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Exposure to phenols during pregnancy and the first year of life in a new type of couple-child cohort relying on repeated urine biospecimens

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ABSTRACT

Background: Parabens, bisphenol A and triclosan have been forbidden or restricted in specific types of consumer goods in Europe and France. Limited biomonitoring data are available in France since the implementation of these regulations, and exposure data on infants is scarce worldwide. Understanding the predictors of phenol urinary concentrations will help identify potential targets for prevention.

Aim: We described levels, variability and predictors of exposure to 12 phenols in pregnant women and infants recruited between 2014 and 2017 in a French couple-child cohort.

Methods: Among 479 pregnant women and 150 of their infants, we studied phenol urinary concentrations in within-subject, within-period pools of repeated urine samples collected during the second and third trimesters of pregnancy (up to 42 samples per woman), at 2 months and 12 months (up to 14 samples per infant). Time trends and associations with demographic, protocol, occupational and behavioral factors were studied using interval censored models to accommodate for undetected and unquantified urine concentrations.

Results: Detection rates were above 90% for bisphenol A, ethylparaben, methylparaben, benzophenone-3 and triclosan and below 5% for bisphenol AF, B, F and triclocarban. Median levels of bisphenol A, bisphenol S, methylparaben, ethylparaben and propylparaben at 12 months were similar or higher than during pregnancy. For pregnant women all phenols but benzophenone-3 and bisphenol S showed a linear decrease between 2014 and 2017 (p-values < 0.02). Women with the shortest education (primary and secondary school) had higher urinary concentrations of triclosan ($\beta = 0.58$ (95% confidence interval (CI), -0.04; 1.20)), ethyl ($\beta = 0.43$ (95%CI, 0.03; 0.84)) and propyl paraben ($\beta = 1.39$ (95%CI, 0.55; 2.24)) than those with the longest education. Cashiers had higher conccentrations of bisphenol S ($\beta = 0.99$ (95%CI, -0.11; 2.09)) but not of bisphenol A ($\beta = -0.04$ (95%CI, -0.26; 0.19)) than unemployed women.

Conclusions: Despite recent regulations, bisphenol A, triclosan and paraben detection rates were high in women and young infants. High bisphenol and paraben median levels at 12 months require further investigation as early infancy is a sensitive period for exposure to environmental contaminants.

1. Introduction

Phenols and parabens are man-made chemicals used in many common products as preservatives (parabens), plasticizers (bisphenols) or antibacterial agents (triclosan). Some of these compounds are endocrine disruptors and their widespread use in industrial applications

Abbreviations: ATS, Akritas-Thiel-Sen; CI, confidence interval; ICC, Intraclass Correlation Coefficient; SG, specific gravity; LOD, limits of detection; LOQ, limit of quantification

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has led to frequent exposure in the general population including vulnerable populations such as pregnant women and children (Haug et al., 2018). These selected phenols can disrupt pathways involved in fetal development (e.g., homeostasis of the steroid or thyroid hormones (Braun, 2017; Mustieles et al., 2015; Nesan et al., 2018)) and several epidemiological studies have reported associations between prenatal exposure to these compounds and health outcomes including child behavior (Jackson-Browne et al., 2019; Mustieles et al., 2015; Philippat et al., 2017) and child growth (Etzel et al., 2017; Ferguson et al., 2017; Lassen et al., 2016; Philippat et al., 2014); some of these associations being supported by animal literature (Rochester et al., 2018).

In France and the E.U., legislations regarding the use of these compounds in consumer products have been implemented in the past decades. Use of parabens and triclosan in cosmetics, and triclosan in mouthwashes and toothpastes was restricted in 2009 and then again in 2014 for methyl, propyl paraben and triclosan (EU regulations 358/2014 and 1004/2014). Bisphenol A was banned from food packaging, infant feeding bottles and kitchenware with effect for the whole population in 2015 (French regulation (n° 2012–1442)). Despite this regulation, recent biomonitoring data in France (2014–2016) showed ubiquitous detection (100%) of bisphenol A in urine of children (6 to 17 years) and adults (Santé publique France, 2019). Among pregnant women French biomonitoring data date back to 2011 for bisphenol A (ELFE national cohort, (Dereumeaux et al., 2016)) and 2006 for the other phenols (EDEN cohort, (Philippat et al., 2017)) preventing us to identify if, in this sensitive population, regulations were followed with a decrease in exposure levels. Although the first year of life is considered to be a period of high sensitivity for the effects of environmental chemicals, data on infant exposure levels to phenols are rare (Kang et al., 2013; Mendonca et al., 2014; Nachman et al., 2015), likely due to the difficulties linked to urine collection in infants in a non-clinical setting.

Understanding the predictors of phenol urinary concentrations is critical to identify potential targets for prevention. Several studies have highlighted predictors of exposure to phenols during pregnancy including socio-economic factors (highest paraben concentrations being observed among women with the highest education levels (Casas et al., 2011; Montazeri et al., 2019)), use of personal care products (positive associations with paraben concentrations (Ashrap et al., 2018; Braun et al., 2013)), specific occupation (cashiers having higher BPA levels (Braun et al., 2011)) and dietary habits (consumption of canned food increased BPA concentrations (Braun et al., 2011)). Most of these studies measured phenols in one to three spot urine samples, which given the short half-life of these compounds, is likely to only give an indication of exposure over the last half-day or day. In addition, studies including infants are scarce (Calafat et al., 2009; Fisher et al., 2019; Kim et al., 2018) and none have taken place in France where laws and behaviors might differently impact exposure levels.

In this study we relied on a French couple-child cohort recruited between 2014 and 2017, with repeated urine samples collected during pregnancy and early infancy to:

1) describe urinary concentrations of 12 phenols during pregnancy and the first year of life and their recent trends over time;
2) explore the associations between sampling protocol, socio-demographic, occupation and behavioral factors and the phenol urinary concentrations among pregnant women and their infants.

2. Methods

2.1. Study population

We relied on the SEPAGES mother-child cohort, in which 484 pregnant women were recruited from Grenoble and its immediate surroundings (less than one hour drive) between July 2014 and July 2017. Eligibility criteria were 1) being pregnant by less than 19 gestational weeks at inclusion, 2) being older than 18 years old, 3) to read and speak French fluently, 4) to be affiliated to the French national security system, and 5) to plan to deliver in one of the four maternity clinics of the area. Multiple pregnancies were excluded. Most included volunteers were recruited by a field worker (90%) in obstetrical ultrasonography practices located in the Grenoble area while the remaining 10% signed up after reading the SEPAGES brochure in a medical center. The study was approved by the relevant ethical comities (CPP: Comité de Protection des Personnes Sud-Est V) and the CNIL (Comité Nationale Informatique et Liberté). Both the mother and the father of the expected child signed an informed consent form for themselves and their infant prior to inclusion.

2.2. Urine samples collection

Women were asked to collect 3 spot urine samples (morning, midday, evening) per day over 7 consecutive days at the second and third trimester of pregnancy and then to collect from their infant one urine sample per day over 7 consecutive days around the second month and first year of life. Infant urine samples were collected using a cotton gaze insert in the diaper. When stool was present in the diapers, participants were asked to re-perform the urine collection.

All the sampling material (collection tubes, cotton gaze) except for the diapers, were provided by SEPAGES fieldworkers. Urine collection tubes and cryotubes were in polypropylene and high-density polyethylene and certified free of bisphenol A by the providers. After collection, spot urine samples were stored at −20 °C in the participant's personal freezer until SEPAGES field workers picked them up at the end of the collection week and transported them to the certified biobank of the Grenoble University Hospital (bb-0033-00069). The biobank thawed the samples at 4°C overnight and made within-subject weekly pools by pooling equal volume of all the spot urine samples collected over the collection week. Pooling biospecimen within-subjects enabled us to take advantage of repeated measures for each subject without increasing the total cost of phenol measurements (Perrier et al., 2016; Vernet et al., 2019).

2.3. Assessments of phenols

Urine weekly pools were sent for phenol assessments to the Norwegian Institute of Public Health (Oslo, Norway) on dry ice with a temperature sensor to confirm that the samples were kept frozen during the transfer. We measured the total (free + conjugated) urinary concentrations of 12 phenols: 4 parabens (methyl, ethyl, propyl, butylparaben), benzophenone-3, triclosan, triclocarban and 5 bisphenols (A, S, F, B, AF) in all available maternal pooled samples using ultra performance liquid chromatography coupled to mass spectrometry (UPLC-MS-MS) as described elsewhere (Sakhi et al., 2018). In brief, to 200 μL of urine sample, internal standards and enzyme solution (beta-glucuronidase/sulfatase in ammonium acetate buffer, pH 5.0) were added. The samples were incubated for 4 h at 37 °C. After 4 h, 40% formic acid were added to stop the enzymatic reaction. The samples were centrifuged and 80 μL of the supernatant was injected into the UPLC-MS-MS system. The accuracy established through a validation experiment of the method ranged from 75% to 120% (Sakhi et al., 2018). Both in-house pooled urine samples and standard reference material from National Institute of Standards and Technology (NIST) were analyzed along with the samples, and the precision was below 26% for the phenols. For funding reasons, total phenols were only measured in the 150 first infants with available samples at 2 months. For the assessments at 12months, 100 infants were randomly selected among those with assessment at 2 months. In addition, free phenol concentrations were measured at the second and third trimester for a subsample of 50 randomly selected women (total, 100 samples) and for all infant samples with a total phenol concentration, as their protocol for urine collection was at higher risk of contamination through diapers. To assess potential contamination from the collection material,

material used for urine collection (urine collection tubes, cryotubes, pipettes, syringes and the plastic tweezers used to extract the infant urine from the cotton inserted in the diapers) was put in contact with LC-MS grade water from J.T. Baker in which phenol free concentrations were then assessed using the methods described above for the urine. Most of the sampling material was tested except diapers (not provided by the study team) and the cotton inserted in the diapers.

2.4. Statistical analyses

Phenols detected in less than 4% of all urine samples were excluded from further analysis. This corresponded to bisphenols F (frequency of detection: 1.7%), B (0.0%), AF (0.2%) and triclocarban (0.8%).

Descriptive analysis: Each phenol had a specific limit of detection (LOD) and limit of quantification (LOQ) (Table 3). First we described for each compound and sampling period the percentage of samples with detectable levels (> LOD) and quantifiable levels (> LOQ), and the 5th, 50th and 95th percentiles. The same descriptive table was then produced on specific gravity corrected concentrations using (Philippat et al., 2013):

$$C_{correctedi} = \frac{C_i * mean(SG) - 1}{SG_i - 1}$$

where C_i was the concentration of sample *i*, SG_i was the specific gravity of sample *i*, *mean(SG)* the average SG in our study population and $C_{correctedi}$ the SG corrected concentration of sample *i*.

Urine concentration variability between sampling periods: To assess the correlation between the different periods of urine collection, we computed Spearman's correlation coefficients (rho) for the 100 mother-infant pairs with measurements at all 4 time points (2nd and 3rd trimesters, 2 months and 12 months). The within pregnancy correlation was computed between the measurement at the second and third trimesters, the within infanthood correlation was computed between the measurement at 2 and 12 months and the *between mother and infant* correlation was computed between the mean measurement at the 2nd and 3rd trimesters and the mean measurement at 2 and 12 months. Samples below LOD were all assigned the same rank, and so were samples between LOD and LOQ. We used the following threshold for the interpretation of rho: < 0.4, weak; 0.4–0.6, moderate; > 0.6, strong correlation.

Association between the free and conjugated concentrations: Detection of unconjugated phenols in urine might results from both external contamination and direct exposure (Calafat et al., 2009; Ginsberg and Rice, 2009; Guidry et al., 2015; Völkel et al., 2002). To assess contamination we regressed the free against conjugated forms using the Akritas-Thiel-Sen (ATS) non-parametric linear regression, that allows for censorship on both sides of the equation (Helsel, D. R., 2012). We hypothesed that a small fraction of free compounds may remain in the urine as a result from direct exposure (Calafat et al., 2009; Ginsberg and Rice, 2009) and that in absence of external contamination, its concentrations would be proportional to the concentration of conjugated compound. This would result in a null intercept of the regression model (i.e., the samples with null concentrations of conjugated phenols should also have null concentrations of free phenols). A significant positive intercept (i.e., detectable levels of free phenols even in samples with no detected conjugated phenols) was thus considered as suggestive of contamination.

Regressions were done separately for mother and infant samples as the two urine sampling protocols were different, with different potential sources of contamination and were restricted to phenols with at least 5% of quantifiable concentrations of free forms. We computed 95% confidence intervals for the intercept by bootstrapping the regression 1000 times.

Predictors of phenol urinary concentrations: Information on potential predictors of phenol urinary concentrations was collected through interviews during study visits and self-administrated questionnaires. Pregnancy and infant samples were studied separately given that predictors of exposure may differ and some variables (such as breastfeeding) are specific to one of the two. Predictors considered for this analysis were selected among the data available in the SEPAGES cohort and guided by the literature:

1) Protocol and sample specific factors: season of sampling (winter, spring, summer, autumn), sampling date, gestational age at sampling (2nd or 3rd trimester, pregnancy model only), transportation time of the samples between the participant's freezer to the biobank's freezer (continuous, ln-transformed due to strong skewness of distribution), time during which the samples remained unfrozen during the pooling procedure (tertiles), specific gravity and number of samples in the pool (continuous).
2) Socio economic factors: education level (until high school; one to 4 years after high school; 5 years or more after high school) and participant characteristics that may impact phenol metabolism: body mass index (BMI) at inclusion (pregnancy model) or infant weight and height (infant model), parity (binary, first infant vs at least second), mother or infant age (continuous).
3) Occupation: for bisphenols and triclosan, the models also included professional occupation at the time of urine sampling using the following categories: 1) unemployed/on maternity leave, 2) jobs that imply regular contact with thermal receipts since they might be at risk for bisphenol exposure (Lee et al., 2018; Thayer et al., 2016) for the bisphenols model; healthcare workers (at risk of triclosan exposure through the use of antibacterial soap for hand washing (MacIsaac et al., 2014)) for the triclosan model and 3) other (including jobs that were not identified at particular risk for phenol exposure (teachers, office workers, sales workers, etc)).
4) Behavioral factors that have been shown to be at risk of exposure for specific phenols. This includes for the maternal bisphenol A model: consumption of canned food (Braun et al., 2011) (never/ever), and smoking (non-smoker versus smoker) (Braun et al., 2011) and for the infant bisphenol A model: breastfeeding and/or formula (Cirillo et al., 2015). Since bisphenol S is suspected to be a substitute of bisphenol A, we also included maternal canned food consumption, maternal smoking during pregnancy and infant source of milk in the models exploring the associations with bisphenol S.

Due to too low variability the following variables were not considered: maternal ethnicity (94% were Caucasian) and marital status (only one woman was not in couple).

We used adjusted parametric survival models to determine the associations between all of these potential predictors (independent variables) and the total phenol urinary concentrations (dependent variable). These models enabled to model phenol concentrations using interval censorship where measures below LOD are defined to be within the interval [0; LOD] and measures between LOD and LOQ are defined to be within the interval [LOD; LOQ] (Helsel, D. R., 2012). These models were fitted using the *survreg* function in R's *survival* package with the phenol concentrations coded in the interval endpoints format using the *Surv* function *interval2* option. Two random effects were added, one for the participant, to take into account repeated measurements for each participant, and one for the measurement batch.

For most phenols, logarithmic transformation did not provide a satisfactory distribution. For this reason, urinary concentrations were boxcox transformed using the *boxcoxCensored* function from R's *EnvStats* package prior to modelling. Missing data on the covariates were imputed using multiple imputation (20 imputations) with the R package *mice*.

As the selection of the covariates was based on a priori hypotheses we did not correct our results for multiple comparison and considered associations with p-values < 0.05 and < 0.1 as suggestive of an association.

Table 1
Characteristics of the study population.

	N	%
Infant sex		
Boy	251	52
Girl	218	46
Missing	10	2
Marital status at recruitment		
In couple	478	100
Not in couple	1	0
Maternal education		
High school + 5 years or more	269	56
High school + 1 to 4 years	179	37
High school or before	28	6
Missing	3	1
Maternal ethnicity		
European	401	84
Other[a]	15	13
Does not know/does not wish to answer/missing	63	3
Parity		
Nulliparous	220	46
≥1 child	259	54
Maternal BMI before pregnancy (kg/m^2)		
(15,18.5]	29	6
(18.5,25]	361	75
(25,30]	65	14
(30,35]	12	2
(35,45]	8	2
Missing	4	1

[a] Africa (N = 3), America (N = 2), Oriental Mediterranean countries (N = 3), South-East Asia (N = 2), Other (N = 5).

2.5. Sensitivity analysis

Several sensitivity analyses were performed. To ensure the robustness of the results for compounds with high censorship rates, logistic regressions where samples were coded as above or below LOQ were performed on bisphenol S and butylparaben. And for all models a complete case analysis was performed. Finally given the low number of cashiers still working at the third trimester of pregnancy we performed the cashier specific models (bisphenol A and bisphenol S) limited to the second trimester of pregnancy.

3. Results

3.1. Characteristics of the study population

Women of SEPAGES cohort were highly educated with 269 (56%) having pursued their studies 5 years or more after high school and mostly were non-smoker during pregnancy (95% and 98% at the second and third trimester, respectively). Most of them had a BMI in the normal range (between 18.5 and 25 (N = 361, 75%) (Tables 1 and 2). Regarding occupations that might be at risk of exposure, 7 women (2%) at the second and 2 (0.5%) at the third trimesters worked as a cashiers while 76 (16%) at the first and 23 (5%) at the third trimester were healthcare workers. Most of the pregnant women reported canned food consumption in their food habits (76% at the second trimester and 67% at the third trimester). Finally breast milk was the exclusive source of milk for 64% and 12% of the infants at 2 and 12 months, respectively.

Mean (SD) collection times were 18 (2) and 34 (2) gestational weeks for the maternal samples and 8 (4) and 53 (3) weeks of age for the infant samples. The median (5–95th centile) number of urine samples per weekly pool was 20 (17–21) during pregnancy, and 6 (4–7) during infanthood. Regarding urine sample storage conditions, most of the participants (between 93 and 98% depending on the sampling period) followed the protocol and stored the urine collected in their freezer during the collection week, the others were stored in the refrigerator.

3.2. Exploration of potential external contamination

Assessments of the sampling material: Among the 66 analyses of the sampling material only bisphenol A, benzophenone-3, and triclosan were detected in respectively 11 (16.6%), 1 (1.5%) and 5 (7.6%) of these analyses. Except for two samples for bisphenol A the detected concentrations were below or close to the LOQ (Supplemental material, Table S1).

Associations between the free and the total concentrations: For all phenols, the median of the ratio free/total concentrations was higher in the infant samples compared to the maternal samples (Supplemental material, Table S2). When regressing the free concentrations against the conjugated, the intercept of the Akritas-Thiel-Sen non-parametric linear regression was significantly greater than zero only for 2 and 12 months infant bisphenol A levels, suggesting that for these samples collected out of a diaper, a contamination may have occurred (Supplemental material, Table S3). For this reason, in the rest of the manuscript we presented for infant levels of bisphenol A the results on the conjugated form, not affected by external contamination if any.

3.3. Detection of phenols in weekly pools

Frequencies of detection for butyl paraben and bisphenol S total concentrations ranged between 23 and 33%, except in the samples collected at 12 months, in which bisphenol S was detected in 78% of the samples. For these two phenols, frequencies of detection of the free forms were also low (≤22% whatever the period). Frequencies of detection of the total concentration were high (≥81%) for the other phenols assessed, with the exception of propylparaben at 2 months that was detected in only 56% of the samples. Regarding the free forms of these phenols, frequencies of detection ranged from 16% (propylparaben at the first trimester of pregnancy) to 95% for bisphenol A at 2 months of age.

Regardless of the period, the highest total form medians were observed for methylparaben followed by bisphenol A (Table 3). These 2 compounds were also those that showed the highest concentrations of free form median (Supplemental material, Table S3).

3.4. Variations of phenol concentrations in pregnant mothers and infants

Comparing specific gravity (SG) across time points showed that samples collected at 2 months (mean SG = 1.004) were more diluted than those collected at the other periods (mean SG ≥ 1.012) (Table 2). For these reasons, when comparing median values across time points, we relied on the SG-corrected concentrations. For all phenols except triclosan and benzophenone-3, the highest median of the total SG-corrected concentrations was observed in the samples collected at 12 months (Table 3). Regarding bisphenol A, median urinary concentration of the conjugated form at 12 months, not impacted by suspected contamination (see above), was similar to the one collected in the second and third trimester of pregnancy and higher than those observed at 2 months (Wilcoxon rank sum test $p < 0.0001$).

Correlation coefficients between measurements at the second and third trimester were high for benzophenone-3 and triclosan (rho above 0.65) and low for all of the other phenols assessed (rho < 0.35). While the absolute values of the correlation coefficients were lower, a similar pattern (i.e., higher correlation coefficients for benzophenone-3 and triclosan compared to the other phenols) were observed when looking at the correlation between the other periods. All correlation coefficients between 2 and 12 months were below 0.18 except for triclosan (0.43) and benzophenone-3 (0.36). Similarly, between mean maternal and mean infant samples correlations were below 0.26 except for triclosan (0.44) and benzophenone-3 (0.58) (Table 4).

Table 2
Characteristics of the study population that varied with the timing of urine sampling.

	Second trimester		Third trimester		2 month		12 months	
	N	%	N	%	N	%	N	%
Samples stored in freezer at home								
Yes	447	94	423	93	145	95	98	98
No	12	3	6	1	2	1	0	0
Missing	18	4	27	6	5	3	2	2
Season of sampling								
Winter	113	24	78	17	17	11	20	20
Spring	141	30	117	26	28	18	27	27
Summer	119	25	150	33	46	30	36	36
Autumn	97	20	103	23	60	39	17	17
Missing	7	1	8	2	1	1	0	0
Year of sampling								
2014	42	9	7	2	0	0	0	0
2015	149	31	134	29	34	22	0	0
2016	207	43	201	44	117	77	26	26
2017	72	15	106	23	0	0	74	74
Missing	7	1	8	2	1	1	0	0
Weekly canned food eating habit								
Never	45	9	55	12	/	/	/	/
Ever	364	76	306	67	/	/	/	/
Missing	68	14	95	21	/	/	/	/
Infant feeding mode								
Breastfeeding only	/	/	/	/	97	64	12	12
Formula only	/	/	/	/	24	16	74	74
Other[a]	/	/	/	/	31	20	13	13
Missing	/	/	/	/	0	0	1	1
Maternal occupation								
Cashier	7	1	2	0	/	/	/	/
Healthcare worker	76	16	23	5	/	/	/	/
Other	274	57	116	25	/	/	/	/
Unemployed/On maternity leave	82	17	279	61	/	/	/	/
Missing	38	8	36	8	/	/	/	/
Mother smoked during sampling trimester								
No	411	86	410	90	/	/	/	/
Yes	23	5	7	2	/	/	/	/
Missing	43	9	39	9	/	/	/	/
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Defreeze time[b] (hours)	452	23 (7)	423	22 (3)	141	22 (2)	97	22 (3)
Transport time[c] (hours)	456	1.0 (1.5)	440	1.2 (4.3)	143	1.6 (3.4)	98	3.5 (13.0)
N of samples included in the pool	475	20 (1)	453	20 (2)	152	6 (1)	100	6 (1)
Specific gravity	477	1.018 (0.005)	456	1.017 (0.005)	152	1.004 (0.001)	100	1.012 (0.004)
Infant or maternal age (weeks or years)	470	33.0 (3.9)	448	33.2 (3.8)	151	8.3 (3.7)	100	52.8 (2.7)
Gestational age at sampling (weeks)	470	17.5 (1.7)	448	33.5 (2.1)	/	/	/	/
Infant weight (kg)	/	/	/	/	144	4.8 (0.6)	91	9.5 (1.1)

[a] Other included those who relied on both breastfeeding and formula (N = 31 at 2 months and 11 at 12 months) or neither (N = 2 at 12 months).
[b] Time during which the sample was thawed at 4 °C during the polling procedure.
[c] Time between the moment the sample left the participant's home and its arrival at the biobank.

3.5. Correlation between compounds

Overall, the within sample correlation coefficients observed between phenols and SG were higher in the infant samples than the ones observed in the maternal samples. For both maternal and infant samples, the highest correlation coefficients were observed between parabens (Supplemental Material, Tables S5 and S6). In infant samples we also observed moderate correlation between bisphenol A and ethylparaben (rho = 0.55) and between bisphenol A and benzophenone-3 (rho = 0.48). All the other correlation coefficients between phenols were below 0.40 (Supplemental material, Tables S5 and S6).

For all phenols, correlation with SG was higher in the infant than in the maternal samples (Supplemental Material, Tables S5 and S6). As an example, correlation coefficient between bisphenol A and SG was 0.72 in the infant samples compared to 0.26 in the maternal samples.

3.6. Factors associated with phenol concentrations

Protocol and sample specific factors: Maternal urine samples were collected between August 2014 and November 2017 while infant samples were collected between August 2015 and November 2017. Maternal urinary concentrations of phenols showed a decrease over time (p-value < 0.04, Table 5) for all phenols except bisphenol S ($\beta = -0.06$, 95%CI: −0.25; 0.13) and benzophenone-3 (−0.04, 95%CI: −0.18; 0.10). Such time trends were not observed for infant levels except for propylparaben ($\beta = -1.34$, 95%CI: −2.85; 0.17) (Table 6). Maternal bisphenol A concentration was lower in winter compared to all other seasons, while butylparaben, benzophenone-3 and triclosan were higher in summer (Table 5). The duration of the urine sample transport between the participant's home and the storage facility was negatively associated with maternal methylparaben and infant ethylparaben (Table 5). The time the sample spent at 4 °C during the pooling procedure was positively associated with benzophenone-3 and methyl paraben in the maternal model but negatively associated with bisphenol A in infants (Table 6). The number of samples included in the pool was negatively associated with benzophenone-3 in the maternal model and positively associated with triclosan in the infant model.

Table 3
Distribution of the total phenol crude (µg/L) and SG adjusted urinary concentrations assessed in weekly pools among pregnant women and infants of the SEPAGES cohort.

	Second trimester (N = 477)							Third trimester (N = 456)			
					Percentiles					Percentiles	
	LOD	LOQ	% > LOD	% > LOQ	5	50	95	% > LOD	% > LOQ	5	50
Total (free + conjugated) crude concentration											
Bisphenol A	0.04	0.1	99	99	0.66	2.01	8.58	98	98	0.51	1.8
Bisphenol A-conj[a]	0.04	0.1	/	/	/	/	/	/	/	/	/
Bisphenol S	0.1	0.4	25	21	< LOD	< LOD	3.07	28	23	< LOD	< LOD
Methylparaben	0.04	0.1	100	100	2.66	12.4	287	100	100	2.85	12.4
Ethylparaben	0.04	0.1	100	99	0.24	0.7	33.1	99	99	0.21	0.72
Propylparaben	0.04	0.1	82	73	< LOD	0.45	65.9	81	74	< LOD	0.63
Butylparaben	0.07	0.2	25	11	< LOD	< LOD	0.72	24	12	< LOD	< LOD
Triclosan	0.04	0.1	98	98	0.21	0.92	185	98	98	0.18	0.86
Benzophenone-3	0.04	0.1	100	100	0.27	1.18	35.6	100	100	0.22	0.97
Total (free + conjugated) concentration, adjusted for specific gravity											
Bisphenol A	0.04	0.1	99	99	0.64	1.71	7.92	98	98	0.51	1.67
Bisphenol A-conj[a]	0.04	0.1	/	/	/	/	/	/	/	/	/
Bisphenol S	0.1	0.4	25	21	< LOD	< LOD	2.98	28	23	< LOD	< LOD
Methylparaben	0.04	0.1	100	100	2.58	10.6	214	100	100	2.78	11.6
Ethylparaben	0.04	0.1	100	99	0.25	0.61	28.6	99	99	0.24	0.66
Propylparaben	0.04	0.1	82	73	< LOD	0.39	59.9	81	74	< LOD	0.57
Butylparaben	0.07	0.2	25	11	< LOD	< LOD	0.66	24	12	< LOD	< LOD
Triclosan	0.04	0.1	98	98	0.2	0.79	178	98	98	0.19	0.81
Benzophenone-3	0.04	0.1	100	100	0.26	1.04	32.3	100	100	0.21	0.89

	Third trimester (N = 456)	2 months (N = 152)					12 months (N = 100)				
	Percentiles			Percentiles					Percentiles		
	95	% > LOD	% > LOQ	5	50	95	% > LOD	% > LOQ	5	50	95
Total (free + conjugated) crude concentration											
Bisphenol A	9.36	99	98	0.15	0.46	2.69	100	100	0.87	2.57	8.47
Bisphenol A-conj[a]	/	96	88	< LOQ	0.25	1.93	97	97	0.21	1.6	4.8
Bisphenol S	3.02	33	2	< LOD	< LOD	< LOQ	78	44	< LOD	< LOQ	1.56
Methylparaben	2550	100	99	0.19	1.45	2650	100	100	2.57	20.4	1140
Ethylparaben	25.8	91	57	< LOD	0.13	19.8	100	100	0.21	0.88	209
Propylparaben	142	56	49	< LOD	< LOQ	156	83	74	< LOD	0.62	102
Butylparaben	0.77	26	5	< LOD	< LOD	0.20	23	8	< LOD	< LOD	0.23
Triclosan	179	98	89	< LOQ	0.17	1.45	99	95	< LOQ	0.25	1.52
Benzophenone-3	27.5	87	70	< LOD	0.16	3.5	100	97	0.11	0.38	2.36
Total (free + conjugated) concentration, adjusted for specific gravity											
Bisphenol A	9.22	99	98	0.61	1.74	7.41	100	100	1.27	3.31	10.6
Bisphenol A-conj[a]	/	96	88	0.19	1	5.7	97	97	0.22	2.22	6.45
Bisphenol S	2.95	33	2	< LOQ	< LOQ	1.1	78	44	< LOD	0.41	2
Methylparaben	2530	100	99	0.79	5.4	11,400	100	100	3.68	29.5	1600
Ethylparaben	24	91	57	0.11	0.52	61.5	100	100	0.29	1.14	297
Propylparaben	159	56	49	< LOQ	0.39	570	83	74	< LOD	0.87	156
Butylparaben	0.75	26	5	< LOQ	< LOQ	0.85	23	8	< LOD	< LOQ	0.26
Triclosan	191	98	89	0.26	0.71	5.64	99	95	0.12	0.37	1.55
Benzophenone-3	22.5	87	70	0.11	0.65	11.5	100	97	0.17	0.52	4.39

[a] Conjugated form, only displayed for the infants.

Table 4
Spearman correlation coefficients between periods.

	T2-T3	M2-Y1	Mother-Infant[a]
Bisphenol A	0.19	0.07	0.20
Bisphenol S[b]	/	/	/
Methylparaben	0.24	0.18	0.08
Ethylparaben	0.35	0.17	0.26
Propylparaben	0.30	0.11	0.21
Butylparaben[b]	/	/	/
Triclosan	0.65	0.43	0.44
Benzophenone-3	0.70	0.36	0.58

[a] Correlation coefficients between the mean measure during pregnancy and the mean measure during infanthood.
[b] Correlation coefficients were not computed for bisphenol S and butyl paraben because of the low frequencies of detection for these phenols.

Participant characteristics: Women with the shortest education had higher urinary concentrations of triclosan, ethyl and propylparaben (Table 5). While not significant, a similar pattern was observed with methyl (0.15 (95% Confidence Interval (CI): −0.04; 0.33)) and butylparaben (β = 0.14, 95%CI: −0.16; 0.44). Such associations with maternal education were not observed among infants (Table 6).

We did not observe clear association between maternal age and phenol urinary concentrations, while infant age was positively associated with bisphenol A (conjugated form) and methylparaben (Table 6). We observed a negative association between parity and maternal urinary concentrations for all phenols except bisphenol S (β = 0.34, 95% CI: 0.09; 0.59). Parity was also negatively associated with the infant benzophenone-3 urinary concentration (β = −0.47, 95%CI: −0.83; −0.10). No association was observed between pre-pregnancy maternal body mass index, infant weight and maternal or infant phenol concentrations (Tables 5 and 6, p-values > 0.09).

Occupation: Having a job that involved contact with a receipt (N = 7 at the second trimester and N = 2 at the third trimester) tended to be positively associated with maternal urinary concentration of bisphenol S (β = 0.99, 95%CI: −0.11; 2.09) but not bisphenol A (β = -0.11, 95%CI: −0.72; 0.51). The positive association with bisphenol S remained even if it was less strong when limited to samples from the second trimester (β = 0.46, 95%CI: −0.99; 1.90), Supplemental material, Table S12). We did not observe a clear association between being a healthcare worker and triclosan concentrations (Table 5).

Behaviour: No clear relationship was found between reporting eating canned food and maternal urinary concentrations of bisphenol A (β = 0.02, 95%CI: −0.19; 0.22) but bisphenol S urinary concentrations were marginally higher (β = 0.28, 95%CI: −0.08; 0.63). Urinary bisphenol A concentration for infants that were drinking formula were not statistically different (β = 0.05, 95%CI: −0.23; 0.32) from those that were breastfed.

Sensitivity analysis: Complete case analyses (Supplemental material, Table S7 and S8) were consistent with the imputed data models. So was the logistic regressions on BPS and BUPA (Supplemental material, Table S9 and S10).

4. Discussion

In our couple-child population recruited between 2014 and 2017, frequencies of detection were high for bisphenol A, methyl, ethyl, propyl parabens, triclosan and benzophenone-3 and low for bisphenols AF, B, F, S, butylparaben and triclocarban. After standardization for urine dilution, median concentrations among 12 month infants were higher (bisphenol S, methyl, ethyl, propyl parabens) or of similar order (bisphenol A conjugated) than those observed in their mothers during pregnancy. Inversely for triclosan and benzophenone-3, concentrations were higher during pregnancy. Maternal urinary concentration of most phenols, except for bisphenol S and benzophenone-3, decreased with year of urine collection, suggesting decreasing exposure over time. No such decrease was observed in infants.

4.1. Strengths and limitations

Multiple urine samples were collected and pooled (within subject, within period) following an approach we developed to limit bias in dose response functions (Perrier et al., 2016; Vernet et al., 2019). Infant samples were collected in early infancy (≤12 months), a period that has rarely been considered in previous studies describing phenol exposure in the general population. This study is also the first to report data on exposure to bisphenol A and its potential substitutes among French pregnant women and infants, since its ban from food containers in France in 2015. The parametric survival models we relied on accept multiple levels of censorship and enabled us to use the information provided by samples below LOD and below LOQ. This was especially relevant for compounds with many such samples like bisphenol S and butylparaben.

We observed high levels of free bisphenol A in infant samples. Previous studies looking at bisphenol A levels in infants have reported low detection rates of free forms (Nachman et al., 2015; Volkel et al., 2011) or high proportion of conjugated forms (90% of the total) (Calafat et al., 2009) suggesting that young infants are able to produce conjugated bisphenol A. We suspect our high levels of free forms might have resulted from external contamination from the diapers or the cottons used to collect the infant urine, which were not tested. This led us to present results for the conjugated forms for infant bisphenol A, not impacted by contamination. Another limitation of our infant sampling protocol is that fibers of diapers and cotton can bind the free, but not the conjugated forms of triclosan and bisphenol A (Ye et al., 2010). However, phenols are mostly excreted as conjugate (Ye et al., 2010) and, if it occurred this phenomenon should only have marginally decreased the infant total triclosan and bisphenol A concentrations. To our knowledge, no study has explored the binding power of fibers for the other assessed phenols.

Pooling allowed us to decrease assay cost compared to the situation where phenols would have been assessed in each spot sample collected. However, we cannot exclude that some random error was introduced by the pooling procedure. We pooled the exact same volume of all the micturitions with no consideration of total urine volume or dilution leading to an overrepresentation of the voids with low volume in the pool. Further studies relying on repeated samples may want to consider pooling procedures a priori standardized for urine dilution (Weinberg et al., 2019).

4.2. Phenol urinary concentrations: Comparison with previous studies

Compared to a previous study among French pregnant women recruited between 2003 and 2006 (EDEN cohort), SEPAGES median paraben and triclosan concentrations were 84 to 97% lower, depending on the compound. Benzophenone-3 and bisphenol A median concentrations were respectively 53 and 31% lower (Fig. 1). Caution is warranted in interpreting these differences because of disparities in socio-demographic characteristics (e.g., SEPAGES women had overall done longer studies) and geographical location (SEPAGES and EDEN women were not recruited in the same cities) across cohort. Part of the differences in phenol urine concentrations might also have resulted from the regulatory changes that occurred between 2003 and 2006 (Eden cohort) and 2014–2017 (SEPAGES cohort). Compared to the French national cohort ELFE whose recruitment took place in 2011, median bisphenol A concentration was higher in our cohort (median of 2.0 at the second trimester and 1.8 at the third trimester compared to 0.8 µg/L in ELFE (Dereumeaux et al., 2016)). This might reflect difference in urine collection protocol. The ELFE cohort assessed bisphenol A in a spot urine samples collected at delivery while we assessed bisphenol A in pooled samples collected at the 2nd and 3rd trimesters of

Table 5
Adjusted associations between subject and sampling characteristics and the box-cox transformed phenol urinary concentrations for pregnant women of SEPAGES cohort (N = 477 and 456 mothers in their second and third trimesters of pregnancy, respectively).

	Bisphenol A		Bisphenol S		Methylparaben		Ethylparaben		Propyparaben		Butylparaben		Triclosan		Benzophenone 3	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Specific gravity	0.05	(0.04; 0.06)	−0.02	(−0.04; 0.01)	0.02	(0.02; 0.03)	0.07	(0.05; 0.08)	0.08	(0.04; 0.11)	0.01	(0.00; 0.03)	0.05	(0.04; 0.07)	0.03	(0.02; 0.04)
Date of sampling	−0.17	(−0.30; −0.05)	−0.06	(−0.25; 0.13)	−0.11	(−0.17; −0.05)	−0.21	(−0.36; −0.07)	−0.75	(−1.07; −0.43)	−0.19	(−0.29; −0.10)	−0.34	(−0.50; −0.17)	−0.04	(−0.18; 0.10)
Season of sampling																
Winter																
Spring	0.34	(0.17; 0.50)	0.07	(−0.25; 0.39)	0.07	(−0.01; 0.14)	0.09	(−0.07; 0.25)	−0.39	(−0.84; 0.07)	−0.02	(−0.15; 0.11)	0.05	(−0.12; 0.23)	0.07	(−0.04; 0.18)
Summer	0.49	(0.31; 0.67)	0.03	(−0.30; 0.36)	0.01	(−0.08; 0.09)	0.12	(−0.06; 0.30)	−0.34	(−0.84; 0.16)	0.17	(0.03; 0.31)	0.36	(0.17; 0.55)	0.27	(0.14; 0.40)
Autumn	0.2	(0.01; 0.38)	0.10	(−0.24; 0.44)	0.00	(−0.08; 0.08)	0.07	(−0.11; 0.25)	−0.39	(−0.89; 0.11)	0.02	(−0.12; 0.16)	0.15	(−0.04; 0.35)	−0.09	(−0.21; 0.04)
Defreeze time																
Short																
Medium	−0.08	(−0.22; 0.07)	0.21	(−0.07; 0.48)	0.10	(0.03; 0.16)	−0.06	(−0.21; 0.09)	0.05	(−0.35; 0.46)	−0.03	(−0.15; 0.09)	0.05	(−0.12; 0.22)	0.13	(0.02; 0.23)
Long	0.04	(−0.11; 0.18)	0.12	(−0.15; 0.39)	0.06	(−0.00; 0.13)	0.05	(−0.09; 0.20)	−0.04	(−0.45; 0.36)	0.00	(−0.12; 0.12)	0.07	(−0.10; 0.24)	0.17	(0.07; 0.27)
Transport time	−0.02	(−0.10; 0.06)	0.02	(−0.12; 0.16)	−0.06	(−0.10; −0.03)	−0.02	(−0.09; 0.06)	−0.1	(−0.31; 0.11)	0.03	(−0.03; 0.09)	−0.04	(−0.13; 0.05)	0.05	(−0.01; 0.11)
Number of samples	0	(−0.05; 0.04)	0.03	(−0.05; 0.10)	−0.01	(−0.03; 0.01)	0.02	(−0.02; 0.07)	−0.09	(−0.20; 0.02)	0.00	(−0.04; 0.03)	0.01	(−0.04; 0.06)	−0.04	(−0.07; −0.00)
Period of sampling																
2nd trimester																
3rd trimester	−0.11	(−0.24; 0.01)	0.03	(−0.22; 0.28)	0.09	(0.04; 0.14)	0.08	(−0.02; 0.18)	0.69	(0.40; 0.99)	0.09	(0.00; 0.17)	0.01	(−0.13; 0.15)	−0.18	(−0.26; −0.10)
Parity																
First child																
Second or more	−0.15	(−0.31; 0.00)	0.34	(0.09; 0.59)	−0.06	(−0.15; 0.03)	−0.15	(−0.35; 0.04)	−0.53	(−0.93; −0.12)	−0.1	(−0.25; 0.04)	−0.09	(−0.34; 0.16)	−0.49	(−0.69; −0.28)
Maternal age[a]	0.00	(−0.10; 0.10)	−0.1	(−0.26; 0.06)	0.03	(−0.03; 0.09)	0.09	(−0.03; 0.22)	0.2	(−0.06; 0.47)	−0.02	(−0.12; 0.07)	−0.05	(−0.21; 0.11)	0.01	(−0.13; 0.14)
Pre pregnancy BMI	0.00	(−0.02; 0.02)	0.01	(−0.02; 0.05)	0.00	(−0.01; 0.01)	−0.01	(−0.03; 0.02)	−0.02	(−0.08; 0.03)	−0.01	(−0.03; 0.01)	−0.03	(−0.06; 0.00)	0.01	(−0.02; 0.04)
Maternal education																
High school + 5y																
High school + 1 to 4y	−0.03	(−0.19; 0.13)	−0.09	(−0.34; 0.16)	0.06	(−0.03; 0.15)	0.15	(−0.04; 0.35)	0.87	(0.46; 1.28)	0.12	(−0.03; 0.27)	0.21	(−0.07; 0.49)	−0.16	(−0.37; 0.05)
High school or less	−0.19	(−0.53; 0.15)	−0.08	(−0.63; 0.47)	0.15	(−0.04; 0.33)	0.43	(0.02; 0.83)	1.39	(0.54; 2.24)	0.14	(−0.16; 0.44)	0.62	(0.04; 1.20)	−0.02	(−0.45; 0.41)
Occupation																
Unemployed/maternity leave																
Cashier	−0.11	(−0.72; 0.51)	0.99	(−0.11; 2.09)												
Healthcare worker													0.04	(−0.25; 0.34)		
Other	−0.05	(−0.19; 0.09)	0.2	(−0.07; 0.46)									−0.03	(−0.23; 0.17)		
Smoking at sampling																
No																

(*continued on next page*)

Table 5 (*continued*)

	Bisphenol A		Bisphenol S		Methylparaben		Ethylparaben		Propyparaben		Butylparaben		Triclosan		Benzophenone 3	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Yes	−0.23	(−0.59; 0.13)	−0.47	(−1.11; 0.17)												
Canned food during sampling																
Never																
Ever[b]	−0.01	(−0.22; 0.19)	0.28	(−0.08; 0.63)												

[a] Maternal age expressed in 5 year increments.

[b] Canned food consumption was originally expressed as more than once per week or less than once per week, both categories were combined.

pregnancy.

This study is the first in France to report urinary concentration of infants under one year. Compared to other countries, bisphenol A median at 2 months (0.5 μg/L) was lower or of similar order than those observed in the US (1.8 μg/L, age range, 3 to 18 months (Mendonca et al., 2014)) and Germany (< LOQ of 0.45 μg/L, age range, 1 to 5 months (Volkel et al., 2011)). At 12 months, the median of the total bisphenol A concentration (2.6 μg/L) was lower than the one reported at 12 months in American infants (median of 3.7 μg/L (Stacy et al., 2016)). Two studies reported urinary concentrations of parabens (Korea, (Kang et al., 2013)) and triclosan (USA, (Stacy et al., 2017)) among infants younger than one year. Compared to these studies, median values observed in our population were lower.

Our study was the first to assess urinary concentrations of triclocarban, bisphenol S, F, B, AP during infanthood. The frequency of detection was low (< 4%) for bisphenol F, B, AP and triclocarban in these samples, while for bisphenol S, frequency of detection ranged between 33% (2 months) and 78% (12 months) suggesting widespread exposure to these compounds among infants in France.

4.3. Comparison across periods

In line with a previous study that reported increased creatinine levels in infants aged between 2 weeks and 14 months of age (Jackson et al., 2016), urine samples were more diluted at 2 months compared to those collected at the other time points, suggesting that urine dilution should be considered when comparing biomarker concentrations across age. Median urinary concentrations (SG-corrected) of several phenols were higher (bisphenol S, methyl, ethyl, propyl paraben) or of similar ranges (bisphenol A conjugated) at 12 months when compared to pregnancy levels. The opposite was observed for triclosan and benzophenone-3. In line with our results, previous studies have reported higher bisphenol A and lower triclosan concentrations at 12 months, compared to pregnancy (Braun et al., 2011; Stacy et al., 2016). Parabens and benzohenone-3 were not assessed at 12 months in these studies.

Even for phenols for which we did not observe contamination in infant samples, we observed higher free / total ratio at both 2 and 12 months when compared to their mother. While we cannot exclude an artefact due to difference in sampling protocol between mothers and infants (maternal samples were frozen right after collection while the infant urine sometimes stayed several hours in the diaper, before being collected and frozen, which could have led the conjugated forms to start degrading (Ye et al., 2007)), this may also reflect differences in metabolism between pregnant women and infants (Lu and Rosenbaum, 2014; Nachman et al., 2014).

4.4. Temporal variability of phenol total concentrations

For bisphenol A and parabens we observed higher temporal variability than intraclass correlations (ICC) reported in previous studies also relying on weekly pools of urine biospecimens collected during pregnancy (Casas et al., 2018; Vernet et al., 2018). The opposite was observed for benzophenone-3 and triclosan (lower variability in our study population, Supplementary Material, Table S11).

To our knowledge, this study is the first providing data on intra-individual variability of phenol concentrations in infants, as previous studies recruited 1 to 9 years old children (reviewed by Casas et al., 2018) and suggested moderate to high variability for these compounds.

Spearman correlation coefficients between maternal and infant concentrations were low (bisphenol A, parabens) to moderate (triclosan, benzophenone-3) suggesting that infant values could not be predicted from those of their mother.

Table 6
Adjusted associations between subject and sampling characteristics and the box cox-transformed phenol urinary concentrations in infants of SEPAGES cohort (N = 152 two months old and 100 one-year old infants).

	Bisphenol A[a]		Bisphenol S		Methylparaben		Ethylparaben		Propyparaben		Butylparaben		Triclosan		Benzophenone 3	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Specific gravity	0.06	(0.02; 0.10)	0.00	(−0.02; 0.03)	0.08	(0.00; 0.17)	0.16	(0.07; 0.24)	0.23	(0.06; 0.41)	0.00	(0.00; 0.00)	0.1	(0.06; 0.13)	0.12	(0.07; 0.18)
Date of sampling	0.17	(−0.19; 0.54)	−0.01	(−0.25; 0.23)	0.32	(−0.53; 1.17)	−0.05	(−0.93; 0.83)	−1.34	(−2.85; 0.17)	0.00	(−0.02; 0.02)	0.25	(−0.22; 0.71)	0.49	(−0.04; 1.01)
Season of sampling																
Winter																
Spring	−0.16	(−0.50; 0.19)	0.10	(−0.14; 0.34)	0.07	(−0.71; 0.85)	0.24	(−0.56; 1.03)	0.81	(−0.77; 2.38)	0.00	(−0.01; 0.01)	0.11	(−0.25; 0.48)	−0.19	(−0.68; 0.30)
Summer	0.19	(−0.13; 0.52)	0.20	(−0.03; 0.43)	0.4	(−0.36; 1.16)	0.7	(−0.08; 1.48)	0.84	(−0.65; 2.32)	0.00	(−0.01; 0.01)	0.14	(−0.23; 0.52)	0.23	(−0.25; 0.72)
Autumn	−0.30	(−0.65; 0.04)	0.09	(−0.15; 0.32)	0.14	(−0.67; 0.94)	0.11	(−0.71; 0.93)	0.15	(−1.37; 1.67)	0.00	(−0.01; 0.01)	0.25	(−0.15; 0.65)	−0.03	(−0.56; 0.49)
Defreeze time																
Short																
Medium	−0.10	(−0.35; 0.15)	−0.23	(−0.40; −0.06)	0.02	(−0.55; 0.59)	0.54	(−0.02; 1.10)	0.41	(−0.81; 1.63)	0.00	(−0.01; 0.00)	−0.1	(−0.34; 0.15)	−0.11	(−0.47; 0.25)
Long	−0.29	(−0.55; −0.03)	0.06	(−0.12; 0.23)	−0.22	(−0.82; 0.38)	0.19	(−0.40; 0.78)	0.21	(−1.06; 1.48)	0.01	(0.00; 0.01)	−0.06	(−0.32; 0.21)	−0.12	(−0.50; 0.27)
Transport time	0.05	(−0.04; 0.15)	−0.01	(−0.07; 0.05)	−0.16	(−0.37; 0.05)	−0.27	(−0.48; −0.06)	0.07	(−0.38; 0.51)	0.00	(−0.00; 0.00)	0.09	(−0.01; 0.19)	0.04	(−0.09; 0.18)
Number of samples	0.00	(−0.09; 0.09)	0.02	(−0.04; 0.09)	0.08	(−0.12; 0.28)	0.19	(−0.02; 0.39)	0.3	(−0.12; 0.72)	0.00	(−0.00; 0.00)	0.12	(0.02; 0.21)	0.03	(−0.10; 0.16)
Parity																
First child																
Second or more	−0.12	(−0.34; 0.10)	0.00	(−0.15; 0.16)	0.26	(−0.29; 0.80)	0.25	(−0.31; 0.81)	0.25	(−0.69; 1.18)	0.00	(−0.01; 0.01)	0.1	(−0.20; 0.40)	−0.47	(−0.83; −0.10)
Maternal education																
High school + 5y																
High school + 1 to 4y	0.06	(−0.17; 0.29)	0.09	(−0.07; 0.26)	0.62	(0.04; 1.21)	0.46	(−0.14; 1.06)	0.65	(−0.35; 1.65)	0.00	(−0.01; 0.01)	0.46	(0.14; 0.79)	−0.07	(−0.46; 0.32)
High school or less	−0.11	(−0.61; 0.40)	0.29	(−0.07; 0.65)	−0.66	(−1.92; 0.59)	−0.45	(−1.75; 0.84)	−1.8	(−4.01; 0.41)	0.01	(−0.02; 0.04)	0.07	(−0.63; 0.76)	−0.16	(−1.01; 0.68)
Infant sex																
Boy																
Girl	0.06	(−0.18; 0.29)	−0.05	(−0.22; 0.11)	−0.08	(−0.65; 0.50)	−0.14	(−0.73; 0.45)	0.37	(−0.63; 1.37)	0.00	(−0.02; 0.01)	−0.21	(−0.53; 0.11)	0.05	(−0.34; 0.43)
Age	0.15	(0.06; 0.24)	0.02	(−0.04; 0.08)	0.23	(0.04; 0.42)	0.12	(−0.07; 0.31)	0.28	(−0.08; 0.64)	0.00	(−0.00; 0.01)	0.04	(−0.06; 0.14)	0.02	(−0.11; 0.15)
Height[b]	−0.14	(−0.47; 0.18)	0.26	(0.05; 0.47)	−0.34	(−1.04; 0.36)	0.14	(−0.58; 0.85)	−0.53	(−1.83; 0.78)	0.00	(−0.01; 0.01)	−0.19	(−0.55; 0.18)	−0.32	(−0.81; 0.17)
Weight	−0.06	(−0.25; 0.14)	−0.12	(−0.24; 0.01)	−0.01	(−0.43; 0.41)	−0.02	(−0.46; 0.42)	0.08	(−0.75; 0.91)	0.00	(−0.01; 0.00)	−0.03	(−0.23; 0.17)	0.1	(−0.20; 0.40)
Feeding mode at time of sample																
Breastfeeding only																
Formula only	0.05	(−0.23; 0.32)	0.12	(−0.07; 0.31)												
Other	0.07	(−0.21; 0.35)	0.08	(−0.12; 0.27)												

[a] Models for infant bisphenol A computed on the conjugated forms due to suspected sample contamination.
[b] Child height expressed in 5 cm increments.

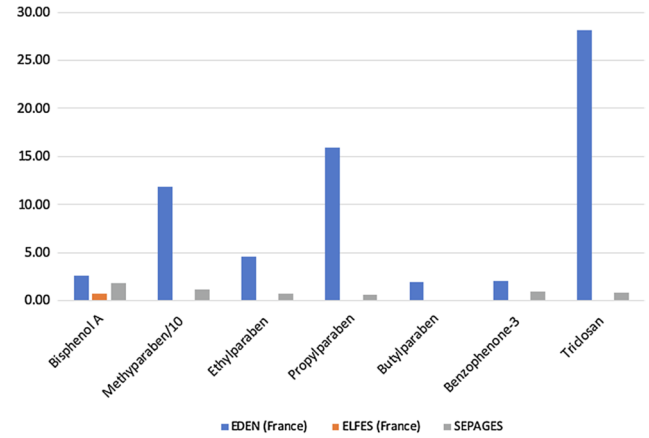

Fig. 1. Phenol median comparison with previous French cohorts (ELFE and EDEN). Legend: recruitment years were 2003–2006 for EDEN (Philippat et al., 2017), 2011 for ELFE (Dereumeaux et al., 2016) and 2014–2017 for SEPAGES. The SEPAGES concentrations displayed on this figure correspond to the concentrations measured in the 477 maternal urine samples collected at the 3rd trimester of pregnancy.

4.5. Predictors of phenol concentrations

Protocol and sample specific factors: Maternal urinary concentrations of all phenols except bisphenol S and benzophenone-3 decreased with increased year of collection. This might result from specific regulations that took place in France between 2014 and 2017 (e.g. bisphenol A was banned from food packaging in 2015) and behavioral modifications in the general population, possibly in link with better awareness regarding the potential harmful effects of these compounds (e.g., use of paraben-free cosmetics). Such a decrease over time was not observed in infants, for whom however the sampling time range was shorter. Compared to winter, we observed increased maternal, but not infant, urinary concentrations of bisphenol A, benzophenone-3, butyl-paraben and triclosan in summer. Both benzophenone-3 and bisphenol A have been detected in sunscreens (Dodson et al., 2012), which may partly explain these associations. We do not have an explanation for triclosan and butylparaben, for which no association with season was observed in a previous study among French pregnant women (Mortamais et al., 2012). Gestational age at sampling was positively associated with parabens and negatively with benzophenone-3. These associations might result from physiological changes occurring during pregnancy as well as changes in behavior over the pregnancy.

We observed a few associations between either the sample transport time (decreased methyl (maternal) and ethyl (infant) paraben concentrations) and the sample defreeze time (increased maternal benzophenone-3 and methyl paraben and decreased infant bisphenol A). This was unexpected since (Ye et al., 2007) reported that while the conjugated form degrades, the total concentrations of these phenols are relatively stable over several days even if stored at room temperature (Ye et al., 2007). Given this and the fact that these associations were not consistent between the infant and the maternal samples such associations should be interpreted cautiously.

Participant characteristics and socio-economic factors: Urinary concentrations of most phenols tended to increase with infant age, which might reflect changes in behavior that occur between 2 and 12 months including diet diversification and development of hand to mouth behavior.

Women with the shortest education had higher urinary concentrations of triclosan, ethyl and propyl paraben than those with the longest education. No difference was observed for the other phenols. These results were not consistent with those reported among six European cohorts that suggested lower paraben concentrations in low (primary) or middle (secondary) education groups when compared to the high education group (Montazeri et al., 2019). Comparison across studies should be done with caution since only 6% of our study population did not go to university compared to 48% in (Montazeri et al., 2019). In addition, for a given educational category, behavior and awareness regarding sources of phenol exposure might differ across countries.

Occupation: Higher bisphenol A concentrations have been reported among cashiers (Braun et al., 2011). We did not highlight such an association, however despite our limited power (low number of cashiers), we observed higher bisphenol S concentrations among women handling receipts during working days. This was consistent with a recent study conducted in France in 2014 among cashiers (N = 17) and non-professionally exposed workers (N = 15) (Ndaw et al., 2018), and suggests that bisphenol S may have replaced bisphenol A in thermal receipts. Use of bisphenol A, but not bisphenol S, in thermal receipts will be limited in 2020 in EU (EU regulation 2016/2235).

Healthcare workers did not have higher triclosan concentrations compared to non-working women. We were limited to study this association since we knew the profession of each woman but did not collect information on the use of antibacterial soap at work (some but not all healthcare institutions use antibacterial soap) nor on the average number of times the participants washed their hands during a work shift, which could be highly variable across health workers (World Health Organisation, 2009)).

5. Conclusion

The median values of the urinary concentrations of phenols measured between 2014 and 2017 in the SEPAGES cohort were lower than in a previous cohort of French pregnant women (EDEN 2003–2006) but detection rates were still high for bisphenol A, parabens and triclosan in both mothers and their infant. This would suggest that exposure to these compounds is still widespread in the general population. In addition, infant values could not be predicted from those of their mother.

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CRediT authorship contribution statement

Matthieu Rolland: Methodology, Formal analysis, Writing - original draft. **Sarah Lyon-Caen:** Investigation, Writing - review & editing. **Amrit K. Sakhi:** Resources, Writing - review & editing. **Isabelle Pin:** Investigation. **Azemira Sabaredzovic:** Writing - review & editing. **Cathrine Thomsen:** Resources, Writing - review & editing. **Rémy Slama:** Writing - review & editing, Funding acquisition, Conceptualization. **Claire Philippat:** Writing - original draft, Supervision, Funding acquisition, Conceptualization. **:** .

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105678.

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