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## Use of personal care products during pregnancy in relation to urinary concentrations of select phenols: A longitudinal analysis from the SEPAGES feasibility study



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### ABSTRACT

**Background:** Exposure to certain synthetic phenols is of growing concern, in particular among pregnant women, because of their endocrine disrupting nature. Many phenols are still authorized in personal care products (PCP). We aimed to assess if use of PCPs, by pregnant women could influence their urinary concentrations of synthetic phenols.

**Methods:** We used a panel design with intense urine sample collection. Eight women completed a diary with exact time and use of PCPs in three weeks. We measured the concentrations of phenols (four parabens, bisphenol A and S, two dichlorophenols, triclosan, and benzophenone-3) in 178 urine samples, collected during 7 consecutive days at 3 time points during pregnancy. We characterized PCP use as the total number of PCP applications or as a single PCP use (yes/no) in three time windows (0–6, 6 to 12 and 12 to 24h before each urine sample collection). We used adjusted linear and Tobit regressions to assess associations between PCP use and phenol urinary concentrations.

**Results:** The total number of PCP applications was positively associated with ethylparaben, propylparaben and butylparaben concentrations. We observed a peak in urinary concentration of ethylparaben, butylparaben and propylparaben at 2.86, 2.55 and 2.67 h since last PCP use, respectively and twelve different types of PCPs were positively associated with at least one of these parabens. The bisphenol S concentration increased by 12.4% (95%CI: confidence interval: 5.9; 19.3) for each additional PCP application in the 12 to 24 time window and use of specific PCPs such as anti-stretchmarks cream, facial cleanser and shower gel. Associations varied by time window.

**Conclusion:** Our study showed that PCP use was associated with a short-term increase in the urinary concentration of ethylparaben, butylparaben and propylparaben, but not methylparaben. This study also reported a

**Abbreviations:** CI, confidence interval; EU, European Union; GW, gestational weeks; ICC, intra-class correlation coefficient; PCP, personal care product; SD, standard deviation

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positive association between the use of PCPs and the bisphenol S concentration, a finding that warrants further investigation in cohorts with repeated collection of urine samples and detailed information on PCP use.

## 1. Introduction

Phenols constitute a family of aromatic chemical substances of natural and synthetic origin characterized by the presence of a hydroxyl group ( $C_6H_5-OH$ ). Certain synthetic phenols such as benzophenone-3, bisphenols A and S, 2,4- and 2,5-dichlorophenol, triclosan and specific parabens are suspected endocrine disruptors (Boberg et al., 2010; Huang et al., 2014; Krause et al., 2012; Wetherill et al., 2007). Toxicological and epidemiological studies have suggested that prenatal exposure to several phenols or their precursors may be associated with various adverse developmental, neurobehavioral, metabolic and respiratory effects in the offspring (Ali and Elgoly, 2013; Halden et al., 2017; Rochester, 2013; Ruszkiewicz et al., 2017).

These synthetic compounds are used in various consumer products including food and beverages (parabens), pharmaceuticals (parabens), herbicides/pesticides (2,4-dichlorophenol), thermal receipts, polycarbonate plastics and epoxy resins (bisphenols), as well as personal care products (PCP) (parabens, as preservatives; benzophenone-3 as a sunblock and triclosan as a microbicide). According to the European Union (EU) regulation No 1223/2009, isopropyl, isobutyl, phenyl, benzyl and pentyparaben are banned from cosmetics, while methyl, ethyl, butyl and propylparaben are still authorized up to 0.4% or 0.8% of product weight in mixtures or in singular use, respectively (EC Regulation, 2014). Triclosan is authorized up to 0.3% (EC Regulation, 2014). Although not known to be used as ingredients, bisphenols have been detected in various PCPs (Dodson et al., 2012; Liao and Kannan, 2014; Lu et al., 2018), likely because of leaching from the packaging (Le et al., 2008). In the EU, the presence of bisphenols in PCPs is not regulated but bisphenol A is recognized as a substance of very high concern. Bisphenol S is of emerging concern based on toxicological results, with similar endocrine disrupting effects as bisphenol A (Qiu et al., 2019) and a few human studies suggesting associations with deleterious health outcomes (Ranci re et al., 2019).

Previous epidemiological studies of pregnant women (Ashrap et al., 2018; Braun et al., 2014; Fisher et al., 2017; Meeker et al., 2013), adults, and children (Berger et al., 2018; Ferguson et al., 2017; Fillol et al., 2019; Kim et al., 2018; Nassan et al., 2017; Philippat et al., 2015) reported that use of PCPs (either the total number of PCPs or the use of specific PCPs) was associated with increased urinary concentrations of parabens, triclosan, benzophenone-3 and bisphenol A.

With a few exceptions (Fisher et al., 2017; Koch et al., 2014; Nassan et al., 2017), most previous studies characterized use of PCPs as a binary variable (Yes/No) or as the frequency of use in the 24–48 h prior to urine collection, without assessing the exact time of PCP use. These may not be the relevant time windows since experimental studies of non-pregnant humans reported excretion of various phenols to peak between 2 and 11 h after dermal or oral exposure (Janjua et al., 2008; Morrison et al., 2017; Queckenberg et al., 2010; Shin et al., 2019; V lkel et al., 2002), suggesting that it would be relevant to look at shorter time windows than those considered in most previous studies (24–48 h prior to urination).

To finely characterize associations between PCP use and the urinary concentrations of 10 phenols including bisphenol S, we used a panel design with intense urine collection (8–80 urine samples per participant) and detailed information on PCP use (including timing of use).

First, we assessed if PCP use within 0–6, 6–12 and 12–24 h prior to urination was associated with increases in phenol urinary concentrations, and then looked at the time elapsed between PCP use and urine collection with the aim of detecting peaks in phenol urinary concentrations following product use.

## 2. Methods

### 2.1. Study population

The study population consisted of a sub-sample of the SEPAGES-feasibility (Suivi de l'exposition   la pollution atmosph rique durant la Grossesse et Effets sur la Sant ) cohort that recruited 40 pregnant women before the 17th gestational week (GW, calculated from the date of the last menstrual period) from private obstetrical practices (Grenoble, France) between July 2012 and July 2013 (Ouidir et al., 2015; Vernet et al., 2018). Exclusion criteria were inability to write or speak French; being under 18 years of age; planning to give birth outside of the four maternity hospitals of the Grenoble urban area; and not being enrolled in the French social security system. This feasibility cohort was approved by the appropriate ethical committees including the Comit  de Protection des Personnes Sud-Est, the Commission Nationale de l'Informatique et des Libert s, the Comit  Consultatif sur le Traitement de l'Information en mati re de Recherche dans le domaine de la Sant  and the Agence Nationale de s curit  du M dicament et des produits de sant . All participating women provided written informed consent for biological measurements and data collection. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subject research.

### 2.2. Urine collection during pregnancy, assessment of phenol biomarker concentrations and specific gravity

Pregnant women were followed up for 7 consecutive days at three points during pregnancy (median at 13 GW (min–max: 10–18); 23 GW (min–max: 21–26) and 32 GW (min–max: 29–33)) and during these weeks of follow-up, were asked to collect a sample of all their urine voids and to record the exact date and time of each micturition. Each spot urine sample was collected in a polypropylene container provided by the study team. After collection, urine spot samples were stored at 4  C in the participants' home refrigerators until collection by study staff which occurred two or three times per week. The samples were transported in coolers to the INSERM research center (Institute for Advanced Biosciences (IAB), Grenoble), where specific gravity, a marker of urine dilution was measured using a handheld PAL 10-S refractometer (Atago, Bellevue, WA, USA). Samples were then aliquoted into polypropylene cryovials and frozen at –80  C.

We took advantage of a previous project which aimed to finely characterize variability of phenol urinary biomarker concentrations and relied on the eight women of the SEPAGES-F cohort with the smallest percentage of missing voids (< 5% over the 3 weeks of follow-up) (Vernet et al., 2018). For these women, phenols concentrations were analyzed in a total of 178 samples: 130 (73%) belonged to two women for whom we had no missing void in week 1 (72 voids from woman 1, 42 voids from woman 2) plus 8 voids each, randomly selected during the second and the third collection weeks; and 48 samples from the remaining six women for whom 8 voids each were randomly selected over the 3 weeks of follow up (Vernet et al., 2018).

Urine samples were sent on dry ice to the CDC (Atlanta, GA, USA) where phenols were quantified using online solid-phase extraction high-performance liquid chromatography-isotope dilution-tandem mass spectrometry (Zhou et al., 2014). Total urinary concentrations of 2,4- and 2,5-dichlorophenols, benzophenone-3, bisphenol A, bisphenol S, triclosan, butylparaben, methylparaben, ethylparaben, and propylparaben were quantified. 2,4- and 2,5-dichlorophenol are not expected to

be found in PCPs and were only included in this study as controls (i.e., no association with PCP was expected for these compounds).

### 2.3. Use of personal care products and confounders

Relying on the date and exact time of each use of PCP reported by the women (the list of PCPs is given in Table 3), we characterized PCP use in relation to each urine void as the total number of PCP applications as well as the use of specific PCPs (yes/no) in the 0–6, 6–12 or 12–24 h before urine collection.

In addition, women provided the date and exact time of food and drink consumption during the follow up weeks. At the start of the study, we also collected information about their anthropometry (weight and height), demographic characteristics, and social economic status including age, parity, marital status, education level and profession.

### 2.4. Statistical methods

For phenols with more than 90% detection frequency, associations between use of PCPs and phenol urinary concentration were assessed using adjusted linear regression, where concentrations below the limit of detection (LOD) were replaced by the specific instrumental reading values or with the lowest instrumental reading value divided by the square root of two, when no signal was detected.

To study the associations for phenols with less than 90% detection frequency, we used Tobit models where concentrations below the LOD were considered left-censored (Helsel, 2011; Lubin et al., 2004).

The explained variable in these models was the phenol concentration, and all concentrations were ln-transformed prior to analysis to approach normal distribution.

We considered the total number of PCP applications and the use of specific PCP in the 0–6, 6–12 or 12–24 h before each urine collection as the explanatory variables.

In addition, for all phenols, when we identified a significant positive association with the specific PCPs, we generated timing of exposure (time of PCP use) as the time since last use of any of the identified PCPs. We then assessed the association between the phenol concentrations and timing of exposure with the aim of detecting peaks in phenol concentration. For this analysis, time since last use of a PCP was coded as restricted cubic splines (5 knots).

Adjustment factors were identified *a priori* as possibly associated with the use of PCP and/or the phenol urinary concentrations. These included the women (fixed effect), specific gravity, time (categories: 0000–0600, 0601–1200, 1201–1800, 1801–2359 h) and day (weekday/weekend) of urine collection as well as the use of PCP (as the total number of applications or specific PCP use (yes/no)) in the time windows other than the one studied (e.g., analysis looking at the association with PCP use in the 12–24 h time window was adjusted for PCP use in the 0 to 6 and 6–12 h time windows).

In the models exploring the associations of urinary phenol concentrations with use of a specific PCP (yes/no), for power reasons, PCPs were not considered if the frequency of use was less than five times in any of the time windows. These included mouth wash, nail polish, sunscreen, eye shadow and thermal spring water in all windows, intimate soap in the 0 to 6 and 6–12 h windows, intimate soap in the

6–12 h time windows and toothpaste in the 12–24 h time window.

Depending on the analysis, effect estimates were reported as the percent change in the phenol urinary concentration, either 1) for an additional PCP application (analysis relying on the total number of PCP applications); or 2) in a period in which a PCP had been used, compared to a period without PCP use (analysis relying on specific PCP use).

### 2.5. Sensitivity analyses

We considered other adjustment factors suspected to be associated with phenol urinary concentrations including gestational age at sampling, and, for the phenols likely to be found in food (parabens and bisphenols (Liao et al., 2013; Liu et al., 2018; Rudel Ruthann et al., 2011)), the time elapsed since the last meal (food or drink).

For comparison with previous studies, we also considered use of PCP 24 h before urination (Supporting information, Fig. S3).

With the exception of the two dichlorophenols considered as negative controls, the studied phenols were selected because they have been previously detected in various PCPs (Dodson et al., 2012; Guo et al., 2014; Liao and Kannan, 2014; Lu et al., 2018). In addition, higher urinary concentrations of paraben urinary concentrations in relation to use of multiple or single PCPs have been consistently reported in previous studies (Ashrap et al., 2018; Berger et al., 2018; Braun et al., 2014; Ferguson et al., 2017; Fillol et al., 2019; Fisher et al., 2017; Husøy et al., 2019; Kim et al., 2018; Larsson et al., 2017; Meeker et al., 2013; Nassan et al., 2017; Philippat et al., 2015). Given the consistency in results for an association between PCP use and most of the studied phenols, we decided to not correct our analysis for the number of tests performed (Rothman, 1990). However, because we were aware that chance findings cannot be rule out, in the discussion section we gave more weight to the associations that were previously described in the literature while other associations should be considered as hypothesis generating.

All analyses were carried out using STATA/SE 14 (StataCorp, College Station, TX, USA) and R version 3.4.3 statistical software.

## 3. Results

### 3.1. Study participants

The eight women included in this study were aged between 26.7 and 37.6 years old at enrolment; five were nulliparous; two primiparous and one was multiparous. All women had a college degree (Table 1).

### 3.2. Urinary phenol concentrations

Of the 178 urine samples collected over the three periods of follow up, 8% (n = 13) were collected between 00 and 6:00, 34% (n = 62) between 6:01 and 12:00, 26% (n = 46) between 12:01 and 18:00 and 32% (n = 57) between 18:01 and 23:59 h. Most samples (71%) were collected during a weekday.

Phenols were detected in more than 74% of the urine samples except for benzophenone-3 that was only detected in 35% (n = 62) of the samples. The highest concentrations were observed for the four parabens, followed by triclosan and bisphenol A (Table 2). Spearman

**Table 1**

Characteristics of the eight women of the SEPAGES feasibility study for whom spot urine samples were analyzed for phenol concentrations.

|   | Woman 1 | Woman 2 | Woman 3 | Woman 4 | Woman 5 | Woman 6 | Woman 7 | Woman 8 |
|---|---------|---------|---------|---------|---------|---------|---------|---------|
| Age (years)                                   | 33.5    | 27.4    | 26.7    | 30.8    | 37.6    | 30.6    | 28.9    | 28.0    |
| Years of education after high school          | 6       | 6       | 5       | 7       | 9       | 5       | 5       | 5       |
| Height (cm)                                   | 169     | 167     | 162     | 170     | 167     | 169     | 173     | 157     |
| Weight before pregnancy (kg)                  | 58      | 76      | 71      | 69      | 59      | 62      | 60      | 53      |
| Number of children                            | 1       | 1       | 0       | 0       | 2       | 0       | 0       | 0       |
| Number of urine samples included in the study | 8       | 8       | 80      | 8       | 50      | 8       | 8       | 8       |

**Table 2**Distribution of urinary phenol concentrations ( $\mu\text{g/L}$ ) in 178 urine samples collected from eight women of the SEPAGES feasibility study.

| Biomarker          | LOD | % > LOD | Percentiles |       |      | GM    | Max    |
|--------------------|-----|---------|-------------|-------|------|-------|--------|
|                    |     |         | 5           | 50    | 95   |       |        |
| Benzophenone-3     | 0.3 | 35      | < LOD       | < LOD | 17.2 | 0.8   | 378.5  |
| Bisphenol A        | 0.1 | 99      | 0.2         | 1.6   | 8.9  | 1.5   | 30.4   |
| Bisphenol S        | 0.1 | 97      | 0.1         | 0.3   | 2.6  | 0.3   | 212    |
| 2,4 dichlorophenol | 0.1 | 99      | 0.1         | 0.3   | 1.4  | 0.3   | 6.2    |
| 2,5 dichlorophenol | 0.1 | 98      | 0.1         | 0.4   | 9.2  | 0.5   | 278.4  |
| Methylparaben      | 1.0 | 99      | 3.7         | 128   | 4080 | 129.0 | 8730   |
| Ethylparaben       | 1.0 | 83      | < LOD       | 6.1   | 1262 | 6.4   | 203.5  |
| Propylparaben      | 0.1 | 100     | 0.2         | 14.9  | 4962 | 12.1  | 1253.6 |
| Butylparaben       | 0.1 | 90      | < LOD       | 2.0   | 88.2 | 1.6   | 335.4  |
| Triclosan          | 1.0 | 74      | < LOD       | 1.8   | 28.1 | 1.6   | 1474.8 |

LOD: Limit of detection, GM: geometric mean, Max: maximum.

**Table 3**Number of urine samples for which specific PCPs were used in the 0–24 h preceding urine collection ( $^a\text{N} = 169$ ).

| PCPs                     | 0–6 h        |        | 6–12 h       |        | 12–24 h      |        | 0–24 h       |        |
|--------------------------|--------------|--------|--------------|--------|--------------|--------|--------------|--------|
|                          | $^a\text{N}$ | (%)    | $^a\text{N}$ | (%)    | $^a\text{N}$ | (%)    | $^a\text{N}$ | (%)    |
| Toothpaste               | 78           | (46.2) | 93           | (55.0) | 136          | (80.5) | 166          | (98.2) |
| Face cream               | 59           | (34.9) | 58           | (34.3) | 85           | (50.3) | 136          | (80.5) |
| Deodorant                | 47           | (27.8) | 34           | (20.1) | 57           | (33.7) | 129          | (76.3) |
| Makeup remover           | 16           | (9.5)  | 35           | (20.7) | 58           | (34.3) | 106          | (62.7) |
| Mascara                  | 41           | (24.3) | 32           | (18.9) | 44           | (26.0) | 112          | (66.3) |
| Foundation               | 38           | (22.5) | 31           | (18.3) | 39           | (23.1) | 103          | (60.9) |
| Bar soap                 | 25           | (14.8) | 25           | (14.8) | 39           | (23.1) | 85           | (50.3) |
| Shower gel               | 26           | (15.4) | 13           | (7.7)  | 33           | (19.5) | 66           | (39.1) |
| Shampoo                  | 21           | (12.4) | 18           | (10.7) | 30           | (17.8) | 67           | (39.6) |
| Body cream               | 12           | (7.1)  | 14           | (8.3)  | 28           | (16.6) | 49           | (29.0) |
| Conditioner              | 15           | (8.9)  | 15           | (8.9)  | 20           | (11.8) | 48           | (28.4) |
| Lip/Chapstick            | 17           | (10.1) | 17           | (10.1) | 21           | (12.4) | 43           | (25.4) |
| Perfume                  | 11           | (6.5)  | 8            | (4.7)  | 15           | (8.9)  | 32           | (18.9) |
| Contour                  | 16           | (9.5)  | 8            | (4.7)  | 16           | (9.5)  | 36           | (21.3) |
| Facial cleanser          | 11           | (6.5)  | 8            | (4.7)  | 13           | (7.7)  | 26           | (15.4) |
| Anti-stretchmarks' cream | 10           | (5.9)  | 6            | (3.6)  | 12           | (7.1)  | 23           | (13.6) |
| Hand cream               | 6            | (3.6)  | 4            | (2.4)  | 11           | (6.5)  | 20           | (11.8) |
| Intimate soap            | 4            | (2.4)  | 3            | (1.8)  | 5            | (3.0)  | 12           | (7.1)  |
| Thermal spring water     | 5            | (3.0)  | 2            | (1.2)  | 3            | (1.8)  | 8            | (4.7)  |
| Eye shadow               | 4            | (2.4)  | 1            | (0.6)  | 1            | (0.6)  | 6            | (3.6)  |
| Sunscreen cream          | 1            | (0.6)  | 0            | (0)    | 2            | (1.2)  | 3            | (1.8)  |
| Nail polish              | 1            | (0.6)  | 0            | (0)    | 1            | (0.6)  | 2            | (1.2)  |
| Mouth wash               | 1            | (0.6)  | 0            | (0)    | 1            | (0.6)  | 2            | (1.2)  |

 $^a\text{N}$ : Including urine samples collected after the first report of PCP use.**Table 4**Adjusted percent change ( $\beta$ ) in the phenol urinary concentrations in relation to the total number of PCP applications in the last 0 to 6, 6 to 12 and 12–24 h ( $\text{N} = 169^a$  urine samples of 8 women).

|                    | 0–6 h   |               | 6–12 h  |               | 12–24 h |               |
|--------------------|---------|---------------|---------|---------------|---------|---------------|
|                    | $\beta$ | 95% CI        | $\beta$ | 95% CI        | $\beta$ | 95% CI        |
| Benzophenone-3     | -23.4   | [-42.6; 2.2]  | -16.5   | [-37.0; 10.7] | 7.0     | [-14.2; 33.4] |
| Bisphenol A        | -5.7    | [-10.6; -0.5] | -4.1    | [-9.4; 1.5]   | 3.7     | [-1.3; 8.9]   |
| Bisphenol S        | 1.2     | [-5.1; 8.0]   | 4.6     | [-2.4; 12.1]  | 12.4    | [5.9; 19.3]   |
| 2,4 dichlorophenol | -2.0    | [-4.6; 0.6]   | -0.2    | [-3.0; 2.6]   | 1.6     | [-0.8; 4.0]   |
| 2,5 dichlorophenol | -2.2    | [-4.8; 0.6]   | -0.6    | [-3.5; 2.4]   | 2.4     | [-0.1; 5.0]   |
| Methylparaben      | 0.5     | [-6.1; 7.5]   | 2.7     | [-4.4; 10.4]  | 4.1     | [-2.1; 10.8]  |
| Ethylparaben       | 7.9     | [0.9; 15.4]   | -0.7    | [-7.6; 6.6]   | -1.2    | [-7.1; 5.0]   |
| Propylparaben      | 7.5     | [-1.8; 17.7]  | 11.1    | [0.9; 22.3]   | 12.9    | [3.9; 22.7]   |
| Butylparaben       | 14.8    | [5.9; 24.5]   | 5.3     | [-3.4; 14.7]  | -3.7    | [-10.5; 3.7]  |
| Triclosan          | -0.1    | [-9.5; 10.3]  | 3.2     | [-7.1; 14.6]  | 5.5     | [-3.7; 15.5]  |

Effect estimates are reported as the percent change in phenol urinary concentration for an additional PCP application in the studied time window.

Adjustment factors: woman, specific gravity, hour and day of urine sample collection and use of PCP in other time windows than the window considered (i.e. for the 0–6 h window, we adjusted for PCP use in the 6 to 12 and 12–24 h windows, for the 6–12 h window, we adjusted for use in the 0 to 6 and 12–24 h windows and for the 12–24 h window, we adjusted for use in 0–6 and 6–12 h windows).

 $^a\text{N}$ : Including urine samples collected after the first report of PCP use.

correlation coefficients were higher between compounds of similar chemical structures: among the parabens (Spearman's coefficient ( $\rho$ ) = 0.57–0.97) and between the dichlorophenols ( $\rho$  = 0.53). We also observed moderate positive correlations between bisphenol A and 2,4 dichlorophenol ( $\rho$  = 0.50) and between triclosan and the dichlorophenols ( $\rho$  = 0.49 and 0.53 for 2,4- and 2,5- dichlorophenol, respectively). Spearman correlation coefficients between the phenols and specific gravity ranged from -0.12 (propylparaben) to 0.79 (2,4-dichlorophenol, [Table S3](#)). The intraclass correlation coefficients (ICC) for these compounds were previously discussed in detail by [Vernet et al. \(2018\)](#). Briefly, we observed high to moderate within-day variability, with ICCs ranging from 0.03; (95% CI: 0.00, 0.15) for ethylparaben to 0.50 (95% CI: 0.26, 0.73) for bisphenol S ([Vernet et al., 2018](#)).

### 3.3. Use of personal care products

Women reported use of over 23 different PCPs listed in [Table 3](#). The most frequently used PCPs through the day were toothpaste (used in the last 24 h for 98% of the urine samples), face cream (80%), deodorant (76%) and makeup remover (63%) ([Table 3](#)). The median number of PCP applications varied by time window and was 1 (min: 0, max:16), 1 (min: 0, max:15) and 3 (min:0, max: 12) in the 0 to 6, 6 to 12 and 12–24 h windows preceding urination, respectively.

### 3.4. Associations between use of PCPs and paraben urinary concentrations

For three of the four parabens assessed, we observed positive associations with the total number of PCP applications, and these varied

by time window across parabens (Table 4). In the 0 to 6 time window, the concentrations of ethylparaben and butylparaben increased by 7.9% (95%CI = 0.9; 15.4) and 14.84% (95%CI = 5.9; 24.5) for each additional PCP application, respectively, while the propylparaben concentration increased by 11.1% (95%CI = 0.9; 22.3) and 12.9% (95%CI = 3.9; 22.7) for each additional PCP application in the 6–12 h and 12–24 h time windows respectively. No clear association was observed for methylparaben in all considered time windows (lowest p-value = 0.2) nor for ethylparaben and butylparaben in the longer time windows (6–12 and 12–24 h, lowest p-value = 0.24).

Among the 18 different PCPs considered in the specific PCP analysis, 12 were associated with increased urinary concentrations of one paraben or more in at least one time window. These corresponded to 48 positive associations (25%) out of the 192 tests performed in our main analysis for parabens (17 PCPs \* 4 parabens in 0–6 h time window, 16 PCPs \* 4 parabens in 6–12 h time window and 18 PCPs \* 4 parabens in 12–24 h time window, Fig. 1, Table S6). These PCPs included toothpaste (ethylparaben, butylparaben), face cream (ethylparaben, propylparaben, butylparaben), hand cream (propylparaben, butylparaben), makeup-remover (all parabens), colored cosmetics: mascara (all parabens), foundation (methylparaben, propylparaben, butylparaben), contour and lip/chap stick (ethylparaben, propylparaben, butylparaben), bar soap (methylparaben, ethylparaben), shampoo (propylparaben), facial cleanser (ethylparaben) and perfume (propylparaben, butylparaben). As observed with the total number of PCP applications, the positive associations for ethylparaben and butylparaben were mostly observed in the 0–6 h window. Most of the positive associations for methylparaben were observed in the 12–24 h window.

Relying on the time elapsed since last PCP use, we observed a peak in urinary concentration of ethylparaben, butylparaben and propylparaben at 2.86, 2.55 and 2.67 h since last use of a PCP respectively. No peak was observed for methylparaben, for which concentrations tended to remain constant with the time elapsed since last PCP use (Fig. 2).

### 3.5. Other phenols and PCP use

Bisphenol S concentrations increased by 12.4% (95% CI = 5.9; 19.3, Table 4) for each additional PCP use in the past 12–24 h. No association was seen in the earlier time windows. In line with these results, in the analysis relying on time since last PCP use, we observed a peak in bisphenol S urinary concentration at 14.2 h since last PCP use (Fig. 2). Specific PCPs such as anti-stretchmarks cream (in the 0 to 6 and 6–12 h windows), facial cleanser and shower gel (in the 6 to 12 and 12–24 h windows) were positively associated with bisphenol S (Fig. 1, Table S6).

No positive associations were observed with bisphenol A and the number of PCP applications, in all three time windows considered. In the single PCP use models, the only positive association observed for this compound was with makeup remover use in the 0 to 6 time window (Fig. 1, Table S6). The concentration of bisphenol A tended to remain constant with the time elapsed since last PCP use (Fig. 2).

Null associations were observed with the number of PCP applications and concentrations of triclosan, benzophenone-3, 2,4 and 2,5 dichlorophenol. Regarding use of specific PCPs, triclosan concentrations increased with use of deodorant in the 12–24 h window and lip/chapstick in the 6–12 h window, but remained constant with time elapsed since last PCP use. Use of deodorant was associated with an increase in the 2,4-dichlorophenol urinary concentration (Fig. 1, Table S6).

Benzophenone-3 was excluded from the specific PCP use analysis because of the non-convergence of the Tobit model, probably in relation to the relatively high percentage of samples with non-detectable concentrations of this phenol (65%).

### 3.6. Sensitivity analysis

Adjusting for time since last meal and gestational age at urine sampling did not change our main results (Tables S4 and S5, and Fig. S2). For comparison with previous studies, results for the 0–24 h time window are displayed in the Supporting Information Fig. S3.

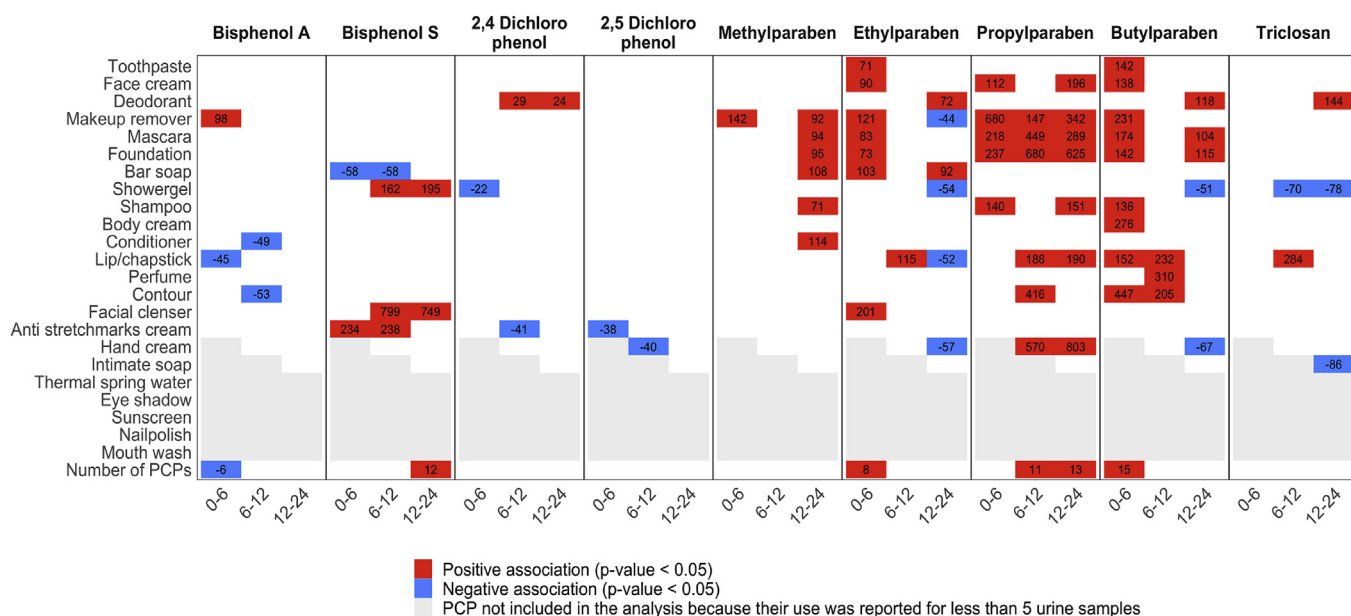
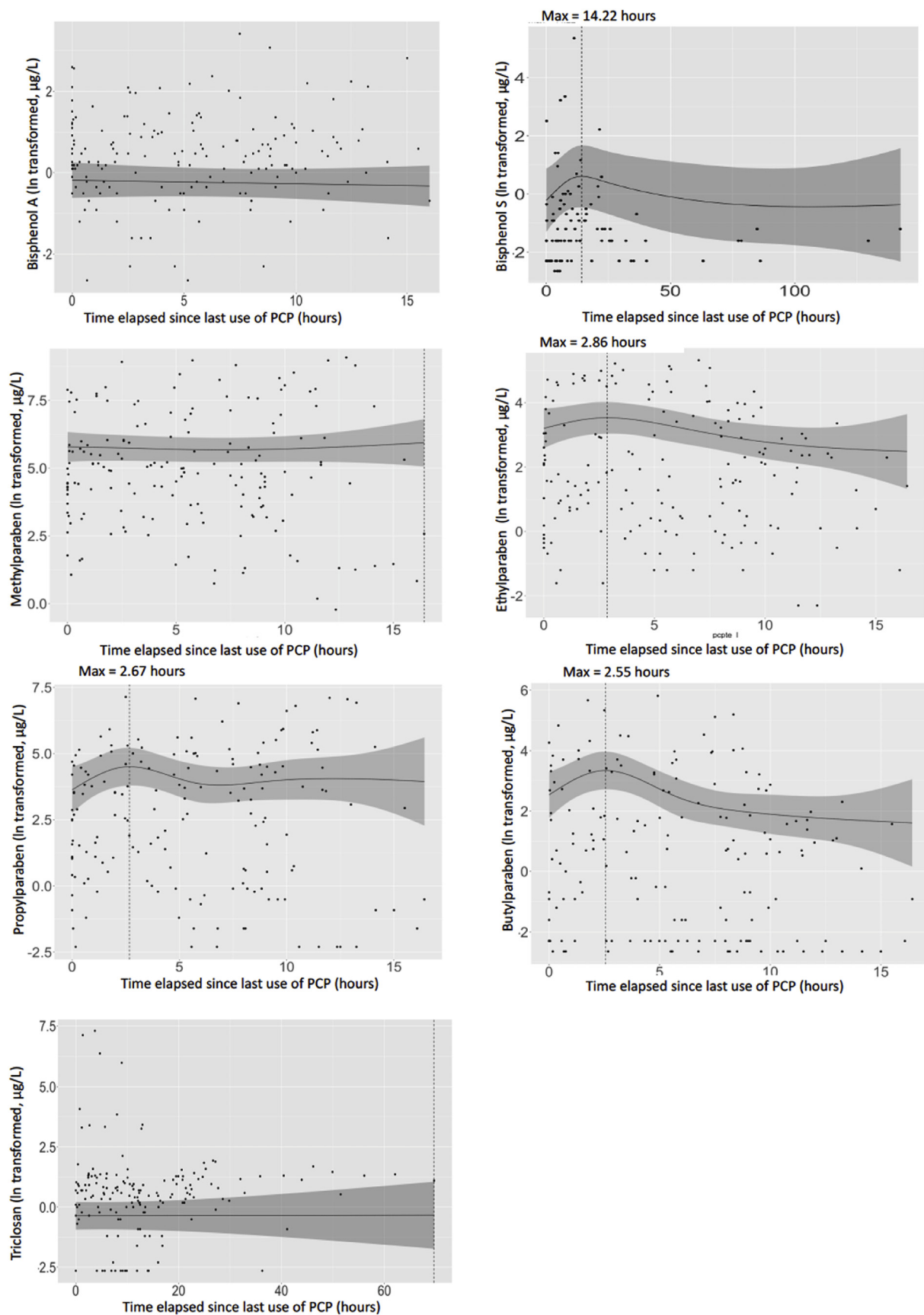


Fig. 1. Adjusted percent change in phenol urinary concentrations with specific PCP use (yes/no) and the total number of PCP applications in the past 0 to 6, 6 to 12 and 12 to 24 h. Adjustment factors were woman (fixed effect), specific gravity, day and hour of urine sample collection and use of PCP in other windows than the window considered. Only associations with p-value below 5% are displayed.



**Fig. 2.** Adjusted associations between the time elapsed since last use of PCP, modeled using restricted cubic splines with 5 knots, and phenol urinary concentrations. Max: time since last use of PCP (in hours) at which highest predicted concentration was observed. Adjustment factors were woman (fixed effect), specific gravity, time and day of urine collection.

#### 4. Discussion

This study relying on detailed information on intra-individual variations in PCP use and phenol concentrations of eight women in which 178 urine samples were analyzed, suggested that use of many PCPs were positively associated with urinary concentrations of ethylparaben, butylparaben, propylparaben and bisphenol S. These increases in urinary concentrations were observed within 0–6 h for ethylparaben and butylparaben, or 12–24 h for bisphenol S after PCP use. Results were unclear for propylparaben, with the analysis relying on time since last use suggesting that the maximal value was attained at approximately 3 h after PCP use (Fig. 2), while the analysis relying on the total number of applications (Table 4) suggested associations in the 6 to 12 and 12–24 h time windows.

##### 4.1. Strengths and limitations

We relied on repeated urine samples to quantify urinary phenol concentrations and we simultaneously collected information on the type of PCP used and the exact time of use. This allowed us to precisely characterize temporal relations between PCP use and phenol urinary concentrations, and to consider shorter time windows of exposure to PCPs (0–6 and 6–12 h prior to urination) than those considered in previous studies which were usually longer than 24 or 48 h prior to urination (Ashrap et al., 2018; Berger et al., 2018; Braun et al., 2014; Ferguson et al., 2017; Meeker et al., 2013; Nassan et al., 2017; Philippat et al., 2015; Stacy et al., 2017).

Previous studies relying on these longer time windows may have missed the rise in phenol urinary concentrations reported in toxicokinetic studies within a few hours following PCP use (between 2 and 11 h depending on the compounds and the routes of exposure) (Moos et al., 2016; Queckenberg et al., 2010; Sandborgh-Englund et al., 2006; Völkel et al., 2002). In addition, for two of the eight women included, we assessed phenol concentrations in all of the urine samples of a week ( $n = 114$ ). Although restricted to two subjects, this design is ideal if one seeks to detect a rise in urinary concentrations of short-lived compounds after a given exposure (e.g., use of PCPs) because all the urine samples produced after the given exposure are available.

Our small sample size (eight pregnant women) is a result of the tradeoff between building on within-subject (temporal) contrasts than between-subject contrasts. Generally, studies like ours, relying on within-subject contrasts are less prone to confounding bias (for example due to differences between subjects using and those not using specific PCPs). The downside is the limited between-subject variability both in terms of metabolism and pattern of use of PCPs, that limits generalizability of findings. For comparison, to our knowledge, one of the two previous studies with such detailed information on both urinary phenol concentrations and PCP use, was also restricted to eight participants (Koch et al., 2014). Furthermore, we cannot rule out residual confounding arising from other factors not extensively assessed in our study such as use of pharmaceuticals (Dodge et al., 2015; Soni et al., 2005), exposure to thermal receipts' ink (Liao and Kannan, 2011) and diet, which are sources of some of the studied phenols.

##### 4.2. Associations between use of PCPs and parabens' urinary concentrations

Parabens are commonly used as preservatives in a wide range of PCPs, alone or in combination (Dodson et al., 2012; Guo et al., 2014). The total number of PCP applications was associated with higher urinary concentrations of ethylparaben, propylparaben and butylparaben; these findings are in line with former findings of studies among pregnant women (Braun et al., 2014; Fisher et al., 2017) and non-pregnant adults and children (Nassan et al., 2017; Philippat et al., 2015). For these three parabens, we observed a peak in the urinary concentration at approximately 3 h after the last PCP use. This timing is in between what was reported following oral (about 2 h for butylparaben and

propylparaben among non pregnant individuals (Moos et al., 2016; Shin et al., 2019)) and dermal exposure (8 h for butylparaben in men (Janjua et al., 2008)), suggesting that urinary concentrations may result from a combination of exposure sources and routes.

Ethylparaben, propylparaben and butylparaben were positively associated with various specific PCPs. Some of these associations were consistent with previous studies; this was in particular the case of associations of these three parabens with creams, colored cosmetics (mascara, foundation and contour) and hair care products (shampoo and conditioner) (Ashrap et al., 2018; Berger et al., 2018; Braun et al., 2014; Fisher et al., 2017; Kim et al., 2018; Meeker et al., 2013; Philippat et al., 2015); of ethylparaben with cleansers (Fisher et al., 2017); and of butylparaben with deodorant (Fisher et al., 2017; Philippat et al., 2015), perfume and toothpaste (Fisher et al., 2017). Other associations were highlighted for the first time by our study; for all three parabens with makeup remover and for ethylparaben with bar soap, deodorant and toothpaste. Compared to previous studies of pregnant women that assessed associations between PCP use and urinary concentrations, the median concentration of ethylparaben and butylparaben were higher in our study (Ashrap et al., 2018; Braun et al., 2014; Fisher et al., 2017; Larsson et al., 2017) while the propylparaben median was similar to that reported in Sweden and Puerto Rico (Ashrap et al., 2018; Larsson et al., 2017) but lower than those reported in the USA (Braun et al., 2014).

Similar to other parabens, methylparaben has been detected in a wide range of PCPs in the USA (Dodson et al., 2012; Guo et al., 2014). In our study this paraben was not clearly associated with the number of PCP applications in all three time window considered, nor with the time elapsed since last PCP use. This could relate to having other predominant sources than PCP use, such as diet (Liao et al., 2013) or pharmaceuticals use (Dodge et al., 2015; Soni et al., 2005) that were not extensively considered in this study. When PCPs were considered separately, methylparaben exhibited positive associations with four, including makeup-remover, colored cosmetics, conditioner and bar soap. Our results for colored cosmetics and soap were in line with previous studies of pregnant women (Ashrap et al., 2018; Braun et al., 2014; Fisher et al., 2017; Meeker et al., 2013), adolescent girls (Berger et al., 2018) and non-pregnant adult women (Fillol et al., 2019; Philippat et al., 2015). The median concentration of methylparaben in our study was higher than that reported in three of these studies (Ashrap et al., 2018; Braun et al., 2014; Fisher et al., 2017) and lower than that in Braun et al. (2014).

In summary, the associations between the paraben concentrations and PCPs were observed in varying time windows. For a given route of exposure, half-life and excretion time are expected to be relatively similar across the four parabens studied (Janjua et al., 2008; Moos et al., 2016; Shin et al., 2019). The differences in time windows could therefore be due to difference in routes of exposure across parabens.

##### 4.3. Other phenols and PCP use

Studies assessing phenols in PCPs from the USA and China reported presence of bisphenol A and S in lotions, shampoo, conditioner, facial cleansers, sunscreens, lipsticks and toothpaste (Dodson et al., 2012; Liao and Kannan, 2014; Lu et al., 2018).

In our study, bisphenol S urinary concentration increased with total number of PCP applications in the 12–24 h time window. We observed a peak in urinary concentration 14.2 h after last PCP use. Specific PCPs attributed to this increase were anti-stretchmarks cream, facial cleanser and shower gel, similar to PCPs in which bisphenol S was previously detected in other regions. Two previous studies among Puerto Rican pregnant women (Ashrap et al., 2018) and Norwegian female and male adults (Husøy et al., 2019) did not highlight any associations with PCP use within 24 h prior to urine collection for this phenol, thus our results should be interpreted with caution.

We observed no positive associations with bisphenol A, although



positive associations with mouthwash use have been previously reported (Meeker et al., 2013). Bisphenol A has recently been recognized as a substance of very high concern in the EU (ECHA, 2017).

Our results did not strongly support associations between triclosan and the number of PCP applications. In the analysis of specific PCPs analysis, two of the observed associations for triclosan were positive (i.e., increased triclosan concentration following use of deodorant and lip/chap stick) while the other two were negative (i.e. decreasing triclosan concentration in relation to intimate soap and shower gel). Contrary to a previous publication (Philippat et al., 2015), no significant association between toothpaste use and triclosan concentration was observed. In the EU, triclosan concentration in toothpaste is limited to a concentration of 0.3% of product weight. We were limited in studying previously reported positive associations between triclosan concentrations and liquid soap, hair spray and sunscreen (Ashrap et al., 2018; Berger et al., 2018; Meeker et al., 2013; Stacy et al., 2017) because of low use of such PCPs in our study population. Concentrations of triclosan in our study were lower than those recorded among pregnant women from Puerto Rico (Ashrap et al., 2018; Meeker et al., 2013).

We observed no association between aggregated PCP use and benzophenone-3 concentrations. Unfortunately we did not have enough variability for both use of sunscreen (reported less than 5 times) and benzophenone-3 concentrations (only 35% of detection) to study this association.

## 5. Conclusion

Among eight French pregnant women, we observed that the use of PCPs was associated with a short-term increase in urinary concentration of ethylparaben, butylparaben and propylparaben and to some extent (for specific PCP use only) with methylparaben. This was consistent with previous studies conducted among pregnant women and non-pregnant individuals in America and Sweden. This study also reported that use of various PCPs was associated with increased bisphenol S concentrations, a possible substitute of bisphenol A with suspected endocrine disrupting capacity (Qiu et al., 2019). This finding needs replication in further studies.

## Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijheh.2020.113518>.

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