as demonstrated elsewhere (Pecheux et al., 2022). Having said that, one of the advantages of the substance-by-substance approach used in our analyses is that it helped to identify exposure factors to a single chemical regardless of simultaneous exposure to other substances. It was not possible to identify occupational exposure to pesticides from agricultural factors based on the present study, because the number of agricultural workers in Esteban was too small. For this, future studies with a more appropriate design would be required.

Finally, given the absence of an internal toxicological reference value for many of the pesticide biomarkers we studied, the biological levels measured in urine and serum samples in Esteban do not necessarily reflect a health risk.

## 5. Conclusions

Esteban is the first HBM study in France to describe exposure to five families of pesticides in the general French population (adults and children) in 2014–2016. This article describes the levels of exposure to certain pesticides already studied only in adults in the French national HBM survey ENNS conducted a decade before Esteban. It also presents for the first time data on a new selection of pesticide families, including carbamates and herbicides. We found that pesticide exposure levels in France varied by chemical substance and chemical family, and by age category. French adults and children were still widely exposed to pyrethroid compounds because organochlorine pesticides had been replaced first by organophosphorus pesticides, and then by pyrethroids (broad-spectrum insecticides, which are still used today against a wide variety of pests). Concentration levels for pesticide compounds were globally lower than those from the French ENNS survey, with the exception of the deltamethrin metabolite Br2CA. However, a significant proportion of the population was still exposed to prohibited chemicals like lindane, with quantifiable concentrations in almost half of the adults and children. In addition, depending on the calculation assumptions, one to ten out of one hundred children in France could have urinary 3-

BPA concentrations above the recent health-based HBM guidance values derived for the general population (HBM-GV<sub>GenPop</sub>). We found that concentration levels of pesticide compounds in France were similar to those from studies elsewhere in Europe and in North America, with the exception of  $\beta$ -HCH, DMTP metabolite, and Br2CA, whose levels were higher in France. Esteban enabled us to identify some factors of pesticide exposure, which can be acted on to improve public health. This is the case for the use of antiparasitics on domestic animals, which was associated with higher exposure to pyrethroids in adults and children. Our results also showed that regular consumption of products from organic farming was associated with lower concentration levels of pesticide exposure, in particular for pyrethroid metabolites and specific organochlorine compounds. The further of the national HBM programme in France should confirm the current downward trends in exposure levels to organophosphate, organochlorine and pyrethroid pesticides observed in Esteban, and provide initial data on exposure trends for carbamates, cyclodienes, and herbicides, including glyphosate and its metabolite AMPA. Future surveys will also enable us to broaden the list of pesticide molecules to be measured, as those measured in Esteban represent only a tiny fraction of the pesticides which the French population is exposed to.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that may have influenced the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ijheh.2023.114265>.

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