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Exposure of the French population to bisphenols, phthalates, parabens, glycol ethers, brominated flame retardants, and perfluorinated compounds in 2014–2016: Results from the Esteban study

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ABSTRACT

Background: As part of the French Human Biomonitoring (HBM) programme, the Esteban study described, among other things, biomarkers levels of various chemicals in adults (18–74 years old) and children (6–17 years old). This paper describes the design of the study and provides, for the first time, data on the biological exposure of the general French population to a wide range of contaminants posing a threat to human health which are currently found in domestic environments.

Methods: Esteban is a cross-sectional study conducted on a nationwide sample of the French general population. Exposure biomarkers of six families of contaminants deemed detrimental to adults' and children's health were measured in biological samples collected either at participants' homes by a nurse, or brought to a National Health Insurance examination centre. All participants were randomly selected (2503 adults and 1104 children). The geometric mean and percentiles of the distribution of levels were estimated for each biomarker. Most of the descriptive statistical analyses were performed taking into account the sampling design.

Results: Results provided a nationwide description of biomarker levels. Bisphenols (A, S and F), and some metabolites of phthalates and perfluorinated compounds (PFCs) (specifically, PFOS and PFOA) were quantified in almost all the biological samples analysed. Higher levels were observed in children (except for PFCs). Levels were coherent with international studies, except for bisphenols S and F, brominated flame retardants (BFRs) and parabens (with higher levels reported in the USA than in France).

Conclusion and perspectives: This study is the first to provide a representative assessment of biological exposure to domestic contaminants at the French population level. Our results show that the French general population was exposed to a wide variety of pollutants in 2014–2016, and identify the determinants of exposure. These findings will be useful to stakeholders who wish to advocate an overall reduction in the French population's exposure to harmful substances. Similar future studies in France will help to measure temporal trends, and enable public policies focused on the reduction of those chemicals in the environment to be evaluated.

1. Introduction

In order to constantly develop national biomonitoring programmes, countries in Europe and in North America have implemented several studies over many years (e.g., GerES (Becker et al., 2009), Flehs (Reynders et al., 2017) Nhanes (Calafat, 2012), and CHMS (Haines et al., 2017)). As part of the European Environment & Health Action Plan 2004–2010, the process of harmonizing biomonitoring practices between the European Union member countries began with the Cophes project (Consortium to Perform Human Biomonitoring on a European

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Scale). This work continues today with the HBM4EU project (European Human Biomonitoring Initiative) as part of the European H2020 programme. In the French context, the law resulting from the country's first environment summit (*Grenelle I de l'environnement* (law n ° 2009-967 of August 3, 2009)) led to the development of a national biomonitoring programme designed to estimate the exposure of the general population to various environmental substances. The programme had two components: the first was the implementation of a cross-sectional study in the general population of mainland France, named Esteban (measuring health, environment, biomonitoring, physical activity and nutrition indicators), which was implemented in 2014–2016. As well as monitoring exposure to chemical substances, Esteban included chronic disease and nutritional surveillance dimensions. The second component used perinatal data from a subsample of participants in the previously implemented (2011) Elfe cohort study (Dereumeaux et al., 2016; Dereumeaux et al., 2017).

Human biomonitoring (HBM) is one approach for monitoring human exposure to chemical substances. It involves the analytical measurement of biomarkers (e.g., environmental chemicals or their metabolites) in easily obtainable human biological fluids and tissues (e.g., urine, blood, hair) (Angerer et al., 2006). As HBM represents a comprehensive measure of exposure from all sources and routes of uptake, it enables investigators to estimate exposure when certain sources are unknown or are ambiguous (Wittassek et al., 2011). This is particularly true for chemicals present in food and those used in a variety of everyday products (including food packaging) which are responsible for widespread human exposure. This article presents the first results of the biomonitoring component of the Esteban study for six families of chemical substances present in everyday objects in the French general population's daily environment (e.g., cosmetics, varnishes, paints, solvents, textiles, stove adhesive coatings, plastic toys). These six families include three bisphenols (A, F and S), phthalates, parabens, glycol ethers, brominated flame retardants (BFRs), and perfluorinated compounds (PFCs), all of which are toxic to humans (in particular carcinogenic or endocrine disruptor effects) (Birnbaum and Staskal, 2004; Lau et al., 2007; Ye et al., 2006; Chen et al., 2002; Manikkam et al., 2013; Chevalier and Fenichel, 2015).

2. Material and methods

2.1. Study design

Esteban is a cross-sectional study of the general population living in mainland France during the period 2014–2016 aged between 6 and 74 years old. In total, 2503 adults (18–74 years old) and 1104 children (6–17 years-old) were included during four different periods between April 2014 and March 2016, in order to take seasonal differences into account.

Approval for the study was obtained from the French data protection authority and a bioethics committee.

2.2. Recruitment of participants

Randomly selected households first received an information letter about the study. In the subsequent days, these households were contacted by telephone in order to seek their agreement to participate and to select one eligible individual (adult or child) living in the household for the study. A few days later, a field interviewer visited households that had agreed to participate to explain what the study would involve, collect the eligible person's written informed consent, and distribute a self-administered questionnaire. Esteban collected data on health, nutrition, exposure to chemicals, and socio-demographic characteristics with the aid of two interview-guided questionnaires, four self-administered questionnaires, a 24 h dietary recall, and analysis of fasting biological samples (blood, urine and hair). The latter were collected at a dedicated health examination centre, or at home by a nurse for those who preferred not to go to a centre. Full details of the recruitment process for Esteban can be found elsewhere (Balicco et al., 2017).

2.3. Sampling frame

Three-stage cluster sampling was used in Esteban. In the first stage, a stratified sample of primary units (municipality or groups of municipalities) was randomly drawn. In the second stage, households were randomly selected in each primary unit using random generation of landline and cell phone numbers. In the third stage, only one individual (adult or child) was randomly selected from among eligible household members using the Kish method to participate in the study (Kish, 1949). Two samples - one for participating adults and one for participating children - were collected separately. Stratification was performed according to two variables: the region (8 geographical areas) and the degree of urbanization (5°: rural, <20 000 inhabitants, 20 000–100 000 inhabitants,greater than 100 000 inhabitants, Paris and its suburbs). The sampling frame of the Esteban study is described in detail elsewhere (Balicco et al., 2017).

For the analysis of chemical biomarker levels, two subsamples (one for adults and one for children) were randomly drawn from all those who had available laboratory data for the spot urine sample they provided. Biomarkers for six families of chemicals were analysed: parabens (N = 998), perfluorinated compounds (N = 993), phthalates (N = 1397), glycol ethers (N = 700), bisphenols (N = 1400) and brominated flame retardants (N = 985).

For each participant subsample, initial statistical weights were calculated. These weights were calibrated using CALMAR software (Deville, 1993) in order to take into account socio-demographic characteristics of the reference population, specifically the general French population aged between 6 and 74 years old. Calibration margins for the adult subsample were age, gender, educational level, not living with a partner, having a child under 18 years old in the household, and study inclusion period. For the child subsample, the calibration margins were age, gender, educational level of the head of the household, head of the household not living with a partner, and study inclusion period.

2.4. Biological sample collection

Biological samples were collected at participants' homes by a nurse or were brought by the participant to a National Health Insurance examination centre. More specifically, participants collected a first morning urine sample at home (150 mL for children and 200 mL for adults) in a polypropylene container and either gave it to a nurse who visited them or brought it themselves to a centre. Fasting blood was collected by venous catheter: 26 mL for children aged 6 to 11 years old, 36 mL for children aged 12 to 17 years old, and 88 mL for adults. After centrifugation, urine and serum samples were then aliquoted in 10 mL, 5 mL, 3 mL and 1.2 mL polypropylene cryotubes, according to the analyses to be made. Biological samples were sent to a biobank, for long-term conservation at − 80 °C.

2.5. Biomarker measurements

The process of prioritizing biomarkers for the French national HBM programme (i.e., Esteban and the perinatal component which used data from the Elfe cohort) is described elsewhere (Fillol et al., 2014). Briefly, biomarkers were first selected depending on their biomonitoring feasibility, exposure relevance, existing regulations for the chemicals being studied, and priorities in terms of health effects. The Delphi consensus method was then used to prioritize these biomarkers according to criteria based on (i) the scientific contribution these analysis would bring in terms of new knowledge in France, (ii) the feasibility of preventing exposure (iii) the logistic and analytical feasibility of measuring the biomarkers, (iv) the interpretation of results, (v) the biomarkers'

characteristics (i.e. specificity, intra-individual variability, etc.), (vi) the public perception of the substances being measured, (vii) exposure characteristics (i.e., origin of the contamination), and (viii) hazard identification for each substance evaluated. The positioning of some groups of biomarkers in the prioritized list was debated in discussions during an expert meeting which ended in the production of a consensual, prioritized list of biomarkers to be included in the national biomonitoring programme.

The analyses of bisphenols, PFCs and BFRs were performed by Laberca/Oniris, Nantes, France. All procedures were written according to ISO-17025 quality assurance guidelines. The PFC quantification method was subsequently ISO-17025 accredited.

More specifically, urinary concentrations of bisphenols (free and total) were quantified using gas chromatography with tandem mass spectrometry (GC–MS/MS). Total bisphenol analysis required enzymatic hydrolysis with overnight incubation at 50 °C in an oven. For each sample, solid-phase extraction (SPE) with molecular imprinted polymer (MIP) columns was first performed, followed by MSTFA (N-methyl-N-trimethylsilyl-trifluoroacetamide) derivatization in order to allow detection and identification by GC–MS/MS (ionization by electronic impact (EI) and detection by Selected Reaction Monitoring (SRM)) (Deceuninck et al., 2015).

Serum concentrations of PFCs were quantified using liquid chromatography with tandem mass spectrometry (LC-MS/MS). The analysis required extraction with a methanolic solution of 0.1 M potassium hydroxide followed by SPE purification with Oasis HLB and Envi Carb cartridges (Kadar et al., 2011; Kadar et al., 2011).

With regard to serum concentrations of BFRs, polybrominated diphenyl ethers (PBDE) and polybrominated biphenyl (PBB) were quantified using gas chromatography with high resolution mass spectrometry (GC-HR/MS), while LC-MS/MS was used for hexabromocyclododecane (HBCD). Analyses required contact with formic acid for 20 min. SPE using a C18 column was used for each sample, before purification with an acid silica gel cartridge (Cariou et al., 2005; Debrauwer et al., 2005).

Analyses of glycol ethers were performed by Labocea, Ploufragan, France. Urinary concentrations were quantified using GC–MS/MS in Multiple Reaction Monitoring (MRM) mode. The procedure included the addition of a TBHAS buffer solution (hydrogenated tetrabutylammonium sulfate), acetone and then derivatization with pentafluorobenzyl bromide after extraction in dichloromethane (Labat et al., 2008).

Analyses of parabens were performed by Labeo, Saint-Contest, France. Urinary concentrations were quantified using LC-MS/MS. The procedure required enzymatic hydrolysis of the urine with glucuronidase (HP-2 type). After incubation, the extracts were centrifuged, purified with methanol and then centrifuged again. Supernatants were diluted before analysis (Moos et al., 2015).

Analyses of phthalates were performed by the Centre de Toxicologie du Québec (CTQ), Institut National de Santé Publique du Québec (INSPQ) (Québec, Canada). Urinary concentrations were quantified using ultra-high-performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS). The procedure involved enzymatic deconjugation followed by liquid–liquid extraction at pH = 3 with hexane/ethyl acetate (50:50). The extracts were dried and resuspended in an acetonitrile/water mixture (25:75) before the chromatographic analysis. The analytical method was described in detail in the framework of the Canadian Health Measures Survey (CHMS) (Canada Health, 2019).

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

The LOD of analytical methods 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 LOQ by performing repeated measurements (n = 10) in the assay matrix (serum, urine, etc.). 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.

The analyses of creatinine were performed by Chemtox, France using the kinetic Jaffe method (Moss et al., 1975).

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 concentration (TL) was calculated using the following formula: $TL = 1.677 * (TC - FC) + FC + TG + PL$ (all expressed in g/L), where TC is the total cholesterol, FC is free cholesterol, TG is triglycerides and PL is phospholipids (Akins et al., 1989).

The calibration curve was performed using 5 to 8 concentration points depending on the family of biomarker analysed and was verified every 100 samples. Likewise, the point on the calibration closest to LOQ was checked every 20 samples. Laboratory blanks were introduced into each batch of samples (every 10 samples) to guarantee non-contamination of the analytical procedure. Internal quality controls (IQC) were measured during the analytical series on several concentration levels to establish control charts and meet the Westgard criteria. Calculations of intermediate fidelity and uncertainty (k = 2) were performed for several concentration levels (near LOQ, medium and high) and were approximately 20% for parabens. The bias and coefficient of variation associated with intermediate fidelity were <30% depending on the concentration levels for bisphenols. Intermediate precision was approximately 20% for all BFR compounds, while increased uncertainty was approximately 50% at low concentrations.

In order to assess the intermediate precision of the analyses, six pairs of replicates were introduced blindly into the analytical series, but not for all biomarkers. In other words, two cryotubes belonging to the same subject with different identifiers were analysed. These six pairs of replicates were analysed, with concordant results for all 17 perfluorinated compounds, for all phthalates, for bisphenols and for BFRs analysed.

Six (five for one biomarker due to a broken cryotube) control samples consisting of ultra-pure water conditioned in a glass ampoule were sent to the laboratories to be assayed under the same conditions as the study samples. None of the control samples had a phthalate, bisphenol or BFR concentration at a quantifiable level, thereby indicating the absence of any contamination due to the sample preparation environment or due to the sample collection and cryopreservation equipment.

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.

As suggested by Barr et al. (2005), we adjusted the urinary biomarker concentrations to account for urine by including creatinine in the results. We also adjusted the serum results of the BFRs to take account of their lipophilic nature by including the serum lipids.

2.6. Statistical analysis

Different descriptive statistical analyses were performed taking into account the sampling design (except for BFRs, glycol ethers, phthalates and parabens for the child subsample as the number of biological samples was too small). The geometric mean, median, and 10th, 25th, 75th and 95th percentiles were estimated for each biomarker.

Left-censored values of biomarkers concentrations (i.e., chemical levels below the LOQ) and other missing values for variables were imputed using multiple imputation by chained equations with Stata (Royston, 2014).

When the proportion of values below the LOQ was greater than 40%, geometric means were not estimated. Moreover, when the LOQ or LOD was above a given percentile estimate, that percentile was not reported in the tables and was denoted as < LOQ or < LOD, respectively.

Table 1
Analytical performances of biomarker measurements analysed in the Esteban study (2014–2016).

Parent compound	Biomarkers	Biological matrix	Volume needed (mL)	Analytical method	LOD (μg L^{-1})	LOQ (μg L^{-1})
Bisphenol A (BP A)	BP A total	Urine	10[a]	GC–MS/MS	0.01	0.09
	BP A free	Urine		GC–MS/MS	0.01	0.09
Bisphenol S (BP S)	BP S total	Urine		GC–MS/MS	0.003	0.006
	BP S free	Urine		GC–MS/MS	0.003	0.006
Bisphenol F (BP F)	BP F total	Urine		GC–MS/MS	0.01	0.02
	BP F free	Urine		GC–MS/MS	0.01	0.03
Di-n-butyl phthalate (DnBP)	Mono-n-butyl phthalate (MnBP)	Urine	2[b]	UPLC-MS/MS	0.40	1.30
Di-*iso*-butyl phthalate (DiBP)	Mono-isobutyl phthalate (MiBP)	Urine		UPLC-MS/MS	0.10	0.44
Di-methyl phthalate (DMP)	Mono-methyl phthalate (MMP)	Urine		UPLC-MS/MS	0.20	0.53
Di-ethyl phthalate (DEP)	Mono-ethyl phthalate (MEP)	Urine		UPLC-MS/MS	1.00	3.30
Butyl-benzyl phthalate (BBzP)	Mono-benzyl phthalate (MBzP)	Urine		UPLC-MS/MS	0.40	1.20
Di-cyclohexyl phthalate (DCHP)	Mono-cyclohexyl phthalate (MCHP)	Urine		UPLC-MS/MS	0.30	0.83
Di-n-octyl phthalate (DnOP)	Mono-n-octyl phthalate (MnOP)	Urine		UPLC-MS/MS	0.20	0.51
Di-n-octyl phthalate (DnOP)	Mono-3-carboxypropyl phthalate (MCPP)	Urine		UPLC-MS/MS	0.10	0.41
Di-isononyl phthalate (DiNP)	Mono-isononyl phthalate (MiNP)	Urine		UPLC-MS/MS	0.40	1.20
Di (2-ethylhexyl) phthalate (DEHP)	Mono-2-ethylhexyl phthalate (MEHP)	Urine		UPLC-MS/MS	0.1	0.36
Di (2-ethylhexyl) phthalate (DEHP)	Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	Urine		UPLC-MS/MS	0.09	0.29
Di (2-ethylhexyl) phthalate (DEHP)	Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	Urine		UPLC-MS/MS	0.20	0.63
2-methoxyethanol (EGME); 1,2 – dimethoxyethane (EGDME); ((2-methoxyethoxy) ethanol) (DEGME); Bis (2-methoxyethyl) ether (DEGDME); 2- (2- (2 – methoxyethoxy) ethoxy) ethanol (TEGME); 1,2-bis (2 methoxyethoxy) ethane (TEGDME)	Methoxyacetic acid (MAA)	Urine	2[c]	GC–MS/MS	3	10
2-ethoxyethanol (EGEE); 1,2-diethoxyethane (EGDEE); 2-(2-ethoxyethoxy) ethanol (DEGEE); diethylene glycol diethyl ether (DEGDEE); triethylene glycol ethyl ether (TEGEE)	Ethoxyacetic acid (EAA)	Urine		GC–MS/MS	3	10
2-butoxyethanol (EGBE); (2-(2-butoxyethoxy) ethanol (DEGBE); 2-(2-(2 -Butoxyethoxy)ethoxy)ethanol (TEGBE)	Butoxyacetic acid (BAA)	Urine		GC–MS/MS	3	10
ethylene glycol phenyl ether (EGPhE)	Phenoxyacetic acid (PhAA)	Urine		GC–MS/MS	3	10
ethylene glycol n-propyl ether (EGnPE)	Propoxyacetic acid (PAA)	Urine		GC–MS/MS	3	10
2-methoxy-1-propanol (1PG2ME)	Methoxyproprionic acid (2-MPA)	Urine		GC–MS/MS	3	10
DEGME, TEGME	Methoxyethoxyacetic acid (MEAA)	Urine		GC–MS/MS	3	10
DEGEE	Ethoxy-ethoxyacetic acid (EEAA)	Urine		GC–MS/MS	3	10
Methyl-paraben	Methyl-paraben	Urine	5[c]	LC-MS/MS	0.2	0.5
Ethyl-paraben	Ethyl-paraben	Urine		LC-MS/MS	0.2	0.5
Isopropyl-paraben	Isopropyl-paraben	Urine		LC-MS/MS	0.2	0.5
Propyl-paraben	Propyl-paraben	Urine		LC-MS/MS	0.2	0.5
Isobutyl-paraben	Isobutyl-paraben	Urine		LC-MS/MS	0.2	0.5
Butyl-paraben	Butyl-paraben	Urine		LC-MS/MS	0.2	0.5
Benzyl-paraben	Benzyl-paraben	Urine		LC-MS/MS	0.2	0.5
Pentyl-paraben	Pentyl-paraben	Urine		LC-MS/MS	0.2	0.5
Heptyl-paraben	Heptyl-paraben	Urine		LC-MS/MS	0.2	0.5
Polybromodiphenylethers (PBDE)	PBDE	Serum	7[e]	GC-HRMS	0.00007–0.0006	0.00021–0.018
Deca-bomodiphenylether 209 (Deca-BDE 209)	Deca-BDE 209	Serum		GC-HRMS	0.0015	0.0045
Polybrominated biphenyl (PBB)	PBB-153	Serum		GC-HRMS	0.002	0.006
Hexabromocyclododecane (HBCD)	(α, β, γ) HBCD	Serum		LC-MS/MS	0.001	0.003
Perfluorobutanoïc acid (PFBA)	PFBA	Serum	2	LC-MS/MS	0.2	0.5
Perfluoropentanoïc acid (PFPA)	PFPA	Serum		LC-MS/MS	0.02	0.05
Perfluorohexanoïc acid (PFHxA)	PFHxA	Serum		LC-MS/MS	0.05	0.20
Perfluoroheptanoïc acid (PFHpA)	PFHpA	Serum		LC-MS/MS	0.05	0.20
Perfluorooctanoïc acid (PFOA)	PFOA	Serum		LC-MS/MS	0.02	0.05
Perfluorononanoïc acid (PFNA)	PFNA	Serum		LC-MS/MS	0.05	0.20
Perfluorodecanoïc acid (PFDA)	PFDA	Serum		LC-MS/MS	0.05	0.20
Perfluoroundecanoïc acid (PFUnA)	PFUnA	Serum		LC-MS/MS	0.02	0.05

(*continued on next page*)

Table 1 (*continued*)

Parent compound	Biomarkers	Biological matrix	Volume needed (mL)	Analytical method	LOD (μg L^{-1})	LOQ (μg L^{-1})
Perfluorododecanoïc acid (PFDoA)	PFDoA	Serum		LC-MS/MS	0.02	0.05
Perfluorobutanesulfonate of sodium (PFBS)	PFBS	Serum		LC-MS/MS	0.05	0.19
Perfluorohexanesulfonate of sodium (PFHxS)	PFHxS	Serum		LC-MS/MS	0.05	0.19
Perfluoroheptanesulfonate of sodium (PFHpS)	PFHpS	Serum		LC-MS/MS	0.05	0.19
Perfluorooctanesulfonate of sodium (PFOS)	PFOS	Serum		LC-MS/MS	0.03	0.10
Pefluorodecanesulfonate of sodium (PFDS)	PFDS	Serum		LC-MS/MS	0.05	0.19
n-ethylperfluoro-1-octanesulfonamide	n-Et-PFOSA-AcOH	Serum		LC-MS/MS	0.02	0.05
n-methylperfluoro-1-octanesulfonamide	n-Me-PFOSA-ACOH	Serum		LC-MS/MS	0.02	0.05
Perfluoro-1-octanesulfonamide	PFOSA	Serum		LC-MS/MS	0.05	0.20

Volume needed for the analysis of: [a]all bisphenols in urine; [b]all phthalates' metabolites; [c]all glycol ethers; [d]all parabens; [e]BFRs; [f]PFCs.

Determinants were not analysed for BFRs, PFCs, parabens or glycol ethers in the child subsample due to the small number of samples.

Determinants of biomarker concentrations were identified using multivariate regression analysis for samples of bisphenols and phthalates in children and all biomarkers in adults. A Generalized linear Model was used. Concentrations were log-transformed in order to improve the normality of the model residuals. Certain determinants (e.g., the use of cream or body care products for parabens or canned foods for bisphenols) were included in the model *a priori* after researching the literature on this subject. In addition, other determinants 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 determinant factors, a natural cubic spline function was fitted.

The determinants considered were: tobacco consumption, wine consumption, use of cosmetics or makeup products, use of cream or body-care products, use of nail polish, use of nail polish remover, vinyl flooring, time spent in one's own car, presence of controlled mechanical ventilation (CMV) system at home, home ventilation frequency, recent exposure to household products or DIY products, and certain dietary factors (the consumption of fish and seafood, cheese, meat and poultry, vegetables, consumption of home-grown eggs, canned foods, prepared or pre-packaged meals, etc.).

Confounding variables were: age and sex of participants, body mass index (BMI), number of children in the household, educational level and urinary creatinine.

The statistical analysis was conducted using Stata software (ICE module for data imputation) and R software (package 'survey' to take into account the sample design) (StataCorp, 2015; Team, 2017).

2.7. Reference values of exposure (RVs)

Reference values of exposure (RVs) are statistical values which give an order of magnitude of the concentration to which the population is exposed. According to Ewers et al. (1999), RVs focus only on the level of exposure of a population to a chemical substance, through a biomarker, and do not provide any criteria for identifying health risks. Accordingly, RVs must not be considered as health-related values.

The strategy used to derive RVs from Esteban biomarker data was inspired by that defined in the ongoing HBM4EU project, whereby RVs are derived from the 95th percentile of the exposure level distribution and its 95% confidence interval. The 95th percentile was chosen to ensure greater comparability between RVs derived from international human biomonitoring studies, and particularly future RVs derived in various European contexts.

More specifically, a 95th percentile estimate and its 95% CI were first derived for each biomarker exposure level distribution from the two samples populations (for both the adult and children subsamples). Then, 95th percentile estimates and 95% CI were derived according to sex, and to the number of specific age groups obtained. This operation was performed only if the sample size of each subsample was above 120 individuals. When 95th percentiles for two separate subsamples were significantly different (i.e., when both 95% CI did not overlap with each other) we chose to derive two separate RVs for each subsample. Otherwise, only one RV was derived for the total sample population.

To define an RV, we rounded the 95th percentile downward to the lowest value within the 95% CI retaining at least two significant figures depending on the scale and on the precision of the analytical method used. In a small number of cases, some RVs were rounded upward to a value above the 95th percentile, in order to make the latter more readable. We did not define an RV when the lower bound of the 95% CI of the 95th percentile was below the LOQ.

3. Results

3.1. Study population

Table 2 shows the main weighted characteristics for the French reference population and for the each population subsamples of the Esteban study – 2503 adults and 1104 children - before the calibration procedure for statistical weights was performed. For the adult subsample, we can observe differences between the study population and the reference population: participation was lower among young adults aged 18–29 years old (9.8% *versus* 20.7%, respectively), single people (26.1% *versus* 34.7%), men (45.6% *versus* 48.7%), and unemployed persons (3.8% *versus* 7.5%). Participation was higher among those with a Master's or Doctorate degree (26.2% *versus* 15.3%), those who were not single (i.e. married, civil union, etc.) (73.9% *versus* 65.3%), employed individuals (65.0% *versus* 63.6%), and pre-retirement and retired people (27.5% *versus* 22.5%). The same trends were observed in the child subsample for data collected about the head of the household.

3.2. Biomonitoring results

Tables 3 and 4 displays biomarker levels for, respectively, the overall population of adults and children living in France in 2014–2106, while Table 5 shows levels of biomarkers for Esteban's child subsample when the number of samples was too low to perform statistical weighting.

Bisphenols A, S and F were detected in almost all of the biological samples. The concentrations of bisphenols A were higher than those of bisphenols S and F.

Most phthalate metabolites studied were quantified in 80 to 99% of samples from adults and children, except for MiNP (<20%), MCHP and MnOP (<1%). The highest concentrations were measured for MEP (51.2 and 71.4 μg/g creatinine in children and adults, respectively), MiBP (47.1 and 38.8 μg/g creatinine, respectively) and the sum of the metabolites of DEHP (27.7 and 22.2 μg/g creatinine, respectively).

With regard to glycol ethers, the results show that the entire population (adults and children) was exposed to at least one of the 8 metabolites analysed. PhAA and MAA were the two most quantified metabolites, and the two with the highest average concentrations.

In order of importance, the (very few) parabens quantified in the

Table 2
Main characteristics of adults and children selected in the Esteban study (2014–2016).

Factors	Sample size	Percentage in the study population (initial weight adjustment)*	Percentage in the target population**
Adults			
Gender			
Male	1141	45.6%	48.7%
Female	1362	54.4%	51.3%
Age – Classes			
18 to 29 years	245	9.8%	20.7%
30 to 44 years	643	25.7%	28.7%
45 to 59 years	916	36.6%	29.3%
60 to 74 years	699	27.9%	21.4%
Single			
Yes	653	26.1%	34.7%
No	1850	73.9%	65.3%
Having children under 18 years old at home			
Yes	871	34.8%	32.0%
No	1632	65.2%	68.0%
Educational level			
No school diploma *or* vocational educational certificate or elementary school certificate	758	30.3%	50.9%
High-school diploma	476	19.0%	19.7%
Bachelor's degree	613	24.5%	14.1%
Master's or Doctorate degree	656	26.2%	15.3%
Occupational situation (head of household)			
Employed	1627	65.0%	63.6%
Unemployed	95	3.8%	7.5%
Student, student in training, unpaid internship	28	1.1%	2.2%
Retired, pre-retired	688	27.5%	22.5%
Housewife or husbehusband	18	0.7%	0.8%
Other inactive category (pensioner, disabled person, etc.)	43	1.7%	3.4%
Children			
Gender			
Boy	572	51.8%	51.1%
Girl	532	48.2%	48.9%
Age – Classes			
6 to 10 years	520	47.1%	42.2%
11 to 14 years	389	35.2%	33.5%
15 to 17 years	195	17.7%	24.4%
Single			
Yes	151	13.7%	22.5%
No	953	86.3%	77.5%
Education level			
No school diploma or vocational educational certificate or elementary school certificate	308	27.9%	52.4%
Bachelor	177	16.0%	17.3%
1st cycle university degree	301	27.3%	14.1%
2nd or 3rd cycle university degree	318	28.8%	16.3%
Occupational situation (head of household)			
Employed	1001	90.7%	84.8%
Unemployed	45	4.1%	8.6%
Student, student in training, unpaid internship	16	1.4%	0.2%
Retired, pre-retired	11	1.0%	2.4%
Housewife or house-husband	19	1.7%	1.3%
Other inactive (pension, disabled, etc.)	12	1.1%	2.7%

* Use of initial weights before the calibration procedure for statistical weights was performed.
** Population Census (data source: The National Institute of Statistics and Economic Studies (INSEE) in 2012).

Esteban study samples were: methyl-paraben, propyl-paraben and ethyl-paraben. Only methyl paraben was quantified in more than 90% of adults and children.

The quantification rates of the measured BFRs varied according to the congeners. The majority were rarely or never quantified. With regard to PBDE congeners, the most quantified, in order of importance, were BDE 153 followed by BDE 47, BDE 100, Deca-BDE 209 or BDE 99.

Esteban estimated the exposure to 17 PFCs present in the environment using serum concentrations. The quantification rates varied according to the PFC: 7 and 6 were quantified in more than 40% of adults and children, respectively. PFOA and PFOS, the biggest contributors to PFC concentrations, were quantified in all the adults' and children's biological samples.

Generally, the levels of contaminants found in children were higher than those measured in adults, except for PFCs.

3.3. Determinants

The main determinants influencing biomarker concentrations for the six families of pollutants studied varied according to the biomarker. No determinant was found for BP A. On the contrary, BP S and BP F concentrations increased with the consumption of canned foods, prepared or pre-packaged meals (for example, BP S concentrations were 45.9% [CI 95%: 10.1; 93.3] higher in adults consuming pre-packaged foods than in those who did not).

For children aged 6–17 years, the frequent use of cosmetics or hair products was a determinant of exposure for phthalates concentrations (DEHP metabolite concentrations were 32.9% [6,0; 66,6] and 36.5% [13,1; 64,8] higher in children who used cosmetics and hair products, respectively, than in those who did not). MMP concentrations were 33.2% [1.1; 75.7] higher in children with less frequent home ventilation

Table 3
Description of urinary concentrations of bisphenols, phthalates, glycol ethers and parabens and serum concentrations of BFRs and PFCs in the population of adults living in France, Esteban (2014–2016) (weighted results).

Biomarkers		n	%>LOQ	GM (95%CI)	P25	P50	P75	P95 (95% CI)
Bisphenols (µg/g creatinine)	BP A total	900	100	2.69 (2.49 ; 2.92)	1.56	2.45	4.49	11.49 (9.81 ; 13.26)
	BP A free	900	27.6	NC	<LOQ	<LOQ	0.15	0.49 (0.38 ; 0.64)
	BP S total	900	100	0.53 (0.46 ; 0.61)	0.19	0.42	1.11	8.49 (5.78 ; 11.22)
	BP S free	900	56.2	0.02 (0.02 ; 0.02)	<LOQ	0.02	0.04	0.24 (0.15 ; 0.33)
	BP F total	900	100	0.31 (0.29 ; 0.34)	0.17	0.28	0.54	1.42 (1.22 ; 1.65)
	BP F free	900	15.6	NC	<LOQ	<LOQ	<LOQ	0.12 (0.10 ; 0.14)
Phthalates (µg/g creatinine)	MnBP	897	99.9	25.4 (23.7 ; 27.2)	15.9	24.8	40.6	88.2 (75.0 ; 98.5)
	MiBP	897	100	38.8 (36.7 ; 40.7)	22.2	36.7	61.8	153.8 (131.9 ; 196.2)
	MMP	897	94.5	3.6 (3.3; 3.9)	2.1	3.5	5.8	14.9 (12.9 ; 17.9)
	MEP	897	100	71.4 (65.8 ; 77.9)	30.9	65.6	143.0	609.7 (472.2 ; 864.8)
	MBzP	897	93.8	8.2 (7.5; 9.0)	4.5	8.0	15.0	41.4 (36.7; 51.5)
	MCHP	897	0.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
	MnOP	897	0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	MCPP	897	80.9	1.33 (1.21; 1.46)	0.73	1.25	2.18	6.16 (5.09; 7.28)
	MiNP	897	17.2	NC	<LOQ	<LOQ	<LOQ	4.7 (4.0; 5.9)
	ΣDEHP*	897		22.2 (20.6; 23.9)	13.4	21.0	34.3	82.7 (71.6; 94.8)
Glycol ethers (µg/g creatinine)	MAA	500	98.4	93 (82; 105)	46	86	169	507 (374; 628)
	EAA	500	51.4	NC	<LOQ	12	29	120 (85; 154)
	BAA	500	37.0	NC	<LOQ	<LOQ	22	78 (59; 115)
	PhAA	500	99.8	328 (275; 392)	96	291	958	5208 (3939; 6578)
	PAA	500	2.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
	2-MPA	500	59.2	18 (16; 21)	8	16	38	147 (105; 188)
	MEAA	500	28.2	NC	<LOQ	<LOQ	13	49 (35; 58)
	EEAA	500	93.8	79 (66; 95)	31	63	164	945 (567; 1477)
Parabens (µg/g creatinine)	Methyl-paraben	600	93.3	8.2 (6.6 ; 10.1)	1.7	6.8	34.0	219.6 (155.7 ; 320.9)
	Ethyl-paraben	600	54.5	NC	<LOQ	1.0	3.3	35.7 (22.3 ; 59.4)
	Isopropyl-paraben	600	0.3	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Propyl-paraben	600	44.5	NC	<LOQ	<LOQ	2.69	59.0 (36.3 ; 85.8)
	Isobutyl-paraben	600	1.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Butyl-paraben	600	8.5	NC	<LOQ	<LOQ	<LOQ	2.4 (1.5 ; 3.7)
	Benzyl-paraben	600	1.3	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Pentyl-paraben	600	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Heptyl-paraben	600	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
BFRs (ng/g lipids)	Di-BDE 15	742	14.8	NC	<LOQ	<LOQ	<LOQ	0.08 (0.05 ; 0.10)
	Tri-BDE 17	742	0.1	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Tri-BDE 25	742	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Tri-BDE 28	742	19.1	NC	<LOQ	<LOQ	<LOQ	0.09 (0.07 ; 0.13)
	Tri-BDE 33	742	0.1	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Tetra-BDE 47	742	98.8	0.24 (0.22 ; 0.26)	0.14	0.22	0.37	1.06 (0.84 ; 1.37)
	Tetra-BDE 66	742	0.5	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Penta-BDE 85	742	0.9	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Penta-BDE 99	742	64.3	0.05 (0.05 ; 0.06)	<LOQ	0.08	0.15	0.22 (0.19 ; 0.24)
	Penta-BDE100	742	82.9	0.07 (0.07 ; 0.08)	0.04	0.07	0.12	0.26 (0.21 ; 0.33)
	Hexa-BDE 153	742	100	0.78 (0.74 ; 0.82)	0.55	0.75	1.04	2.05 (1.67 ; 2.47)
	Hexa-BDE 154	742	0.9	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Hepta-BDE 183	742	7.3	NC	<LOQ	<LOQ	<LOQ	0.41 (0.37 ; 0.47)
	Deca-BDE 209	742	77.9	1.20 (1.12 ; 1.28)	0.79	1.14	1.66	3.96 (3.06 ; 4.98)
	PBB-153	742	90.0	0.21 (0.19 ; 0.23)	0.07	0.23	0.32	0.73 (0.60 ; 0.92)
	α HBCD	742	34.4	NC	<LOQ	<LOQ	0.67	2.31 (1.46 ; 3.19)
	β HBCD	742	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	γ HBCD	742	0.1	NC	<LOQ	<LOQ	<LOQ	<LOQ
PFCs (µg/L serum)	PFBA	744	1.1	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFPA	744	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFHxA	744	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFHpA	744	2.8	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFOA	744	100.0	2.08 (1.97 ; 2.20)	1.46	2.12	3.02	5.26 (4.82 ; 5.67)
	PFNA	744	99.5	0.80 (0.75 ; 0.85)	0.57	0.80	1.10	1.91 (1.66 ; 2.07)
	PFDA	744	89.2	0.34 (0.05 ; 0.06)	0.24	0.32	0.46	0.78 (0.74 ; 0.84)
	PFUnA	744	99.5	0.17 (0.16 ; 0.19)	0.12	0.18	0.25	0.42 (0.39 ; 0.48)
	PFDoA	744	22.3	NC	<LOQ	<LOQ	<LOQ	0.08 (0.08 ; 0.10)
	PFBS	744	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFHxS	744	99.6	1.37 (1.27 ; 1.48)	0.90	1.48	2.11	3.42 (3.07 ; 3.89)
	PFHpS	744	53.4	0.18 (0.16 ; 0.19)	<LOQ	0.19	0.28	0.48 (0.43 ; 0.54)
	PFOS	744	100.0	4.03 (4.03 ; 4.67)	2.78	4.23	6.62	13.54 (11.33 ; 15.59)
	PFDS	744	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	n-Et-PFOSA-AcOH	744	2.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
	n-Me-PFOSA-ACOH	744	24.6	NC	<LOQ	<LOQ	<LOQ	0.13 (0.12 ; 0.18)
	PFOSA	744	0.4	NC	<LOQ	<LOQ	<LOQ	<LOQ

GM: geometric mean; NC: geometric mean was not calculated because of a large amount of left-censored biomarker levels (% quantification < 60%); LOQ: limit of quantification; *ΣDEHP: sum of MEHP, MEOHP and MEHHP

Table 4
Description of urinary concentrations of bisphenols, phthalates and parabens in the overall population of children living in France, Esteban (2014–2016) (weighted results).

Biomarkers		n	%>LOQ	GM (95% CI)	P25	P50	P75	P95 (95% CI)
Bisphenols (µg/g creatinine)	BP A total	500	100	2.25 (2.07 ; 2.45)	1.36	2.15	3.45	7.34 (6.12 ; 9.17)
	BP A free	500	16.2	NC	<LOQ	<LOQ	<LOQ	0.28 (0.18 ; 0.37)
	BP S total	500	99.9	0.44 (0.36 ; 0.54)	0.16	0.34	0.92	8.45 (3.50 ; 16.00)
	BP S free	500	51.4	NC	<LOQ	0.01	0.03	0.25 (0.12 ; 0.56)
	BP F total	500	100	0.26 (0.23 ; 0.30)	0.13	0.21	0.38	2.69 (1.16 ; 4.37)
	BP F free	500	8.6	NC	<LOQ	<LOQ	<LOQ	0.06 (0.05 ; 0.07)
	MnBP	500	100	26.3 (24.0 ; 28.9)	15.6	25.4	39.8	89.0 (72.1 ; 108.4)
Phthalates (µg/g creatinine)	MiBP	500	100	47.1 (42.5 ; 52.8)	26.9	44.4	74.0	187.0 (135.6 ; 246.0)
	MMP	500	99.6	5.2 (4.7; 5.8)	3.0	4.9	8.1	26.8 (18.4; 39.0)
	MEP	500	99.8	51.2 (43.9 ; 59.7)	24.4	46.2	93.0	408.1 (273.5 ; 557.8)
	MBzP	500	99.2	9.8 (8.7; 11.1)	4.6	8.9	17.7	59.6 (47.8; 79.6)
	MCHP	500	0.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
	MnOP	500	0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	MCPP	500	96.8	1.9 (1.7; 2.1)	1.1	1.9	3.1	8.7 (6.4; 10.8)
	MiNP	500	19.2	NC	<LOQ	<LOQ	<LOQ	3.0 (2.4; 4.6)
	ΣDEHP*	500	–	27.7 (24.8; 30.9)	15.7	27.0	42.9	82.7 (71.6; 94.8)
Parabens (µg/g creatinine)	Methyl-paraben	398	94.2	5.3 (3.9 ; 7.2)	1.3	3.3	17.5	311.4 (94.1 ; 712.9)
	Ethyl-paraben	398	29.4	NC	<LOQ	<LOQ	1.3	17.5 (5.8 ; 56.7)
	Isopropyl-paraben	398	0.3	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Propyl-paraben	398	30.9	NC	<LOQ	<LOQ	1.3	45.1 (7.0 ; 137.0)
	Isobutyl-paraben	398	0.8	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Butyl-paraben	398	4.3	NC	<LOQ	<LOQ	<LOQ	0.9 (<LOQ ; 1.3)
	Benzyl-paraben	398	0.5	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Pentyl-paraben	398	0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Heptyl-paraben	398	0	NC	<LOQ	<LOQ	<LOQ	<LOQ

GM: geometric mean; NC: geometric mean was not calculated because of a large amount of left-censored biomarker levels (% quantification < 60%); *ΣDEHP: sum of MEHP, MEOHP and MEHHP.

during the winter.

Vinyl floor covering (*versus* no such covering) was also associated with a higher combined concentration of MnBP, MiBP, MBzP and MEP of 27.4% [4.7; 55.0] in adults and 58.7% [28.1; 96.5] in children. With regard to phthalates, adults who smoked had higher concentrations than non-smokers (31.3% [10.3; 56.4]), as did those who drank wine (22.7% [10.2; 36.6] higher in those who drank 59 mL of wine per day than in those who did not drink wine).

In terms of BFRs, exposure determinants associated with higher concentrations were tobacco consumption, time spent in one's car, cheese consumption and consumption of home-grown meat and poultry. The combined concentration of the 4 most quantified PBDEs increased with the number of hours spent per week in one's car as follows: from more than 18% for 2 to 4 h up to more than 26% for 4 h and more (compared with those who spent<2 h in their car). Higher Deca-BDE 209 concentrations were found in those who consumed home-grown meat and poultry (22.5% [−0.01; 50.2]) than those who did not, and in those who consumed more cheese (13.4% [0.1; 28.5]) than others.

The presence of CMV in all rooms at home and a high ventilation frequency were the determinants most strongly associated with lower concentrations of, respectively, Deca-BDE 209 (15.6% [0.5; 33.1] (*versus* CMV only in one room) and the combined total of the 4 most quantified PBDEs (21.8% [2.5; 44.8]) (*versus* low ventilation frequency).

With regard to PFCs, certain dietary factors such as consuming home-grown eggs (42.9% [22.9; 66.2] for PFOS), fish and seafood consumption (31.6% [17.9; 46.8] for PFUnA) and the consumption of vegetables (18.6% [2.2; 37.6]), as well as the greater frequency of exposure to PFC-containing materials and products during DIY activities (19.1% [2.5; 40.0] for PFNA) were all associated with higher perfluorinated concentrations. A higher frequency of home ventilation was also associated with lower concentrations of PFCs (18.0% [1.4; 37.2] for PFNA and 29.9% [1.1; 66.8] for PFOS).

In terms of parabens and glycol ethers, biomarker concentrations were higher in those who used cream or body care products and makeup, nail polish, nail polish remover, etc. For example, PhAA concentration was 147.1% [59; 284.7] higher in people who used makeup products or nail polish and nail polish remover than in those who did not. Higher methyl-paraben concentrations were associated with more frequent use of creams or body care products: on average over 97.4% [29.6; 200.7] higher for near daily users than in those who used such products less than once a month or never. They were also 207.4% higher in frequent users of cosmetics or nail polish than in less-frequent users [101.7; 368.3].

4. Reference values of exposure

Reference values of exposure (RVs) constructed from our analyses of the data collected in the Esteban study are presented in Tables 6–8. As mentioned above, in the vast majority of cases, only one value was derived for all the adult population and all the children population for each substance. For parabens, two separate sex-dependent values were derived because sex is a known criterion significantly associated with different exposure levels, women usually being more exposed than men. This is also the case for some glycol ethers and BFRs. RVs derived for PFCs depended on age due to their long half-lives.

5. Discussion

The Esteban study, which is one of two components in the French HBM programme, was conducted in 2014–2016. It provides for the first time, a national description of biomarker concentration levels for six families of chemical substances harmful to health which are present in the daily home environments of adults (18–74 years old) and children (6–17 years-old) living in mainland France. Furthermore, the second component of the programme, which used perinatal data from the Elfe study conducted in 2011, made it possible to measure, again for the first time, the exposure levels of bisphenol A, phthalates, PFCs and BFRs in women who gave birth in France (Dereumeaux et al., 2016; Dereumeaux et al., 2017). In Esteban, exposure reference values for the French population were derived for the first time for these substances. Through

Table 5
Description of urinary concentrations of glycol ethers, serum concentrations of BFRs and PFCs in children's samples, Esteban (2014–2016) (unweighted results).

Biomarkers		n	%>LOQ	GM	P25	P50	P75	P95
Glycol ethers (µg/g creatinine)	MAA	200	100	103	60	106	165	346
	EAA	200	58.0	NC	<LOQ	15	34	95
	BAA	200	72.0	16	<LOQ	21	29	74
	PhAA	200	100	494	228	503	1030	3878
	PAA	200	5.0	NC	NC	<LOQ	<LOQ	<LOQ
	2-MPA	200	84.0	21	11	22	37	99
	MEAA	200	54.5	NC	<LOQ	10	24	71
	EEAA	200	85.0	92	32	126	274	1050
BFRs (ng/g lipids)	Di-BDE 15	243	3.3	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Tri-BDE 17	243	0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Tri-BDE 25	243	0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Tri-BDE 28	243	19.3	NC	<LOQ	<LOQ	<LOQ	0.10
	Tri-BDE 33	243	0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Tetra-BDE 47	243	99.6	0.34	0.18	0.28	0.59	1.63
	Tetra-BDE 66	243	0.4	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Penta-BDE 85	243	1.7	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Penta-BDE 99	243	78.2	0.08	0.05	0.07	0.13	0.34
	Penta-BDE100	243	81.1	0.08	0.05	0.08	0.13	0.35
	Hexa-BDE 153	243	96.7	0.39	0.24	0.36	0.57	1.53
	Hexa-BDE 154	243	0.8	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Hepta-BDE 183	243	1.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Deca-BDE 209	243	81.5	1.47	1.10	1.48	1.99	3.58
	PBB-153	243	2.9	NC	<LOQ	<LOQ	<LOQ	<LOQ
	α HBCD	243	13.2	NC	<LOQ	<LOQ	<LOQ	1.36
	β HBCD	243	0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	γ HBCD	243	0.8	NC	<LOQ	<LOQ	<LOQ	<LOQ
PFCs (µg/L serum)	PFBA	249	0.4	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFPA	249	0.4	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFHxA	249	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFHpA	249	5.2	NC	<LOQ	<LOQ	<LOQ	0.17
	PFOA	249	100	1.56	1.26	1.54	1.89	2.76
	PFNA	249	99.6	0.61	0.45	0.57	0.76	1.35
	PFDA	249	71.1	0.24	0.19	0.24	0.31	0.55
	PFUnA	249	95.6	0.12	0.08	0.12	0.16	0.29
	PFDoA	249	8.0	NC	<LOQ	<LOQ	<LOQ	0.06
	PFBS	249	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFHxS	249	99.6	0.79	0.57	0.73	1.05	2.26
	PFHpS	249	3.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PFOS	249	100	2.22	1.55	2.00	2.95	6.12
	PFDS	249	0.4	NC	<LOQ	<LOQ	<LOQ	<LOQ
	n-Et-PFOSA-AcOH	249	1.6	NC	<LOQ	<LOQ	<LOQ	<LOQ
	n-Me-PFOSA-ACOH	249	21.3	NC	<LOQ	<LOQ	<LOQ	0.13
	PFOSA	249	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ

GM: geometric mean; NC: geometric mean was not calculated because of a large amount of left-censored biomarker levels (% quantification < 60%).

comparison with related studies, these values enabled us to estimate whether a specific sub-population, or an individual, is overexposed in specific situations, for example when living close to polluted sites and soils.

Our analyses of Esteban's data on exposure to contaminants of the French population enabled us to make comparisons with published data other European and North American countries. Furthermore, quality assurance in our analyses was reinforced by (i) introducing control samples consisting of ultra-pure water in order to guarantee that samples had not been contaminated by the environment and (ii) using replicates to assess the intermediate precision of the analyses.

Bisphenols (A, S and F) were quantified in all of the samples analysed (99.9% for BPS and 100% for BPA and BPF). In terms of bisphenol concentrations, both adults and children had higher levels of BPA than BPS and BPF, which reflects findings from the USA's NHANES survey (Lehmler et al., 2018). Moreover, BPA concentrations in Esteban were higher than those described in the United States (Lehmler et al., 2018) and in Canada (4) in both children and adults. The concentrations of bisphenols we found for France are closer to those reported in several other European countries including Germany and Belgium (Becker et al., 2009; Covaci et al., 2015). Finally, concentrations of bisphenols F and S in children were lower in Esteban and these European studies than those observed in the US NHANES survey (Lehmler et al., 2018). However, the latter study is older than Esteban and a decrease in these concentrations in the USA may have already started by the time Esteban was implemented, especially as bisphenols S and F substituted bisphenol A sooner in the USA than in France. The same is also possible for the two European studies referenced above (Becker et al., 2009; Covaci et al., 2015), as these were also implemented before Esteban. One of the hypotheses that could explain why no determinant was found for exposure to bisphenol A is the application of a French law in 2015 which banned bisphenol A in packaging, containers and utensils.

Our results show that the two study subsamples (adults and children) had a quantified urinary concentration for at least one phthalates metabolite. MEP, the metabolite of DEP, was the metabolite with the highest concentrations both in adults and children, followed by MiBP, the metabolite of DiBP. Only the metabolites of DCHP (MCHP), DiNP (MniP) and DnOP (MnOP, MCPP) were either rarely or never quantified. All of these observations are consistent with results from biomonitoring studies conducted elsewhere, especially Canada (4) and the United States (Crinnion, 2010), where the levels observed were very similar. It should be pointed out however that data from those studies are 5 years older than those of Esteban. Only the average concentration of MiBP in the French adult population was significantly higher by a factor of 2–3

Table 6
Reference values of exposure for French adults (18–74 years) measured in urine from the Esteban study (2014–2016).

Biomarkers		Population	RV (µg L^{-1})
Bisphenols	BP A total	Adults (18–74 years old)	8.0
	BP S total	Adults (18–74 years old)	6.3
	BP F total	Adults (18–74 years old)	1.0
Phthalates	MnBP	Adults (18–74 years old)	67
	MiBP	Adults (18–74 years old)	129
	MMP	Adults (18–74 years old)	10.8
	MEP	Adults (18–74 years old)	402
	MBzP	Adults (18–74 years old)	31.6
	MCPP	Adults (18–74 years old)	5.3
	MiNP	Adults (18–74 years old)	3.0
	MEHP	Adults (18–74 years old)	6.2
	MEHPP	Adults (18–74 years old)	30.4
	MEOHP	Adults (18–74 years old)	18.5
Glycol ethers	MAA	Adults (18–74 years old)	316
	EAA	Adults (18–74 years old)	58
	BAA	Adults (18–74 years old)	46
	PhAA	Men adults (18–74 years old)	1173
		Women adults (18–74 years old)	6 989
	2-MPA	Adults (18–74 years old)	112
	MEAA	Adults (18–74 years old)	26
	EEAA	Men adults (18–74 years old)	434
		Women adults (18–74 years old)	1165
Parabens	Methyl-paraben	Men adults (18–74 years old)	67
		Women adults (18–74 years old)	380
	Ethyl-paraben	Men adults (18–74 years old)	11
		Women adults (18–74 years old)	35
	Propyl-paraben	Men adults (18–74 years old)	10
		Women adults (18–74 years old)	103
	Butyl-paraben	Men adults (18–74 years old)	0.4
		Women adults (18–74 years old)	3.7

Table 7
Reference values of exposure for French adults (18–74 years) measured in serum from the Esteban study (2014–2016).

Biomarkers		Population	RV (ng L^{-1})
BFRs	Di-BDE 15	Adults (18–74 years old)	0.4
	Tri-BDE 28	Adults (18–74 years old)	0.5
	Tetra-BDE 47	Adults (18–74 years old)	5.9
	Penta-BDE 99	Adults (18–74 years old)	1.2
	Penta-BDE100	Adults (18–74 years old)	1.5
	Hexa-BDE 153	Men adults (18–74 years old)	14.9
		Women adults (18–74 years old)	9.3
	Hepta-BDE 183	Adults (18–74 years old)	2.4
	Deca-BDE 209	Adults (18–74 years old)	22.5
	PBB-153	Men adults (18–74 years old)	5.3
		Women adults (18–74 years old)	3.1
	α HBCD	Adults (18–74 years old)	14.2
Biomarkers		Population	RV (µg L^{-1})
PFCs	PFOA	Adults (18–44 years old)	3.6
		Adults (45–74 years old)	5.9
	PFNA	Adults (18–44 years old)	1.3
		Adults (45–74 years old)	2.1
	PFDA	Adults (18–44 years old)	0.6
		Adults (45–74 years old)	0.9
	PFUnA	Adults (18–44 years old)	0.3
		Adults (45–74 years old)	0.5
	PFDoA	Adults (18–44 years old)	0.06
		Adults (45–74 years old)	0.10
	PFHxS	Adults (18–44 years old)	2.9
		Adults (45–74 years old)	3.8
	PFHpS	Adults (18–44 years old)	0.3
		Adults (45–74 years old)	0.6
	PFOS	Adults (18–44 years old)	8.8
		Adults (45–74 years old)	15.3
	n-Me-PFOSA-ACOH	Adults (18–74 years old)	0.1

than those found in Canada and the United States, respectively, but not higher than that found in the European population taken as a whole (Den Hond et al., 2015). The levels observed for MiBP could be linked to the substitution in industry of DnBP by DiBP (Kasper-Sonnenberg et al., 2014).

Our results from the Esteban exposure data also reveal that between 2014 and 2016, 100% of the child subsample and 99.8% of the adult subsample had quantifiable urinary concentrations for at least one of the 8 metabolites of glycol ethers analysed. PhAA and MAA were the two metabolites most frequently detected in both adults and children (100% of both Esteban subsamples). The concentrations of PhAA, MAA, EEAA, 2-MPA and EAA in adults were close to the levels observed in studies from the Pelagie cohort in pregnant women in France (Cordier et al., 2012; Beranger et al., 2017) between 2002 and 2005. However, the concentrations of PhAA in adults in Esteban were lower than levels measured in 2008 in studies in northern France (Nisse et al., 2017) and in 2013 in Germany (Fromme et al., 2013). Again, it is important to point out the time difference between these two studies and Esteban's implementation.

In terms of parabens, the concentrations from Esteban were lower than those found in European (Moos et al., 2015; Dewalque et al., 2014; Asimakopoulos et al., 2014; Frederiksen et al., 2014) and North American (Calafat et al., 2010; Canada Health, 2013) studies. One possible explanation for the latter is that European regulations are more restrictive regarding the use of parabens in food. In any case, in all international studies referenced here (Moos et al., 2015; Dewalque et al., 2014; Calafat et al., 2010; Canada Health, 2013; Kim et al., 2018), the most frequently quantified parabens, in order of importance, were: methyl-paraben, propyl-paraben, ethyl-paraben, and butyl-paraben.

Quantification rates of the BFRs studied in Esteban varied according to the congeners. Few BFRs congeners were quantified. BFRs are persistent organic pollutants (POPs) (Stockholm Convention), the sale and use of which have been reduced or stopped by European legislation. Accordingly, from 1983, Directive 76/769 / EEC prohibited the use of PBBs in textiles which make contact with the skin. PBBs have not been produced since 2000. In 2003, a modification to this directive prohibited the use of two commercial mixtures of PBDEs, namely penta-BDE and octa-BDE, at concentrations greater than 0.1% by mass. Furthermore, PBBs and PBDEs, irrespective of their concentration, have been banned

Table 8
Reference values of exposure for French children (6–17 years) measured in urine from the Esteban study (2014–2016).

Biomarkers		Population	RV (µg L^{-1})
Bisphenols	BP A total	Children (6–17 years old)	7.0
	BP S total	Children (6–17 years old)	8.3
	BP F total	Children (6–17 years old)	2.0
	MnBP	Children (6–17 years old)	90
Phthalates	MiBP	Children (6–17 years old)	162
	MMP	Children (6–17 years old)	23.5
	MEP	Children (6–17 years old)	492
	MBzP	Children (6–17 years old)	61
	MCPP	Children (6–17 years old)	8.7
	MiNP	Children (6–17 years old)	3.0
	MEHP	Children (6–17 years old)	8.6
	MEHPP	Children (6–17 years old)	47.1
	MEOHP	Children (6–17 years old)	38.2
Parabens	Methyl-paraben	Girls (6–17 years old)	810
		Boys (6–17 years old)	55
	Ethyl-paraben	Girls (6–17 years old)	52
		Boys (6–17 years old)	5
	Propyl-paraben	Girls (6–17 years old)	177
		Boys (6–17 years old)	5

in all new electrical and electronic equipment since July 2006. Finally, in July 2008, a third mixture of PBDEs, specifically BDE 209, was also banned by the European Court of Justice.

The list of the most quantified PBDE congeners in the Esteban data reflected European findings (Kalantzi et al., 2011; Thomas et al., 2006; Fromme et al., 2009), the order of importance being: BDE 153, because of its long half-life, then BDE 47, BDE 100, Deca-BDE 209 or BDE 99. In North America, the PBDE that contributes the most to the total sum of PBDEs concentrations is BDE 47 (Fromme et al., 2016; Sjodin et al., 2003; Rawn et al., 2014; Ospina et al., 2018). Again, concentrations of BFRs in Esteban (i.e., the French population) were similar to those found in other European countries (Kalantzi et al., 2011; Thomas et al., 2006; Fromme et al., 2009) but were lower than those measured in North American countries except for BDE 209 (Fromme et al., 2016; Sjodin et al., 2003; Rawn et al., 2014; Ospina et al., 2018).

In Esteban, the quantification rates of PFCs measured in the serum matrix varied from one PFC to another. It is important to point out that the same perfluorinated compounds - including PFOS and PFOA - were quantified in Esteban as in all international biomonitoring studies performed to date (Haines et al., 2017; CDC, 2018). Concentrations varied from one country to another and according to the specific PFC measured. More specifically, some PFCs were lower in the United States (CDC, 2018) and Canada (Canada Health, 2013) but higher in Spain (Frederiksen et al., 2013).

Our results from data on biomarkers collected in the Esteban study show that on average, the youngest children had higher concentrations of all the contaminants measured except for PFCs. This reflects previous findings with higher concentrations observed in young children than in adolescents and adults (Becker et al., 2009; Frederiksen et al., 2013; Casas et al., 2013). Several hypotheses could explain these differences including more frequent skin and 'hand-to-mouth' contact for everyday products (toys, paints, etc.) containing the substances measured in Esteban, and higher exposure levels than adults, linked, for example, to increased exposure to household dust or to lower body weight relative to their food intake (Correia-Sá et al., 2017).

The exposure determinants found for the six families of pollutants analysed in the Esteban study are consistent with those found in the international studies cited above (Becker et al., 2009; Calafat, 2012; Haines et al., 2017) and with existing knowledge available on these substances. They differ depending on the substance. In particular, our results show that food consumption does not appear to be the only source of exposure to these substances and that the use of cosmetics and care products increases the levels of parabens and glycol ethers, while more frequent home ventilation is associated with lower concentrations of perfluorinated and brominated flame retardants.

Associations highlighted in our analyses should be interpreted with caution as cross-sectional studies cannot determine the causality between the potential sources of exposure studied and the concentrations of pollutants measured. This is particularly the case for biomarkers with short half-lives such as bisphenols, glycol ethers, parabens and phthalates. In addition, due to the high circadian variability of urinary phenol concentrations for the same individual and the fact that only one spot urine sample was collected per individual, it is not possible to exclude the risk of error in the estimation of individual exposure to bisphenols. However, the large overall sample size in Esteban ($N = 2503$ for adults and 1104 for children) allowed us to obtain a satisfactory population-based estimate. Accordingly, the absence of any association between a potential source of exposure and the concentration of a particular biomarker does not mean that this source of exposure should be excluded. Conversely, demonstrating an association between a source of exposure and the concentration of a specific biomarker suggests the need to continue exploring this exposure pathway.

As mentioned in the results section, in most cases in the present analyses only one reference value of exposure was derived for the two population subsamples and for each substance. However, for some parabens, glycol ethers and BFRs, two separate gender-specific values were derived, and for these substances, we observed that women were usually more exposed than men. A hypothesis mentioned in other studies with similar findings (Cordier et al., 2012; Nisse et al., 2017; Kim et al., 2018) was the more frequent use by women of (i) care products (shampoo, make up, nail polish, skin cream, etc.) for parabens and glycol ethers, and (ii) household products for glycol ethers. This hypothesis was confirmed in our multivariate analysis which was based on responses to questionnaires. So too was the hypothesis that the two values derived for PFCs probably depended - at least partly - on the long half-life characteristics of these compounds (Lau et al., 2007).

The fact that the Esteban data analysed here were collected according to standardized protocols adds validity to our results. However, some limitations of our analyses must be considered. First, selection bias is possible given that many households did not agree to participate. Indeed, participation trends in Esteban were similar to those seen in previous related studies (Falq et al., 2011; Saoudi et al., 2014; Saoudi et al., 2012): less participation by young adults (between 18 and 35 years old), single people (in adults), men, unemployed persons, and more participation by individuals with a high-school diploma and above, persons in a relationship, employed people, and pre-retired and retired individuals. However, given that the sampling design characteristics (calibrated survey weights, stratification, clustering) were taken into account in our statistical analysis, it seems reasonable to suppose that any potential impact of selection bias was limited. Accordingly, our population exposure estimates can be considered representative of the French population living in mainland France for 2014–2016 and are therefore suitable for use as reference values for the monitoring of these six families of contaminants.

A second limitation is that collecting a first voided urine specimen raises the question of measurement variability, specifically for short half-life biomarkers such as bisphenols, parabens, glycol ethers and phthalates. However, while the characterization of an individual concentration would probably require repeated measurements, thanks to the large sample size in Esteban, one measurement would seem sufficient to describe exposure at the population level.

6. Conclusions

This article presents the first French data on exposure to six families of pollutants found in the domestic environment (collected in the Esteban study). Our results show that exposure to these substances is generalized in both children and adults. Our analyses also show that it is important to conduct studies on the child population as they are particularly vulnerable, given the higher concentrations of these substances we found in them than in adults.

Exposure levels were comparable with those found internationally except for parabens, BFRs (except BDE-209) and bisphenols S and F whose levels are higher in the United States. However, there is little comparative data and many of the studies which we made comparisons with here were much older than Esteban.

As the substances investigated are of concern in terms of human toxicity, our results advocate the development of tools to prevent exposure. They also confirm the necessity to promote and to assess the efficiency of current and future public policies for regulation of such substances. Furthermore, the analyses performed here enabled us to establish exposure reference values which are useful for decision makers.

Our analysis of exposure determinants also helped us to identify hypotheses for reducing exposure of populations. The frequency of home ventilation, the consumption of canned foods, prepared or pre-packaged meals, and the use of certain care products, are all examples of determinants which influence the concentrations of these substances.

In terms of prospects, temporal trends can be investigated when these measurements are repeated in future related surveys.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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