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Biomarkers of exposure to environmental contaminants in French pregnant women from the Elfe cohort in 2011

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ABSTRACT

Background: As part of the perinatal component of the French Human Biomonitoring (HBM) program, biomarkers levels of various chemicals have been described among pregnant women having given birth in continental France in 2011 and who have been enrolled in the Elfe cohort (French Longitudinal Study since Childhood). This paper describes the design of the study and provides main descriptive results regarding exposure biomarkers levels.

Methods: Exposure biomarkers were measured in biological samples collected at delivery from pregnant women randomly selected among the participants in the clinical and biological component of the Elfe cohort (n = 4145). The geometric mean and percentiles of the levels distribution were estimated for each biomarker. The sampling design was taken into account in order to obtain estimates representative of the French pregnant women in 2011.

Results: Results provide a nation-wide representative description of biomarker levels for important environmental contaminants among pregnant women who gave birth in France in 2011. Bisphenol A (BPA), and some metabolites of phthalates, pesticides (mainly pyrethroids), dioxins, furans, polychlorobiphenyls (PCBs), brominated flame retardants (BFRs), perfluorinated compounds (PFCs) and metals (except uranium) were quantified in almost 100% of the pregnant women. Some compounds showed a downward trend compared to previous studies (lead, mercury), but others did not (pyrethroids) and should be further monitored.

Conclusion and perspectives: The present results show that French pregnant women are exposed to a wide variety of pollutants, including some that have been banned or restricted in France.

1. Introduction

Human biomonitoring (HBM) is the analytical measurement of biomarkers (e.g. environmental chemicals or their metabolites) in easily accessible human biological fluids and tissues (e.g. urine, blood, hair) (Angerer et al., 2006). As HBM represents an integral measure of exposure from all relevant sources and routes of uptake, it permits exposure assessment when exposure sources are unknown or ambiguous (Wittassek et al., 2011). This is particularly true for chemicals present in food or used in a variety of everyday life products, including food packaging, and responsible for a widespread human exposure.

Since 1980s in France, HBM studies have been conducted in order to: improve the understanding of human exposure to environmental chemicals; identify spatial and temporal trends; help regulators initiating policy measures aiming to reduce environmental exposure; and monitor existing policies (Frery et al., 2012b). Even though pregnancy appears to be a period of vulnerability regarding developmental and reproductive adverse effects for the child, only a few surveys have measured internal concentrations (i.e. body burden) of environmental chemicals among a large population of pregnant women in France. Studies conducted in France have mainly focused on general population (Falq et al., 2011; Saoudi et al., 2014) or have been conducted on pregnant women at a regional level (Seine Saint Denis district of Paris and Rhone-Alpes region in southeast France (Vandentorren et al., 2011), Bretagne region in northwest France (Chevrier et al., 2009), cities of Nancy and Poitiers (Philippat et al., 2014)).

The French HBM program is implemented by Santé publique France, the French national public health agency. This program currently consists in two cross-sectional national population-based biomonitoring surveys: a perinatal component based on a random selection of pregnant women enrolled in the French Longitudinal Study since Childhood

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(Elfe) and a general population survey coupled with health examinations and with a nutritional component: Environment, Health, Biomonitoring, physical Activity, Nutrition (Esteban).

The primary aim of the perinatal component of the French HBM program is to describe internal concentrations of environmental contaminants among pregnant women having given birth in continental France in 2011. Additional objectives were: to compare the biomarkers levels with those observed in previous surveys (e.g. in other European HBM programs) and to identify and quantify the determinants of exposure. This paper describes the study design and the main descriptive results of the survey.

2. Material and methods

2.1. Study design

The Elfe cohort has been launched in 2011 and has enrolled 18,000 children for a projected 20 years follow up in order to characterize the relationship between the environment and the development, health and socialization of the children. The environment of the child is characterized with a multidisciplinary approach assessing socioeconomic, geographic, familial, behavior-related, physical, chemical and microbiological exposures. The design of the cohort has been previously described (Charles et al., 2011; Vandentorren et al., 2009). More details are also available in the website: http://www.elfe-france.fr/index.php/en/.

Some specific aspects of the study design (questionnaires, sampling protocols, transportation conditions, and analytical methods) have been defined and validated by a pilot survey conducted in 2007 (Vandentorren and Oleko, 2011). This pilot has enrolled about 300 mother-child couples in two French regions (Rhône-Alpes and Seine-Saint-Denis). Some emerging pollutants were monitored in this pilot study: bisphenol A (BPA), phthalates, brominated flame retardants (BFRs), perfluorinated compounds (PFCs), some pesticides and their metabolites (atrazine, glyphosate, carbamates, pyrethroids), and organotin compounds (Vandentorren et al., 2013).

For the national scale study, a two-stage random stratified sampling design was used (maternity and pregnant women). For the first stage, maternity hospitals were randomly selected from a sampling frame stratified by institution status (private/public), authorization type (depending on the number of births attended by year) and region (5 regional clusters). Maternity wards that carried out <365 births a year were excluded. Finally 349 maternity hospitals were randomly selected among the 542 in France and 320 accepted to participate in the Elfe cohort. Then, a subset of 211 maternity hospitals has been selected for participating in the biological data collection, after exclusion of maternity units attended <500 deliveries per year, those participating in the cord blood collection for The French Agence de la biomédecine and those located at over 150 km from one of the biobanks. The comparison between the characteristics of the maternity units selected for the biological collection and those initially selected is presented in Supplemental material. In second stage of sampling, the mothers were selected exhaustively.

2.2. Study participants

The perinatal component of the French HBM program is based on a random selection of mothers enrolled in the Elfe cohort. The study population consists of pregnant women (>18 years) who gave birth to a single or two living babies, after 33 weeks or more of gestation, in one of the 211 maternity hospitals participating in the biological data collection located in continental France. These pregnant women were enrolled between the 27th of June 2011 and the 4th of July 2011, or between the 27th of September 2011 and the 4th of October 2011, or between the 28th of November 2011 and the 5th of December 2011. They had to give their consent to participating in the biological samples collection (urine, blood, cord blood and hair) and to have at least one available biological sample.

For each biomarker a subsample of participants was selected among pregnant women who accepted to participate in the biological component of the Elfe cohort. The number of pregnant women per maternity stratum was chosen in such a way as to preserve the original distribution according to the institution status, authorization type, and geographical area of the maternity unit. Finally, a total of 4145 pregnant women had at least one biomarker measured.

2.3. Biological samples collection

Exposure biomarkers were measured in biological samples of the pregnant woman collected at delivery, just after her admission to the maternity unit (urine), in the delivery room (blood and cord blood) or within the first few days following birth (hair). Urine samples were collected prior to any use of medical devices to prevent external contamination by BPA or phthalates that may be present in these products.

Spot urine samples were collected in a 150 mL polypropylene container; blood was collected by venous catheter and stored in one or two dry 10 mL tubes and cord blood was sampled in 6 mL EDTA tubes. All samples were stored at +4 °C in the hospital and transferred in refrigerated trucks twice a day to biobanks where they were processed.

Samples of urine were aliquoted in four 10 mL and ten 2 mL polypropylene cryotubes. Following centrifugation, serum was aliquoted in four or five 2 mL polypropylene cryotubes. Whole cord blood was aliquoted from EDTA tubes to 0.5 mL straws. Urine and maternal blood samples were stored at −80 °C and cord blood straws were stored at −196 °C. Time between sampling and freezing did not exceed 36 h for all samples. Selected samples were sent to the laboratories that carried out the biomarkers analysis (<−60 °C, 24 h). Samples were stored at −20 °C and protected from light at laboratories.

At maternity, a strand of hair was cut in the occipital area of the pregnant woman's head. It was then stapled to a paper card, indicating the orientation (tip/root) of the strand. Cards were individually placed in envelopes, and were stored and transported at ambient temperature. Samples selected for biomarker analysis were sent (by air post) to the laboratory that carried out the analysis.

2.4. Biomarkers measurements

The process of biomarkers prioritization has been previously described (Fillol et al., 2014). Briefly, biomarkers were first selected owing to the biomonitoring feasibility, the exposure relevance, the existing regulations for the compounds, and the priorities in terms of health effects; then a Delphi consensus method was applied to prioritized these biomarkers according to criteria based on the contribution in terms of new knowledge in France, the feasibility of the prevention, the logistic and analytic feasibility, the feasibility of results' interpretation, the biomarker characteristics (i.e. specificity, intra-individual variability, etc.), the social perception, the exposure characteristics (i.e. origin of the contamination) and the hazard identification. Finally, biomarkers from this list analyzed in the perinatal component of the French HBM program were both well-known pollutants (e.g. lead, mercury and dioxins) and emerging substances (e.g. phthalates, bisphenol A (BPA), pesticides and perfluorinated compounds). The list of these biomarkers is given in Table 1.

For each biomarker analyzed in the study, the type and volume of biological material, as well as the analytical method and the limits of detection (LOD) and quantification (LOQ) are given in Table 2.

The analyses of BPA (free and total), metabolites of phthalates, atrazine (and metabolites), glyphosate (and metabolite), propoxur (and metabolite), metabolites of dialkyl phosphate insecticides (DAP) and chlorophenols were performed by Labocea, Plouzané, France. The urinary concentrations of free BPA and total BPA (free plus conjugated) were quantified by gas chromatography coupled to tandem mass spectrometry

Table 1
Biomarkers monitored in the perinatal component of the French HBM program.

Biomarkers	Abbreviation	CID[a]	CAS no.
Metals			
Lead	Pb	5352425	7439-92-1
Mercury	Hg	23931	7439-97-6
Aluminum	Al	5359268	7429-90-5
Antimony	Sb	24814	7440-36-0
Arsenic	As	5359596	7440-38-2
Cadmium	Cd	23973	7440-43-9
Cesium	Cs	5354618	7440-46-2
Chromium	Cr	23976	7440-47-3
Cobalt	Co	104730	7440-48-4
Nickel	Ni	935	7440-02-0
Tin	Sn	5352426	7440-31-5
Uranium	U	23989	7440-61-1
Vanadium	V	23990	7440-62-2
Bisphenol			
Bisphenol A total	Total BPA	6623	80-05-7
Bisphenol A unconjugated	Free BPA	6623	80-05-7
Phthalates			
Monoethyl phtalate	MEP	75318	2306-33-4
Mono-n-butyl phthalate	MnBP	8575	131-70-4
Mono-isobutyl phthalate	MiBP	92272	30833-53-5
Monobenzyl phthalate	MBzP	31736	2528-16-7
Mono-2-ethylhyexyl phthalate	MEHP	20393	4376-20-9
Mono-(2-ethyl-5-oxohexyl)phthalate	MEOHP	119096	40321-98-0
Mono-(2-ethyl-5-hydroxyhexyl)phthalate	MEHHP	170295	40321-99-1
Mono-(2-ethyl-5-carboxypentyl)phthalate	MECPP	148386	40809-41-4
Mono-carboxy-isooctyl phthalate	MCiOP	–	898544-09-7
Mono-(4-methyl-7-hydroxyoctyl) phthalate	MHiNP	–	–
Mono-(4-methyl-7-oxooctyl) phthalate	MOiNP	–	936022-00-3
Herbicides			
Atrazine	–	2256	1912-24-9
Atrazine mercapturate	–	178512	138722-96-0
Atrazine desethyl	–	22563	6190-65-4
Atrazine desisopropyl	–	13878	1007-28-9
Atrazine-desethyl-desisopropyl	–	18831	3397-62-4
Atrazine-2-hydroxy	–	16553	2163-68-0
Atrazine-desethyl-2-hydroxy	–	107740	19988-24-0
Atrazine-desisopropyl-2-hydroxy	–	81748	7313-54-4
Atrazine-desethyl-desisopropyl-2-hydroxy	Ammeline	12583	645-92-1
Glyphosate	–	3496	1071-83-6
Aminomethylphosphonic acid	AMPA	14017	1066-51-9
Carbamate			
Propoxur	–	4944	114-26-1
2-isopropoxy-phenol	2-IPP	20949	4812-20-8
Chlorophenols			
4-monochloro-phenol	4-MCP	4684	106-48-9
2,4-dichloro-phenol	2,4-DCP	8449	120-83-2
2,5-dichloro-phenol	2,5-DCP	66	583-78-8
2,4,5-trichloro-phenol	2,4,5-TCP	7271	95-95-4
2,4,6-trichloro-phenol	2,4,6-TCP	6914	88-06-2
Pentachloro-phenol	PCP	992	87-86-5
Dialkylphosphates	DAP		
Di-methyl-phosphate	DMP	13134	813-78-5
Di-methyl-thiophosphate	DMTP	168140	1112-38-5
Di-methyl-di-thiophosphate	DMDTP	12959	756-80-9
Di-ethyl-phosphate	DEP	654	598-02-7
Di-ethyl-thiophosphate	DETP	655	2465-65-8
Di-ethyl-di-thiophosphate	DEDTP	9274	298-06-6
Pyrethroids			
3-phenoxybenzoic	3-PBA	19539	3739-38-6
4-fluoro-3-phenoxybenzoic acid	F-BPA	157032	77279-89-1
Cis-3-(2,2dibromovinyl)-2,2-dimethylcyclopropane-carboxylic acid	Cis-DBCA	181248	63597-73-9
Cis-3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid	Cis-DCCA	91658	55701-05-8
Trans-3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid	Trans-DCCA	91658	55701-03-6
Dioxins	PCDD		
2,3,7,8-tetraCDD	–	15625	1746-01-6
1,2,3,7, 8-pentaCDD	–	38439	40321-76-4
1,2,3,4,7,8-hexaCDD	–	38251	39227-28-6
1,2,3,6,7,8-hexaCDD	–	42540	57653-85-7
1,2,3,7,8,9-hexaCDD	–	29575	19408-74-3

Table 1 (*continued*)

Biomarkers	Abbreviation	CID[a]	CAS no.
1,2,3,4,6,7,8-heptaCDD	–	37270	35822-46-9
OctaCDD	OCDD	18636	3268-87-9
Furans	PCDF		
2,3,7,8-tetraCDF	–	39929	51207-31-9
1,2,3,7,8-pentaCDF	–	42138	57117-41-6
2,3,4,7,8-pentaCDF	–	42128	57117-31-4
1,2,3,4,7,8-hexaCDF	–	51130	70648-26-9
1,2,3,6,7,8-hexaCDF	–	42140	57117-44-9
1,2,3,7,8,9-hexaCDF	–	51720	72918-21-9
2,3,4,6,7,8-hexaCDF	–	43495	60851-34-5
1,2,3,4,6,7,8-heptaCDF	–	38199	67562-39-4
1,2,3,4,7,8,9-heptaCDF	–	41510	55673-89-7
OctaCDF	OCDF	38200	39001-02-0
Polychlorobiphenyls dioxin-like	PCB-DL		
3,3′,4,4′-tetrachlorobiphenyl	PCB 77	36187	32598-13-3
3,4,4′,5-tetrachlorobiphenyl	PCB 81	51043	70362-50-4
2,3,3′,4,4′-pentachlorobiphenyl	PCB 105	36188	32598-14-4
2,3,4,4′,5-pentachlorobiphenyl	PCB 114	53036	74472-37-0
2,3′,4,4′,5-pentachlorobiphenyl	PCB 118	35823	31508-00-6
2′,3,4,4′,5-pentachlorobiphenyl	PCB 123	47650	65510-44-3
3,3′,4,4′,5-pentachlorobiphenyl	PCB 126	63090	57465-28-8
2,3,3′,4,4′,5-hexachlorobiphenyl	PCB 156	38019	38380-08-4
2,3,3′,4,4′,5′-hexachlorobiphenyl	PCB 157	50891	69782-90-7
2,3′,4,4′,5,5′-hexachlorobiphenyl	PCB 167	40479	52663-72-6
3,3′,4,4′,5,5′-hexachlorobiphenyl	PCB 169	36231	32774-16-6
2,3,3′,4,4′,5,5′-heptachlorobiphenyl	PCB 189	38306	39635-31-9
Polychlorobiphenyls no dioxin-like	PCB-NDL		
2,4,4′-trichlorobiphenyl	PCB 28	3448	7012-37-5
2,2′,5,5′-tetrachlorobiphenyl	PCB 52	37248	35693-99-3
2,2′,4,5,5′-pentachlorobiphenyl	PCB 101	37807	37680-73-2
2,2′,3,4,4′,5′-hexachlorobiphenyl	PCB 138	37035	35065-28-2
2,2′,4,4′,5,5′-hexachlorobiphenyl	PCB 153	37034	35065-27-1
2,2′,3,4,4′,5,5′-heptachlorobiphenyl	PCB 180	37036	35065-29-3
Brominated flame retardants	BFRs		
2,2′,4-tribromodiphenyl ether	PBDE 17	14274807	147217-75-2
2,4,4′-tribromodiphenyl ether	PBDE 28	39506	49690-94-0
2,2′,4,4′-tetrabromodiphenyl ether	PBDE 47	22833475	40088-47-9
2,3′,4,4′-tetrabromodiphenyl ether	PBDE 66	15509893	189084-61-5
2,2′,3,4,4′-pentabromodiphenyl ether	PBDE 85	177368	182346-21-0
2,2′,4,4′,5-pentabromodiphenyl ether	PBDE 99	13766702	32534-81-9
2,2′,4,4′,6-pentabromodiphenyl ether	PBDE 100	13766702	32534-81-9
2,2′,4,4′,5,5′-hexabromodiphenyl ether	PBDE 153	13766703	36483-60-0
2,2′,4,4′,5,6′-hexabromodiphenyl ether	PBDE 154	13766703	36483-60-0
2,2′,3,4,4′,5′,6-heptabromodiphenyl ether	PBDE 183	3034400	68928-80-3
Decabromodiphenyl ether	PBDE 209	14410	1163-19-5
Hexabromobiphenyl ether	PBB 153	13766703	36483-60-0
1,2,5,6,9,10-hexabromocyclododecane	HBCD-α/β/γ	18529	3194-55-6
Perfluorinated compounds	PFCs		
Heptafluorobutyric acid	PFBA	9777	375-22-4
5H–octafluoropentanoic acid	PFPA	120227	376-72-7
Perfluorohexanoic acid	PFHxA	67542	307-24-4
Perfluoroheptanoic acid	PFHpA	67818	375-85-9
Pentadecafluorooctanoic acid	PFOA	9554	335-67-1
Perfluorononanoic acid	PFNA	67821	375-95-1
Perfluorodecanoic acid	PFDA	9555	335-76-2
Perfluoroundecanoic acid	PFUnA	77222	2058-94-8
Perfluorododecanoic acid	PFDoA	67545	307-55-1
Perfluorobutane sulfonic acid	PFBS	67815	375-73-5
Perfluorohexane-1-sulfonic acid	PFHxS	67734	355-46-4
Perfluoroheptane sulfonic acid	PFHpS	67820	375-92-8
Heptadecafluorooctane-1-sulfonic acid	PFOS	23669238	2795-39-3
Perfluorodecane sulfonic acid	PFDS	67636	335-77-3
2-(N-ethyl-perfluorooctane sulfonamido) acetic acid	Et-PFOSA-AcOH	–	2991-50-6
2-(N-methyl-perfluorooctane sulfonamido) acetic acid	Me-PFOSA-ACOH	–	2355-31-9
Perfluorooctanesulfonamide	PFOSA	–	754-91-6

[a] PubChem CID http://www.ncbi.nlm.nih.gov/pccompound.

(GC-MS/MS) after an acid extraction for free BPA or after a liquid–liquid extraction and an enzymatic hydrolysis (*Helix pomatia* beta glucuronidase) for total BPA. The urinary concentrations of metabolites of phthalates were measured using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) after a liquid-solid extraction and an enzymatic hydrolysis (*Escherichia coli* beta-glucuronidase). The urinary concentrations of atrazine (and metabolites), propoxur (and metabolite), glyphosate (and metabolite) and DAP metabolites were quantified by ultra-high-

Table 2
Analytical performances of biomarker measurements realized in the perinatal component of the French HBM program.

Biomarkers	Biological sample	Volume needed	Analytical method	LOD	LOQ	Intra-day precision
Lead (μg/L)	Cord blood	0.5 mL	ICP-MS	0.60 μg/L	2.0 μg/L	12.0%
Mercury (μg/g hair)	Hair	5 μg	CVAAS	0.04 μg/g	0.14 μg/g	1.1%
Aluminum (μg/L)	Urine	1.5 mL[a]	ICP-MS	0.30 μg/L	1.0 μg/L	17.6%
Antimony (μg/L)	Urine		ICP-MS	0.003 μg/L	0.04 μg/L	16.7%
Arsenic (μg/L)	Urine		ICP-MS	0.06 μg/L	0.2 μg/L	8.2%
Cadmium (μg/L)	Urine		ICP-MS	0.02 μg/L	0.05 μg/L	13.6%
Cesium (μg/L)	Urine		ICP-MS	0.02 μg/L	0.05 μg/L	15.4%
Chromium (μg/L)	Urine		ICP-MS	0.006 μg/L	0.02 μg/L	18.1%
Cobalt (μg/L)	Urine		ICP-MS	0.006 μg/L	0.02 μg/L	10.6%
Tin (μg/L)	Urine		ICP-MS	0.01 μg/L	0.04 μg/L	9.4%
Nickel (μg/L)	Urine		ICP-MS	0.06 μg/L	0.2 μg/L	19.3%
Uranium (μg/L)	Urine		ICP-MS	0.003 μg/L	0.01 μg/L	6.8%
Vanadium (μg/L)	Urine		ICP-MS	0.02 μg/L	0.05 μg/L	21.3%
BPA	Urine	10 mL	GC-MS/MS	0.10 μg/L	0.30 μg/L	5.9%
MEP	Urine	10 mL[b]	LC-MS/MS	0.17 μg/L	0.50 μg/L	9.9%
MnBP	Urine		LC-MS/MS	0.17 μg/L	0.50 μg/L	10.5%
MiBP	Urine		LC-MS/MS	0.13 μg/L	0.40 μg/L	5.3%
MBzP	Urine		LC-MS/MS	0.10 μg/L	0.30 μg/L	9.3%
MEHP	Urine		LC-MS/MS	0.23 μg/L	0.70 μg/L	11.2%
MEHHP	Urine		LC-MS/MS	0.17 μg/L	0.50 μg/L	8.7%
MEOHP	Urine		LC-MS/MS	0.17 μg/L	0.50 μg/L	11.1%
MECPP	Urine		LC-MS/MS	0.17 μg/L	0.50 μg/L	9.0%
MOiNP	Urine		LC-MS/MS	0.23 μg/L	0.70 μg/L	5.1%
MHiNP	Urine		LC-MS/MS	0.23 μg/L	0.70 μg/L	7.7%
MCiOP	Urine		LC-MS/MS	0.23 μg/L	0.70 μg/L	6.4%
Atrazine	Urine	2 mL[c]	UPLC-MS/MS	0.01 μg/L	0.05 μg/L	3.0%
Atrazine mercapturate	Urine		UPLC-MS/MS	0.005 μg/L	0.02 μg/L	10.0%
Atrazine desethyl	Urine		UPLC-MS/MS	0.001 μg/L	0.003 μg/L	3.3%
Atrazine desisopropyl	Urine		UPLC-MS/MS	0.2 μg/L	0.5 μg/L	6.7%
Atrazine-desethyl-desisopropyl	Urine		UPLC-MS/MS	0.14 μg/L	0.5 μg/L	8.8%
Atrazine-2-hydroxy	Urine		UPLC-MS/MS	0.005 μg/L	0.02 μg/L	9.0%
Atrazine-desethyl-2-hydroxy	Urine		UPLC-MS/MS	0.09 μg/L	0.03 μg/L	9.1%
Atrazine-desisopropyl-2-hydroxy	Urine		UPLC-MS/MS	0.04 μg/L	0.1 μg/L	5.0%
Ammeline	Urine		UPLC-MS/MS	0.07 μg/L	0.2 μg/L	4.6%
Glyphosate/AMPA	Urine	1 mL[d]	UPLC-MS/MS	0.015 μg/L	0.05 μg/L	26.2%
Propoxur/2-IPP	Urine	2 mL[e]	UPLC-MS/MS	0.02 μg/L	0.05 μg/L	7.2%
DMP	Urine		UPLC-MS/MS	0.06 μg/L	0.2 μg/L	2.5%
DMTP	Urine		UPLC-MS/MS	0.2 μg/L	0.6 μg/L	7.4%
DMDTP	Urine		UPLC-MS/MS	0.1 μg/L	0.4 μg/L	8.1%
DEP	Urine		UPLC-MS/MS	0.2 μg/L	0.6 μg/L	8.4%
DETP	Urine		UPLC-MS/MS	0.2 μg/L	0.6 μg/L	1.8%
DEDTP	Urine		UPLC-MS/MS	0.005 μg/L	0.02 μg/L	8.5%
4-MCP	Urine	5 mL[f]	GC-MS	0.05 μg/L	0.15 μg/L	7.8%
2,4-DCP	Urine		GC-MS	0.05 μg/L	0.15 μg/L	3.2%
2,5-DCP	Urine		GC-MS	0.05 μg/L	0.15 μg/L	3.3%
2,4,5-TCP	Urine		GC-MS	0.05 μg/L	0.15 μg/L	3.0%
2,4,6-TCP	Urine		GC-MS	0.05 μg/L	0.15 μg/L	5.8%
PCP	Urine		GC-MS	0.05 μg/L	0.15 μg/L	9.7%
3-PBA	Urine	5.5 mL[g]	GC-MS	0.004 μg/L	0.014 μg/L	3.5%
4-F-3-PBA	Urine		GC-MS	0.005 μg/L	0.015 μg/L	4.9%
cis-DBCA	Urine		GC-MS	0.005 μg/L	0.016 μg/L	4.0%
cis-DCCA	Urine		GC-MS	0.003 μg/L	0.011 μg/L	3.9%
trans-DCCA	Urine		GC-MS	0.006 μg/L	0.019 μg/L	4.9%
Dioxin	Serum	9 mL[h]	GC-HRMS	0.3–1.9 pg/g lip	1.0–5.8 pg/g lip	20.4%
Furan	Serum		GC-HRMS	0.3–1.2 pg/g lip	0.9–3.7 pg/g lip	20.4%
PCB-DL	Serum		GC-HRMS	3.9–45.4 pg/g lip	11.5–136.0 pg/g lip	21.1%
PCB-NDL	Serum		GC-HRMS	17.8–55.3 pg/g lip	53.3–166.0 pg/g lip	14.9%
PBDE	Serum	7.5 mL[i]	GC-HRMS	0.01–0.3 ng/g lip	0.04–1.0 ng/g lip	17.7%
PBB-153	Serum		GC-HRMS	0.2 ng/g lip	0.6 ng/g lip	15.4%
HBCD (α, β, γ)	Serum		HPLC-MS/MS	0.1 ng/g lip	0.3 ng/g lip	21.0%
PFBA	Serum	0.5 mL[j]	LC-HRMS	0.2 μg/L	0.6 μg/L	7.7%
PFPA	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	9.4%
PFHxA	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	6.2%
PFHpA	Serum		LC-HRMS	0.08 μg/L	0.24 μg/L	4.9%
PFOA	Serum		LC-HRMS	0.05 μg/L	0.15 μg/L	8.0%
PFNA	Serum		LC-HRMS	0.05 μg/L	0.15 μg/L	8.4%
PFDA	Serum		LC-HRMS	0.07 μg/L	0.21 μg/L	13.8%
PFUnA	Serum		LC-HRMS	0.06 μg/L	0.18 μg/L	7.0%
PFDoA	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	22.0%
PFBS	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	9.1%
PFHxS	Serum		LC-HRMS	0.05 μg/L	0.15 μg/L	6.6%
PFHpS	Serum		LC-HRMS	0.07 μg/L	0.21 μg/L	6.3%
PFOS	Serum		LC-HRMS	0.05 μg/L	0.15 μg/L	7.0%
PFDS	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	4.2%
Et-PFOSA-AcOH	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	6.6%

Table 2 (*continued*)

Biomarkers	Biological sample	Volume needed	Analytical method	LOD	LOQ	Intra-day precision
Me-PFOSA-ACOH	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	10.6%
PFOSA	Serum		LC-HRMS	0.1 μg/L	0.3 μg/L	8.9%

Volume needed for the analysis of:
[a] All metals in urine.
[b] All phthalates metabolites.
[c] Atrazine and all metabolites.
[d] Glyphosate and AMPA.
[e] Propoxur, 2-IPP and DAP.
[f] Chlorphenols.
[g] Pyrethroids.
[h] Dioxins, furans and PCBs.
[i] BFRs.
[j] PFCs.

performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) after a liquid-solid extraction. Urinary concentrations of chlorophenols were analyzed using gas chromatography coupled to mass spectrometry (GC-MS) after liquid-liquid extraction. These analytical methods were validated according to the standard XPT 90-210 and used in previous studies conducted in France (Chevrier et al., 2011; Vandentorren et al., 2011). Analytical methods of BPA, phthalates, atrazine, propoxur, DAP and chlorophenols are described in detail in Supplemental material.

The analyses of pyrethroids were performed by the Toxicology Center of the National Institute of Public Health of Québec, Canada. The urinary concentrations of pyrethroids were quantified by GC-MS (Agilent 6890 N and Agilent 5973 N) using single ion monitoring (SIM) mode after an acid extraction and an enzymatic hydrolysis (beta-glucuronidase). The analytical method has been described in the framework of the Canadian Health Measures Survey (CHMS) (INSPQ, 2009).

The analyses of metals (except hair mercury) were performed by Chemtox, Illkirch, France. The concentrations of lead in cord blood and other metals in urine (aluminum, antimony, cadmium, cesium, chromium, cobalt, nickel, tin, uranium, vanadium) were quantified by inductively coupled plasma mass spectrometry (ICP-MS). The analytical method has been precisely described elsewhere (Goulle et al., 2003).

The analyses of mercury were performed by the Toxicology Center of the National Institute of Public Health of Québec, Canada. Hair mercury levels were measured in the 3 cm of the strand closest to the root (representing at least 5 μg of hair) using atomic absorption spectroscopy (AAS) coupled with cold vapor generation (CV-AAS), after an acid digestion, according to Democophes (DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale) recommendations (Esteban et al., 2015).

The analyses of dioxins (PCDD), furans (PCDF), PCBs (dioxin-like and no dioxin-like), BFRs and PFCs were performed by Laberca, Nantes, France. PCDD/PCDF and PCB measurements were performed by gas chromatography coupled to high-resolution mass spectrometry (GC-HRMS) (Hewlett Packard and Agilent) coupled to a JMS 700D or a JMS 800D double electromagnetic sector high resolution mass spectrometer (Jeol) (Kim et al., 2011). Chemical analyses of polybrominated diphenyl ethers (PBDEs) were also performed by GC-HRMS after a solid phase extraction (SPE C18) (Cariou et al., 2005). Hexabromocyclododecane (α-, β- and γ-) was quantified by high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) (Cariou et al., 2005), and polybromobiphenyl (PBB-153) was quantified by GC-HRMS (see Supplemental material for details on the analytical method of PBB-153). PFCs were measured by liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS) (Kadar et al., 2011). The analytical method used for the measurement of perfluorooctanesulfonamide (PFOSA) and its metabolites is not given in Kadar et al., 2011, but is described in Supplemental material.

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

Cholesterol and triglyceride levels were determined by Laberca through the enzymatic-colorimetric method, using serum obtained at the same time as the serum used for the persistent organic pollutants analyses. 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).

For each biomarker analysis, calibration standards were prepared by adding appropriate working standard solutions to fresh samples to control calibration in the measurement range (every 20 samples). Laboratory blanks and QC samples (spiked samples) were introduced into each batch of samples (every 10 samples) to verify the accuracy and precision of the measurements at, at least, three concentration levels within the measurement range. For all analyses, repeatability and reproducibility CVs were below 30% for concentration level at the LOQ (see Table 2). Mean standard uncertainty were below 30% in quality controls. Furthermore, a subset ($n = 90$) of control samples made up of glass bottled Evian® water, have been analyzed processing the same way as biological samples (aliquoting, transportation, sample preparation and analytical method). The purpose of these analyses was to ensure the absence of external contamination related to the equipment (e.g. cryotubes) used at every step of the collection and analysis. These tests were performed for chemicals that may be widely present in the environment: BPA, phthalates, pesticides, BFRs, PFCs, metals (e.g. aluminum).

The laboratories that carried out the biomarkers measurements have been chosen by Santé publique France in a call for tenders based on the merits of price, quality, performance, delivery, suitability and experience in HBM studies. These laboratories were certified to the NF EN ISO/CEI 17025 quality management and were COFRAC accredited. They all participated in inter-laboratory comparisons on a regular basis. All results produced by laboratories were validated by Santé publique France through a metrological approach to guarantee their reliability and the compliance with performances required. First, it was verified that the laboratory was respecting commitments on limits of detection and quantification, calibration frequency, internal quality controls frequency, analytical performance announced (repeatability, reproducibility and uncertainty). Then the metrological approach consisted in controlling the quality performances. For instance, laboratory blanks should not be quantified, calibration straight correlation coefficients had to be higher than 0.95, internal quality controls had to cover the required concentrations range and the CVs calculation method for internal quality controls was controlled. Finally, coherence controls were performed to identify potential outliers or unusual values (e.g. unusual high level in comparison to previous studies in general population or total BPA levels higher than free BPA levels).

Several studies (Adibi et al., 2009) suggested that creatinine adjustment might not be the optimal method of urinary dilution adjustment for pregnant women, as urinary creatinine levels may be unusually diluted or concentrated during pregnancy (Cheung and Lafayette, 2013). Therefore, results are presented in μg/L and in μg/g creatinine. Regarding

the increase in glomerular filtration rate during pregnancy (Cheung and Lafayette, 2013), it was also decided to not exclude pregnant women with creatinine levels below 0.3 g/L or upper to 3 g/L (threshold values that would reflect renal impairments in general population (World Health Organization, 1996)).

2.5. Statistical analysis

Different descriptive statistical analyses were performed taking into account the sampling design (except for serum biomarkers). For each biomarker, the geometric mean, median, 25th, 75th and 95th percentiles of the levels distribution were estimated.

In this study, left-censored data (i.e. chemical levels below the LOD or LOQ) were imputed using multiple imputations (ICE: STATA module). This method uses maximum likelihood estimates to approach distribution parameters. Available data were used to impute missing data, so that a complete data set can be created. Because the imputed values cannot be treated as actual measured data, the imputation process was repeated several times to create multiple complete data sets. Each complete data set was analyzed, and the results were combined to account for the uncertainty resulting from Multiple Imputation methods (Little Roderick and Rubin, 2002). If the proportion of results below the LOQs was >40%, geometric means were not calculated for that biomarker. For each biomarker, if the LOQ or LOD was above a given percentile estimate, the percentile was denoted as respectively "<LOQ" or "<LOD" and not reported. The statistical analysis was conducted using STATA 12 and the SURVEY package in R version 3.1.0.

3. Results

3.1. Study population

Table 3 shows the main characteristics of the study population. The proportion of primipara mothers was 43.0%, and mean age was 30.3 years (min: 18 years, max: 47 years). In the present study 42.3% of the pregnant women declared to be single or unmarried, 83% were born in France and about 90% had French nationality. Approximately a third of all pregnant women were overweight (body mass index, BMI 25–30 kg/m^2) or obese (BMI > 30 kg/m^2) before the present pregnancy. About 8% of the pregnant women declared having gestational diabetes during their pregnancy. Almost 30% of the study population did not achieved high school and higher education and 18.1% was unemployed. The proportion of farmers, employees, factory workers, artisans/independent retailers, executives, and intermediate professionals were 0.4, 38.1, 3.4, 2.8, 10.4 and 16.2%, respectively.

Except for serum biomarkers, the sample of pregnant women selected for biological analyses (in urine, cord blood and hair) was representative of the pregnant women having given birth in continental France in 2011. The subsample of pregnant women available for serum analyses was not reflective of the main characteristics of the whole pregnant women population. Indeed, in some regions of France (Picardie, Haute-Normandie, Centre, Ile-de-France) no or very few maternity units participated in the serum collection for the Elfe cohort. This impaired the regional coverage expected to have a representative sample of the pregnant women having given birth in continental France in 2011.

3.2. Biomonitoring results

Biomarker levels among French pregnant women are respectively shown in Tables 4 and 5 (results in μg/g creatinine are not shown).

Lead was quantified (i.e. over the LOQ) in almost all cord blood samples analyzed in the perinatal component of the French HBM program. The mean (geometric mean, GM) cord blood lead level among French pregnant women in 2011 was 8.30 μg/L and P95 was 24.3 μg/L.

Mercury was quantified in 90% of hair samples analyzed. GM of mercury in hair was 0.4 μg/g and P95 was 1.39 μg/g. Other metals measured in urine were also quantified in almost all pregnant women, except uranium. GM urinary concentrations of metals were: 0.12 μg/L (0.17 μg/g creatinine) for cadmium, 11.04 μg/L (15.05 μg/g creatinine) for total arsenic, 0.04 μg/L (0.06 μg/g creatinine) for antimony, 4.93 μg/L (6.72 μg/g creatinine) for cesium, 0.30 μg/L (0.41 μg/g creatinine) for

Table 3
Main characteristics of pregnant women selected in the perinatal component of the French HBM program.

Factors	Sample size	Percentage in the study population (weighted results)[a]	Percentage in the target population[b]
Age – classes[c] (%)			
18 to 21 years	101	6.6%	6.9%
22 to 24 years	202	7.3%	7.1%
25 to 29 years	688	31.5%	31.2%
30 to 34 years	667	33.4%	33.3%
35 to 39 years	259	16.7%	16.9%
≥40 years	53	4.5%	4.7%
Occupational category (%)			
Executive	208	10.4%	NA
Artisan/independent retailer	66	2.8%	NA
Farmer	8	0.4%	NA
Intermediate professional	368	16.2%	NA
Employee	847	38.1%	NA
Factory worker	44	3.4%	NA
Unemployed	190	18.1%	NA
Other	239	10.6%	NA
Residential region in France[c] (%)			
Ile-de-France/Picardie/Centre	396	29.8%	30.1%
North-eastern region	760	19.6%	19.2%
North-western region	370	15.8%	15.5%
South-eastern region	229	19.2%	19.6%
South-western region	215	15.7%	15.6%
Primipara[c] (%)			
Yes	937	43.0%	43.1%
No	1033	57.0%	56.9%
Gestational age (%)			
≤37 weeks	151	8.9%	12.3%
38 to 40 weeks	1428	71.9%	69.2%
>40 weeks	391	19.2%	18.5%
Education level[c] (%)			
None/primary education	423	27.6%	27.8%
High school	425	19.5%	19.9%
Higher education	1122	52.9%	52.3%
Birth place[c] (%)			
France	1808	83.2%	82.3%
Other country	162	16.8%	17.7%
Marital status (%)			
Married	953	56.8%	NA
Single/unmarried	677	42.3%	NA
Divorced/widow	13	0.9%	NA
Nationality (%)			
French	1574	87.6%	86.6%
Foreigner	84	12.4%	13.4%
BMI before pregnancy (%)			
<18,5 kg/m^2	125	7.1%	8.2%
18,5 to 24 kg/m^2	1036	63.4%	64.6%
25 to 29 kg/m^2	280	18.4%	17.3%
≥30 kg/m^2	214	11.1%	9.9%
Gestational diabetes			
No	1477	92.0%	92.5%
Yes	114	8.0%	7.5%

NA: not available.
[a] After adjustment taking into account the weighting scheme.
[b] Corresponding to the French women having given birth in continental France in 2001 (n ~ 754,008 women). Data from the Civil status or French Perinatal Study, 2010 http://www.sante.gouv.fr/enquete-nationale-perinatale-2010.html.
[c] Calibration covariate.

Table 4
Urinary levels of metals and organic compounds among French pregnant women having given birth in 2011 (weighted results).

Biomarkers		n	% > LOQ	GM (CI 95% GM)	P25	P50	P75	P95 (CI 95% P95)
Metals								
Lead (μg/L cord blood)		1968	99.5	8.30 (7.94, 8.68)	5.57	7.78	11.40	24.30 (20.72, 27.11)
Mercury (μg/g hair)		1799	90.9	0.40 (0.37, 0.42)	0.24	0.42	0.72	1.39 (1.30, 1.51)
Aluminum (μg/L urine)[a]		990	–	–	–	–	–	–
Antimony (μg/L urine)		990	70.0	0.04 (0.04, 0.05)	<LOQ	0.05	0.09	0.19 (0.18, 0.21)
Arsenic (μg/L urine)		990	100	11.04 (10.12, 11.89)	5.78	10.33	19.48	59.43 (48.42, 70.00)
Cadmium (μg/L urine)		990	87.8	0.12 (0.11, 0.13)	0.07	0.12	0.22	0.49 (0.41, 0.54)
Cesium (μg/L urine)		990	100	4.93 (4.64, 5.25)	3.18	5.14	7.99	14.96 (13.51, 16.26)
Chromium (μg/L urine)		990	96.2	0.30 (0.27, 0.34)	0.19	0.33	0.68	1.74 (1.37, 2.05)
Cobalt (μg/L urine)		990	100	0.85 (0.80, 0.91)	0.47	0.85	1.51	3.11 (2.83, 3.42)
Nickel (μg/L urine)		990	98.7	1.38 (1.30, 1.47)	0.81	1.50	2.34	4.96 (4.37, 5.52)
Tin (μg/L urine)		990	90.5	0.29 (0.25, 0.33)	0.14	0.33	0.75	2.82 (2.19, 3.66)
Uranium (μg/L urine)		990	27.6	NC	<LOD	<LOD	<LOQ	0.02 (0.02, 0.03)
Vanadium (μg/L urine)		990	95.6	0.28 (0.25, 0.31)	0.17	0.30	0.51	1.41 (1.02, 1.95)
Organic compounds								
Bisphenol A (μg/L urine)	Unconjugated	1764	10.7	NC	<LOD	<LOQ	<LOQ	0.55 (0.45, 0.60)
	Total	1764	73.8	0.69 (0.64, 0.74)	0.30	0.75	1.63	5.28 (4.50, 6.72)
Phthalates (μg/L urine)	MnBP	989	82.2	5.01 (4.05, 6.20)	1.63	8.45	29.12	236.31 (170.40, 324.27)
	MiBP	989	83.1	4.33 (3.46, 5.43)	1.41	6.83	27.07	221.68 (161.54, 288.35)
	MBzP	989	66.6	0.82 (0.68, 0.99)	<LOQ	1.16	5.42	42.80 (32.20, 57.85)
	MEP	989	90.2	35.40 (27.39, 45.39)	7.10	58.66	296.77	2083.80 (1341.46, 2948.28)
	MEHP	989	70.8	1.60 (1.40, 1.84)	<LOQ	1.64	5.39	37.21 (28.79, 53.63)
	MEOHP	989	61.2	0.80 (0.65, 0.99)	<LOD	1.03	4.86	45.05 (33.53, 57.80)
	MEHHP	989	69.1	1.15 (0.93, 1.43)	<LOD	1.72	7.01	57.32 (41.49, 81.41)
	MECPP	989	80.2	3.03 (2.49, 3.68)	0.93	4.54	15.22	93.87 (59.14, 121.45)
	ΣDEHP[b]	989	–	7.36 (6.24, 8.60)	2.24	8.28	28.68	177.14 (137.27, 312.00)
	MHiNP	989	70.4	2.11 (1.68, 2.64)	<LOQ	3.29	15.27	90.97 (70.28, 106.21)
	MOiNP	989	18.0	NC	<LOD	<LOD	<LOQ	8.79 (4.70, 12.73)
	MCiOP	989	82.2	5.19 (4.25, 6.30)	1.79	7.45	23.19	165.85 (131.15, 200.90)
	ΣDiNP[c]	989	–	11.00 (9.10, 12.99)	3.41	13.31	45.42	276.92 (214.92, 320.94)
Herbicides (μg/L urine)	Atrazine	1036	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	A. mercapturate	1036	0.6	NC	<LOQ	<LOQ	<LOQ	<LOQ
	A. desethyl	1036	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	A. desisopropyl	1036	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	A. desethyl desisopropyl	1036	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	A. hydroxy	1036	0.9	NC	<LOQ	<LOQ	<LOQ	<LOQ
	A. hydroxy desethyl	1036	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	A. hydroxy desisopropyl	1036	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Ammeline	1036	0.1	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Glyphosate	1036	0.3	NC	<LOQ	<LOQ	<LOQ	<LOQ
	Ampa	1036	0.1	NC	<LOQ	<LOQ	<LOQ	<LOQ
Carbamate (μg/L urine)	Propoxur	1036	3.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
	2 IPP	1036	17.0	NC	<LOQ	<LOQ	<LOQ	0.25 (0.20, 0.28)
Chlorophenols (μg/L urine)	4-MCP	1036	1.4	NC	<LOQ	<LOQ	<LOQ	<LOQ
	2.4 DCP	1036	6.2	NC	<LOQ	<LOQ	<LOQ	0.21 (<LOQ, 0.35)
	2.5 DCP	1036	4.6	NC	<LOQ	<LOQ	<LOQ	<LOQ
	2.4.5 TCP	1036	0.4	NC	<LOQ	<LOQ	<LOQ	<LOQ
	2.4.6 TCP	1036	0.6	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PCP	1036	4.2	NC	<LOQ	<LOQ	<LOQ	<LOQ
Dialkyl phosphates (μg/L urine)	DMP	1036	28.2	NC	<LOD	<LOD	2.22	64.36 (43.67, 95.11)
	DETP	1036	20.5	NC	<LOD	<LOD	0.29	2.54 (1.95, 3.05)
	DMTP	1036	9.3	NC	<LOQ	<LOQ	<LOQ	2.53 (1.34, 3.75)
	DMDTP	1036	8.5	NC	<LOQ	<LOQ	<LOQ	4.16 (2.34, 6.37)
	DEP	1036	4.3	NC	<LOQ	<LOQ	<LOQ	<LOQ
	DEDTP	1036	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
Pyrethroids (μg/L urine)	3-PBA	1077	99.7	0.36 (0.33, 0.38)	0.18	0.36	0.73	1.89 (1.59, 2.19)
	4-F-3-PBA	1059	5.7	NC	<LOQ	<LOQ	<LOQ	0.02 (<LOQ, 0.30)
	cis-DBCA	1077	99.6	0.23 (0.21, 0.25)	0.11	0.23	0.46	1.38 (1.30, 1.49)
	Cis-DCCA	1056	99.8	0.16 (0.15, 0.17)	0.08	0.16	0.30	0.91 (0.77, 0.98)
	Trans-DCCA	1077	99.3	0.27 (0.25, 0.30)	0.12	0.26	0.57	2.29 (1.61, 2.73)
	∑ Pyrethroids[d]	1056	–	1.18 (1.10, 1.27)	0.61	1.14	2.26	6.20 (5.17, 7.42)

GM: geometric mean; NC: geometric mean not calculated because of large amount of left-censored biomarker levels (% > detection <60%).
[a] Biological measurements not validated because of a blanks contamination.
[b] ΣDEHP: sum of MEHP, MEOHP, MEHHP and MECPP.
[c] ΣDiNP: sum of MHiNP, MOiNP and MCiOP.
[d] ∑Pyrethroids = ∑(3-PBA; cis-DBCA; cis-DCCA; trans-DCCA).

chromium, 0.85 μg/L (1.16 μg/g creatinine) for cobalt, 1.38 μg/L (1.89 μg/g creatinine) for nickel, 0.29 μg/L (0.39 μg/g creatinine) for total tin, 0.28 μg/L (0.38 μg/g creatinine) for vanadium. GM was not calculated for uranium because of the lack of quantified measurements.

Free BPA was quantified in only 33% of pregnant women, whereas total BPA was quantified in almost 74% of pregnant women. GM of total BPA in urine was 0.69 μg/L (0.87 μg/g creatinine) and P95 was 5.28 μg/L (6.03 μg/g creatinine).

Metabolites of phthalates were quantified in almost all pregnant women. GM of metabolites of DEHP was 7.4 μg/L (10.0 μg/g creatinine) and P95 was 177.1 μg/L (152.3 μg/g creatinine). GM of metabolites of DINP was 11.0 μg/L (15.0 μg/g creatinine) and P95 was 276.9 μg/L

Table 5
Serum levels of persistent organic compounds among French pregnant women (unweighted results).

Biomarkers		n	% > LOQ	GM (CI 95% GM)	P25	P50	P75	P95
Dioxins (pg/g lip)	2, 3, 7, 8 – TCDD	207	3.9	NC	<LOD	<LOQ	<LOQ	<LOQ
	1, 2, 3, 7, 8 – PCDD	197	66.0	1.60 (1.51, 1.70)	<LOQ	1.69	2.01	3.01
	1, 2, 3, 4, 7, 8 – HxCDD	187	8.0	NC	<LOQ	<LOQ	<LOQ	1.97
	1, 2, 3, 6, 7, 8 – HxCDD	208	98.6	4.65 (4.35, 4.97)	3.38	4.79	6.42	10.69
	1, 2, 3, 7, 8, 9 – HxCDD	138	13.0	NC	<LOQ	<LOQ	<LOQ	2.20
	1, 2, 3, 4, 6, 7, 8 – HpCDD	208	100	7.98 (7.35, 8.61)	5.18	7.48	10.80	20.48
	OctaCDD (OCDD)	208	100	77.66 (72.72, 83.01)	57.17	74.36	97.60	204.61
	ΣPCDD	128	–	99.48 (91.68, 108.40)	75.21	92.57	120.23	232.81
Furans (pg/g lip)	2, 3, 7, 8 – TCDF	207	1.0	NC	<LOD	<LOQ	<LOQ	<LOQ
	1, 2, 3, 7, 8 – PCDF	207	1.0	NC	<LOD	<LOD	<LOD	<LOQ
	2, 3, 4, 7, 8 – PCDF	208	99.5	3.40 (3.21, 3.61)	2.69	3.34	4.46	6.79
	1, 2, 3, 4, 7, 8 – HxCDF	208	79.3	1.39 (1.33, 1.45)	1.12	1.36	1.73	2.42
	1, 2, 3, 6, 7, 8 – HxCDF	208	87.5	1.50 (1.43, 1.57)	1.24	1.45	1.84	2.64
	1, 2, 3, 7, 8, 9 – HxCDF	207	0.0	NC	<LOD	<LOD	<LOD	<LOQ
	2, 3, 4, 6, 7, 8 – HxCDF	198	3.5	NC	<LOD	<LOQ	<LOQ	<LOQ
	1, 2, 3, 4, 6, 7, 8 – HpCDF	120	22.5	NC	<LOQ	<LOQ	<LOQ	4.14
	1, 2, 3, 4, 7, 8, 9 – HpCDF	207	0.0	NC	<LOD	<LOD	<LOD	<LOQ
	OctaCDF (OCDF)	207	0.5	NC	<LOD	<LOQ	<LOQ	<LOQ
	ΣPCDF	118	–	13.99 (13.41, 14.59)	11.65	14.13	16.04	20.54
PCB (ng/g lip)	PCB 52	52	100	0.14 (0.12, 0.15)	0.10	0.13	0.17	0.27
	PCB 77	207	8.20	NC	<LOQ	<LOQ	<LOQ	0.02
	PCB 81	208	0.0	NC	<LOQ	<LOQ	<LOQ	<LOQ
	PCB 101	206	99.5	0.20 (0.19, 0.22)	0.13	0.20	0.27	0.65
	PCB 105	208	100	1.04 (0.96, 1.12)	0.70	1.02	1.46	3.01
	PCB 114	207	98.1	0.21 (0.19, 0.22)	0.15	0.20	0.29	0.54
	PCB 118	208	100	4.80 (4.46, 5.15)	3.41	4.87	6.33	11.84
	PCB 126	208	83.2	0.02 (0.02, 0.02)	0.01	0.02	0.03	0.04
	PCB 138	208	100	11.13 (10.33, 11.94)	7.54	11.13	15.61	27.25
	PCB 153	208	100	21.45 (19.72, 23.11)	14.04	21.63	31.36	53.98
	PCB 156	208	100	1.98 (1.83, 2.16)	1.36	2.01	3.04	5.02
	PCB 157	189	98.9	0.32 (0.29, 0.35)	0.22	0.31	0.48	0.78
	PCB 167	208	100	0.60 (0.56, 0.65)	0.41	0.61	0.84	1.54
	PCB 169	208	47.6	NC	<LOQ	<LOQ	0.02	0.03
	PCB 180	208	100	15.69 (14.21, 17.07)	9.89	16.11	25.46	42.68
	ΣPCB total[a]	208	–	82.53 (76.41, 88.47)	54.01	84.79	122.35	209.74
BFR (ng/g lip)	BDE 17	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	BDE 28	277	16.2	NC	<LOQ	<LOQ	<LOQ	0.07
	BDE 47	277	99.6	0.24 (0.22, 0.26)	0.13	0.21	0.36	1.23
	BDE 66	277	1.1	NC	<LOD	<LOD	<LOD	<LOD
	BDE 85	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	BDE 99	277	48.4	NC	<LOQ	<LOQ	0.09	0.32
	BDE 100	277	71.8	0.08 (0.07, 0.09)	<LOQ	0.07	0.12	0.33
	BDE 153	277	99.3	0.49 (0.45, 0.52)	0.36	0.46	0.64	1.13
	BDE 154	277	1.1	NC	<LOD	<LOD	<LOD	<LOQ
	BDE 183	277	2.5	NC	<LOD	<LOD	<LOQ	<LOQ
	BDE 209	277	89.9	1.46 (1.38, 1.55)	1.07	1.44	1.97	3.41
	ΣPBDE[b]	277	–	2.78 (2.64, 2.92)	2.12	2.63	3.33	5.66
	Hexa-BB 153	277	1.4	NC	<LOD	<LOD	<LOD	<LOQ
	HBCD	277	12.6	NC	<LOQ	<LOQ	<LOQ	1.49
PFC (μg/L serum)	PFBA	277	0.0	NC	<LOD	<LOD	<LOD	<LOQ
	PFPeA	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	PFHxA	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	PFHpA	277	0.4	NC	<LOD	<LOD	<LOD	<LOQ
	PFOA	277	100	1.49 (1.39, 1.59)	1.07	1.51	2.14	3.70
	PFNA	277	100	0.52 (0.49, 0.55)	0.39	0.48	0.65	1.34
	PFDA	277	67.9	0.26 (0.24, 0.28)	<LOQ	0.25	0.34	0.76
	PFUnA	277	30.3	NC	<LOQ	<LOQ	0.21	0.36
	PFDoA	277	0.4	NC	<LOD	<LOD	<LOD	<LOD
	PFBS	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	PFHxS	277	99.6	0.74 (0.68, 0.79)	0.49	0.73	1.05	2.10
	PFHpS	277	7.2	NC	<LOD	<LOQ	<LOQ	0.24
	PFOS	277	100	3.07 (2.87, 3.27)	2.12	2.96	4.32	7.85
	PFDS	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	Et-PFOSA-AcOH	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	Me-PFOSA-ACOH	277	1.4	NC	<LOD	<LOD	<LOD	<LOD
	PFOSA	277	0.0	NC	<LOD	<LOD	<LOD	<LOD
	ΣPFC	277	–	7.66 (7.29, 8.05)	5.67	7.49	9.75	16.24

GM: geometric mean; NC: geometric mean not calculated because of large amount of left-censored biomarker levels (% > LOQ <60%).
[a] ΣPCB total: sum (PCB 138, 153, 180) * 1,7.
[b] ΣPBDE: sum of BDE 28, 47, 99, 100, 153, 154, 183 and 209.

(226.4 μg/g creatinine). Among metabolites of phthalates analyzed in this study, MEP (metabolite of DEP) was the one that was mainly quantified with the highest levels.

The DEHP metabolite ratios have been calculated for each woman (see Table 6). The mean ratios (arithmetic mean) of MEHP to MEOHP, MEHP to MEHHP and MEHP to MECPP, were respectively 1 to 1.7, 1 to

Table 6
Concentrations ratios between MEHP and oxidized metabolites of DEHP.

	Lowest ratio	Highest ratio	Mean ratio (arithmetic mean)	Median
MEHP:MEOHP	1:0.01	1:42.9	1:1.7	1:0.7
MEHP:MEHHP	1:0.01	1:187.4	1:3.4	1:1.1
MEHP:MECCP	1:0.01	1: 490.4	1:9.5	1:2.9

3.4 and 1 to 9.5. However, variations between minimal and maximal ratios, and between median and mean ratios, were high.

Herbicides (atrazine and metabolites, glyphosate and its metabolite AMPA) were quantified in <1% of the French pregnant women. Propoxur or its metabolite (2-IPP) was quantified in one out of five pregnant women (GM not calculated). Chlorophenols were quantified in one out of ten pregnant women (GM not calculated). One out of two pregnant women had quantified levels of DAP. However, considering every single metabolite, quantifying rates were low (between 0% and 28%). The highest levels among the six DAP metabolites monitored in this study, were observed for dimethyl phosphate (DMP).

Metabolites of pyrethroid pesticides were found in all French pregnant women, with the exception of 4-F-3-PBA. GM of pyrethroids (sum of metabolites) in urine was 1.18 μg/L (1.65 μg/g creatinine) and P95 was 6.20 μg/L (6.89 μg/g creatinine).

Persistent organic pollutants were quantified in almost all pregnant women; however quantification varied depending on the congener. The highest level among dioxins measured in serum was observed for OctaCDD. Among furans the highest level was observed for 2, 3, 4, 7, 8 – PCDF. Serum levels of PCBs non dioxin-like were higher than those measured for PCB dioxin-like. BDE-209 alone contributed to >50% of the total concentration level of all BFR congeners. Five congeners of PFCs (PFOS, PFOA, PFNA, PFHxS and PFDA) contributed to 80% of total internal concentrations to these pollutants. In this paper, the levels given for serum biomarkers are not weighted. GM concentrations (unweighted) were as follows: 9.1 ng/g lip (7.4 pg-TEQ2005/g lip) for total dioxins, furans and PCB-DL, 82.5 ng/g lip (810.8 ng/L) for total PCBs (calculated as the sum of PCB 138, 153, 180 multiplied by 1.7), 2.8 ng/g lip (27.2 ng/L) for total BFRs, 0.8 μg/g lip (7.7 μg/L) for total PFCs.

4. Discussion

4.1. Main findings

BPA, phthalates, pesticides (mainly pyrethroids), dioxins and furans, PCBs, BFRs, PFCs and metals (except uranium) were quantified in almost all women.

Lead levels in cord blood were lower than those measured in previous similar studies conducted among pregnant women in France (Gottot et al., 2014; Smargiassi et al., 2002; Vandentorren et al., 2013; Yazbeck et al., 2006). This finding was consistent with the downward trend in lead exposure observed in France and Europe since 1990 (Bierkens et al., 2011). In comparison with previous studies conducted among pregnant women or women of childbearing age, hair mercury levels in this study were slightly lower than those previously measured in France (Chevrier et al., 2013; Drouillet-Pinard et al., 2010; Huel et al., 2008; Pouzaud et al., 2010), but remained higher than levels measured in some European countries (in central Europe) (Castano et al., 2015) and in United-States (McDowell et al., 2004), probably in relation with higher sea-products consumption among French population (http://faostat.fao.org). Other metallic compounds levels were quite similar to those observed in previous surveys conducted in Spain (Fort et al., 2014), United States (Jain, 2013), Canada (Foster et al., 2012), and Australia (Callan et al., 2013) among pregnant women. The presence of aluminum in some blanks and control water samples highlighted the risk of external contamination by this metal. Therefore biological measurements of aluminum in urine samples were not validated, and could not be presented in this paper.

Based on spot urine sample, total BPA, phthalates and pesticides urinary levels in the perinatal component were slightly lower than those observed in previous studies conducted in France and abroad among pregnant women (Casas et al., 2011; Chevrier et al., 2009; Frederiksen et al., 2014; Mortensen et al., 2014; Philippat et al., 2012; Vandentorren et al., 2013; Ye et al., 2008; Ye et al., 2009). However, total BPA and phthalates levels were similar to those reported in most recent studies also based on spot urine samples collected among pregnant women: TIDES conducted in U.S 2010–2012 (Serrano et al., 2014) and MIREC conducted in Canada 2008–2011 (Arbuckle et al., 2014). These decreases may partly be explained by measures taken to prohibit some of these chemicals (atrazine) and by industrial processes evolutions leading to the substitution of others (BPA, phthalates). However, the methodological differences between studies such as biological samples collection (first urine samples versus spot urine samples) or analytical methods could also explain the concentration differences observed. The mean ratios between DEHP metabolites were within the range of those reported in other publications in the first elimination phase (8 to 14 h post dose), but were somewhat lower than those reported up to 24 h post dose (Koch et al., 2004). Moreover, significant variations were observed between individual ratios suggesting a significant inter-individual variability for these biomarkers in our study. Given the short half-lives of these biomarkers, this variability could be explained by the urine collection method employed in the Elfe cohort, as spot urine collection does not allow homogenizing exposure within the few past hours prior to the urine collection.

On the opposite, pyrethroid levels measured in French pregnant women were higher than those observed in northern America (Castorina et al., 2010). Overexposure of French population to pyrethroids was already highlighted in the French National Nutrition and Health Survey, 2007 (ENNS). One hypothesis put forward was the lifestyle characteristics of the French population including higher domestic use of pesticides (Frery et al., 2012a).

Dioxins and furans levels measured among a selection of French pregnant women were lower than those observed in previous studies conducted in France for general population (women, >18 years) (Anses and Institut de veille sanitaire, 2011; Frery et al., 2007) and nursing women (Frery et al., 2000; Vandentorren et al., 2013). PCBs levels measured in this study were higher than those found in northern America (Foster et al., 2012; Woodruff et al., 2011; Zota et al., 2013), whereas BFRs levels were lower than in northern America (Abdelouahab et al., 2013; Braun et al., 2014; Buttke et al., 2013; Foster et al., 2011; Horton et al., 2013). Although these levels were not representative of the French pregnant women, the differences across countries and over time may partly be related to regulatory specificities taken to limit exposure to these chemicals. PFCs levels were quite similar to those previously found in France and abroad (Braun et al., 2014; Cariou et al., 2015; Fromme et al., 2010; Hoyer et al., 2015; Starling et al., 2014; Velez et al., 2015).

4.2. Strengths and weakness

For the first time in France, the perinatal component of the French HBM program provides a national representative description of biomarkers levels of priority environmental contaminants among pregnant women who gave birth in France in 2011. These results provide relevant information about prenatal exposures that may later impair child health.

Comparisons with results previously obtained in the French population provide hypothesis about the effects of regulations taken to limit exposures to some chemicals or evolutions of industrial processes. Whereas comparisons with results obtained abroad provide insights of potential overexposure in France in relation mostly to other European countries or to northern America.

However interpretation of these findings warrants caution given the specificities of the study design and the methodological aspects of the Elfe cohort. On the one hand, it was not possible to have a nationwide representative description of PCDD/F, PCBs, BFRs and PFCs levels among French pregnant women. This impaired the coverage of all regional specificities that could contribute to overall exposure, such as sea food consumption in coastal regions for exposure to PCBs. On the other hand, short half-life biomarkers (e.g. BPA, di-2-ethylhexyl phthalate, chlorophenols and dialkylphosphates) were measured in spot urine samples instead of usual first morning urines. It may be understandable that inter-individual variability was high for these biomarkers. The existence of an individual misclassification of exposure could not be excluded either, because of the circadian variability of short half-life biomarkers concentrations. Moreover, various metabolic and physiological changes occur in the women during pregnancy, particularly regarding blood volume (Hytten, 1985), glomerular filtration (Cheung and Lafayette, 2013), iron status (Milman, 2006; Rukuni et al., 2015) and calcium metabolism (Pitkin et al., 1979). These adaptations may influence the concentrations of some biomarkers in biological samples, such as blood lead levels (Gulson et al., 2004), other metals concentrations (Barany et al., 2005; Hansen et al., 2011), as well as phthalates and BPA urinary levels (Braun et al., 2012). Therefore, the characteristics of the study population (pregnant versus non pregnant women) have to be highly considered when comparing the results of HBM studies. Other methodological aspects that might impact biomonitoring results should be considered: procedures related to collection of biological samples and progressive improvements in measurements of emerging substances (e.g. BPA) (Lakind et al., 2012).

5. Conclusions

The present results show that French pregnant women may be exposed to a wide variety of pollutants, even if some of them are henceforth banned or restricted in France. Levels observed in this study were usually in the range of those found in previous surveys conducted in France and abroad. However, these finding warrants caution because of a potential exposure misclassification due to the single biomarker measurement, the metabolic changes that occur during pregnancy and the lack of representativeness of some results.

Analysis of characteristics of the mother's environment and behaviors related to biomarkers levels will provide insights on the factors that influence exposures in this subset of the French population. These results will be published in future articles.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.envint.2016.10.013.

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