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Levels, variability and determinants of environmental phenols in pairs of Norwegian mothers and children

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ABSTRACT

Background: Exposure to environmental phenols including parabens, bisphenols (BPs), oxybenzone/benzophenone-3 (BP-3) and triclosan (TCS) is ubiquitous. Due to evidence of their estrogenic activity, they have been considered as chemicals of concern. The exposure of the Norwegian population to these compounds is presently unknown.

Aims: To measure urinary levels of twelve different environmental phenols including four emerging bisphenols: S, F, B and AF (abbreviated as BPS, BPF, BPB and BPAF, respectively) in a healthy Norwegian population. We have calculated short-term variability, estimated daily intakes and investigated important determinants of exposure.

Methods: Urine samples were collected from mothers (n = 48) and their children (n = 56) during spring/summer 2012 in two counties in Norway.

Results: Six environmental phenols namely methyl, ethyl and propyl paraben, BPA, BP-3 and TCS were detected in almost 100% of the urine samples. Among the emerging bisphenols, BPS was detected most frequently in the urine samples (42–48%) followed by BPF (4–15%). Parabens were positively and significantly correlated to each other in both mothers and children. Levels of parabens and BP-3 were higher in mothers compared to children. All mothers and children had lower estimated daily intakes (back calculated from the urinary concentrations) of parabens and BPA than the respective acceptable and tolerable daily intakes (ADIs and TDIs) established by the European Food Safety Authority (EFSA). Observed intraclass correlation coefficients (ICCs) indicated moderate to high reliability of spot urine measurements for all the environmental phenols (ICCs: 0.70–0.97). Use of hair products, deodorants, face and hand creams were significantly associated with higher urinary levels of parabens.

Conclusions: Occurrence of environmental phenols in healthy Norwegian women and children is abundant. Among emerging bisphenols, there is widespread exposure to BPS. A single spot urine sample can be used for estimating short-term exposures of environmental phenols. Urinary levels of parabens were associated with use of PCPs.

1. Introduction

Parabens, bisphenols (BPs), oxybenzone/benzophenone-3 (BP-3), triclosan (TCS) and triclocarban (TCC) are man-made chemicals used in various consumer products. Parabens are alkyl or aryl esters of *para*-hydroxy benzoic acid and have mainly been used as antimicrobial preservatives in food, personal care products (PCPs) and pharmaceuticals (Boberg et al., 2010). Bisphenol A (BPA) is used in manufacturing of polycarbonate plastic and epoxy resins and is found in different products like cans (food and drink), dental sealants, thermal receipts, food packaging and PCPs (Geens et al., 2012). In addition, emerging bisphenols like BPS, BPF, BPAF, BPAP, BPB, BPZ, BPP and bisphenol A

Abbreviations: ADI, acceptable daily intake; BMI, body mass index; BW, body weight; BP, bisphenol; BP-3, oxybenzone/benzophenone-3; BuP, butyl paraben; DEMOCOPHES, Demonstration of a study to Coordinate and Perform Human biomonitoring on a European Scale; EDCs, endocrine disrupting chemicals; EFSA, European Food and Safety Authority; EtP, ethyl paraben; F_{ue}, fraction excreted in urine; ICC, intraclass correlation coefficient; GM, geometric mean; LOD, limit of detection; LOQ, limit of quantification; MeP, methyl paraben; MoBa, Mother and Child Cohort study; MRM, multiple reaction monitoring; MP, mobile phase; MS, mass spectrometry; NA, not analyzed; ND, not detectable; NOAEL, no observed adverse effect level; PCPs, personal care products; PrP, propyl paraben; RSD, relative standard deviation; SCCP, Scientific Committee on Consumer products; SG, specific gravity; SPE, solid phase extraction; ln, natural logarithm; TDI, tolerable daily intake; TCS, triclosan; TCC, triclocarban; UPLC, ultra-performance liquid chromatography; UV, ultraviolet

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diglycidyl ether are used as substitutions for BPA in some of the consumer products (Gramec Skledar and Peterlin Masic, 2016). BP-3 is mainly used as UV filters in sunscreens and as UV stabilizer in some food packaging (Krause et al., 2012). TCS and TCC are used as antimicrobial and antifungal agent in products like toothpaste, soaps, detergents and other hygiene and PCPs (Witorsch and Thomas, 2010). Apart from TCC, all these compounds have a phenol group in their chemical structure and are often referred to as "environmental phenols" as they are known to be widespread in the environment.

Although these environmental phenols are non-persistent chemicals and have short elimination half-lives in humans (parabens: 1–7 h, bisphenols: 6 h, BP-3 and TCS: < 24 h) (Kadry et al., 1995; Kim and Choi, 2014; Moos et al., 2016a; Sandborgh-Englund et al., 2006; Thayer et al., 2015), their widespread use and potential endocrine disrupting properties have made them chemicals of concern (Bergman et al., 2013; Ghazipura et al., 2017). Due to its estrogen activity and reproductive toxicity, BPA has been banned in manufacture of infant feeding bottles in Europe since 2011 (EFSA Panel on Food Contact Materials, 2015). In a recent risk assessment of BPA published by European Food and Safety Authority (EFSA), the tolerable daily intake (TDI) was decreased from 50 μg/kg body weight (bw) to 4 μg/kg bw (EFSA Panel on Food Contact Materials, 2015). Exposure to parabens, BP-3, TCS and TCC have been associated to weak estrogenic activity and some adverse health effects in humans (Bledzka et al., 2014; Giulivo et al., 2016; Kim and Choi, 2014; Wang and Tian, 2015). EFSA has established an acceptable daily intake (ADI) of < 10 mg/kg bw for the sum of methyl paraben (MeP) and ethyl paraben (EtP) (EFSA, 2004). Scientific committee on consumer products (SCCP) has regulated the use of BP-3 and the maximum allowed concentration is 6% in ready for use preparations (SCCP, 2008). The use of TCS is also regulated and is allowed in some cosmetic products up to a concentration of 0.3% (SCCP, 2009).

In Norway, only two studies presenting levels of MeP, propyl paraben (PrP), butyl paraben (BuP), BPA and TCS in 45 Norwegian pregnant women are available (Bertelsen et al., 2014; Guidry et al., 2015). There is only one study available showing TCS levels in Norwegian children (Bertelsen et al., 2013).

Thus, the aim of the present study was to determine the levels of 12 different environmental phenols (four parabens (MeP, EtP, PrP and BuP), five bisphenols (BPA, BPS, BPF, BPB and BPAF), BP-3, TCS and TCC) in Norwegian healthy mother-child pairs. Further, we have studied the diurnal variation and calculated the intraclass correlation coefficients (ICCs) in mothers. The determinants of exposure of these urinary phenols (diet and PCPs) were also investigated in the present study.

2. Materials and methods

2.1. Study subjects and sample collection

The study comprised 48 mothers and 56 children as described elsewhere (Sakhi et al., 2017). In brief, 48 mother-child pairs from 2 different Norwegian counties participated in the study. In addition, siblings of 8 children were also included in the study (in total 56 children). The sampling period was one complete day (24 h) and for most of the participants, it started during the evening of the first day and ended the consequent evening next day (Sakhi et al., 2017). The mothers were encouraged to collect all the spot urine samples during the study period of 24 h. Each spot urine sample was collected in a new container and labelled with day and time of collection. All the mothers provided first morning urine sample. Among 48 mothers, 21 (44%) provided all the spot urine samples, 13 (27%) collected > 3 spot urine samples and 14 collected 2–3 spot urine samples, resulting in a total of 244 spot urine samples. Among 56 children, 54 collected first morning and 53 collected afternoon/evening spot urine samples (in total 114 spot urine samples). The urine sample containers used in the present study were made of high-density polyethylene (HDPE) and the blank samples prepared in these containers showed no detectable concentration of phenols. The samples were stored in a freezer at −20 °C until analysis.

2.2. Analytical method and QA/QC measures

The environmental phenols were determined using on-line solid phase extraction (SPE) prior to ultra-high performance liquid chromatography (UPLC) coupled to tandem mass spectrometry (MS-MS). The present method included 4 parabens (MeP, EtP, PrP and BuP), 5 bisphenols (BPA, BPS, BPF, BPB and BPAF), BP-3, TCS and TCC. This analytical methodology is a modification of the previously published method (Zhou et al., 2014) and is fully validated for the above-mentioned phenols. In brief, labelled internal standards and enzyme solution were added to 200 μL of the sample. After 4 h, the enzymatic reaction was stopped by adding formic acid, the samples were centrifuged and 80 μL of the supernatant was injected into the UPLC-MS-MS system. The ionization of the analytes was performed in an electrospray source in negative mode. A signal to nose (S/N) ratio of 10 was considered as limit of quantification (LOQ). The LOD (S/N ratio of 3) was calculated from the respective LOQs and varied from 0.02–0.10 ng/mL (Table S2). Further details of the method are described in the supplementary information and Tables S1–S2.

The validation was performed at 5 different concentration levels (from 0.2 to 600 ng/mL) obtaining inter and intra precisions lower than 34% and accuracies between 69 and 154% (Table S3 and S4). The validation results were satisfactory for the environmental phenols as demonstrated by the low relative standard deviation (RSD < 26%) obtained using in-house controls and National Institute of Standards and Technology (NIST) reference material (Table S5). Additionally for BPA and TCS, two different inter-laboratory comparisons showed low z-score (between −1.30 and 0.09) and concentrations within the tolerance range (Table S6).

In order to correct for the urinary dilution, both creatinine and specific gravity (SG) were measured in all the spot urine samples as described previously (Sakhi et al., 2017). The SG adjusted concentrations were used in all the statistical analysis, because SG concentrations are less effected by age, gender, BMI, muscle mass, diet, activity and season compared to creatinine concentrations (Johns et al., 2015). The unadjusted and creatinine adjusted concentrations are presented in the supplementary information (Tables S7 and S8).

2.3. Statistical analysis

IBM SPSS version 23 and Stata (StataCorp LLC, Texas, USA) were used for the statistical analyses. The urine samples were grouped into 3 time-periods based on likely indoor exposure and daily routine activities (evening: 16–24 h, morning: 24–8 h and day: 8–16 h) (Sakhi et al., 2017). Many of the environmental phenols are used in different PCPs, which are used mostly in the morning. Thus, the day time-period samples was further divided into two time-periods of 4 h each (early day: 8–12 h and afternoon: 12–16 h) (Sakhi et al., 2017). For children, the urine samples were grouped into two time-periods (morning: 24–8 h and afternoon/evening: 12–18 h) (Sakhi et al., 2017). The mean of the concentration was taken if the participant had more than one urine sample in the specified time-period (number of participants with more than one urine sample in time periods: first evening 28, morning 9, early day 4, afternoon 15 and second evening 1). Wilcoxon test was used to compare (i) environmental phenol concentration between morning time-period (reference) and other time-periods in mothers (ii) environmental phenol concentrations in the morning urine samples with afternoon samples among children and (iii) environmental phenol concentrations in mothers' morning urine samples with the corresponding children samples. Spearman rank test was used to study correlations between different environmental phenols in both mothers and children. The statistical analysis in (ii) and (iii) were done with the

morning time-period (24–8 h) and also with first morning spot urine samples. Similar results were observed and thus only results with morning time-period urine samples are presented.

The daily intakes were estimated from unadjusted morning samples using the following formula:

Estimated daily intakes (ng/day/kg body weight)
= Unadjusted concentration (ng/mL) × 24 h urine volume (mL)
/body weight (kg) × fraction excreted in urine (F_{ue}).

Fixed 24 h urine volumes were used for mothers (1600 mL) and children (820 mL) (Cequier et al., 2017). The F_{ue} values for parabens were taken from Moos et al. (2016b) (MeP: 0.174, EtP:0.137, PrP: 0.10 (mean of iso-PrP and n-PrP)). The F_{ue} value for BPA is 1 since it is completely excreted within 24 h (Teeguarden et al., 2015; Thayer et al., 2015; Volkel et al., 2002). For BP-3 and TCS, there is lack of reliable data showing urinary elimination and thus F_{ue} value was set to 1.

ICCs were used to calculate the within and between person variability in the mothers' levels (ln transformed data) during a 24-hour period. The within and between person variabilities were calculated using mixed linear regression model with random intercept per participant. All the individual spot urine samples per participant (2–8 spot urine samples per participant) were used in calculating ICCs. ICCs above 0.80 were considered as high, 0.40–0.79 as moderate and below 0.40 as low.

We have investigated two groups of determinants based on the mostly likely exposure sources: PCPs and food. The participants registered the use of 12 different PCPs during the study period and the food consumption was assessed through 24-hour recall conducted by a trained researcher. The diet calculation system Kost Beregnings System (KBS) version 7 (Rimestad et al., 2000) was used to calculate the intake of 15 different food groups in the participants. The use of PCPs and intake of different food groups within a day, in both mothers and children are presented in the supplementary information (Tables S9 and S10, respectively). To take into account the repeated environmental phenol measurements per participant and the short-term variability, mixed model regression analysis, with random intercept per participant, was used to identify important determinants of environmental phenols exposure, using ln transformed phenols concentrations as the dependent variables. Mixed models with additional random slope for the time of urine collection were also tested and provided the same results; hence only the random intercept mixed models are presented.

For all the tests, a p-value < 0.05 was considered to be significant.

3. Results

3.1. Environmental phenol concentrations and estimated daily intakes in mothers and children

The mean age of the women and children in the present study were 42 years (range = 32–56 years) and 9 years (range = 6–12 years), respectively. Among mothers, 81% were non-smokers and 79% had a University education of ≥4 years. The mean BMI of mothers and children was 25.0 and 17.1, respectively. Among children, 47% were boys. The concentrations and the detection percent of all the environmental phenols in first morning urine samples are presented in Table 1. Apart from BuP, TCC and the emerging bisphenols (BPS, BPF, BPB and BPAF), the other environmental phenols were almost 100% detected. Among the emerging bisphenols, only BPS and BPF were detected in the urine samples with detection frequency of 42–48% and 4–15%, respectively. Other emerging bisphenols (BPB and BPAF) were not detected in the urine samples. The environmental phenols with > 50% detection were further used in statistical analysis. For the values below LOD, the concentrations calculated by the analysis instrument software program were used in order to avoid bias. For not detectables, the values were replaced with LOD / 2.

For mothers, Fig. 1 shows the median concentrations of the most abundant environmental phenols (detection frequency > 50%) in the different time-periods. The order with respect to median concentrations was: MeP > BP-3 > PrP > BPA > EtP > TCS. For MeP and PrP, morning urine samples (reference; grey bar) were significantly higher compared to evening urine samples (orange bar). The morning urine samples were significantly higher compared to any other time-period during the day for BP-3 and TCS. For BPA and EtP, no significant differences were found between the morning urine samples and other time-periods.

For children, Fig. 2 shows median concentrations of the environmental phenols in morning and afternoon/evening urine samples. As for mothers, MeP had highest and TCS had lowest median

Table 1
Environmental phenol concentrations (SG adjusted, ng/mL) in first morning spot urine sample for mothers (n = 48) and children (n = 54).

Environmental phenols		LOD	Samples > LOD (%)	Mean	Geometric mean	Percentiles							Min	Max
						5	10	25	50	75	90	95		
Mothers (n = 48)														
Parabens	MeP	0.04	100	117	61.5	6.55	12.1	29.4	62.7	171	298	388	2.27	866
	EtP	0.04	100	19.2	3.34	0.28	0.37	0.55	2.05	18.6	65.8	111	0.25	222
	PrP	0.04	99	23.0	5.38	0.22	0.51	1.61	4.47	25.7	65.1	86.1	0.08	303
	BuP	0.07	44	0.75	0.15	< LOD	< LOD	< LOD	0.09	0.48	1.87	5.55	< LOD	10.6
Bisphenols	BPA	0.04	100	3.82	3.02	1.04	1.21	1.84	3.08	4.14	7.80	11.6	0.94	14.4
	BPS	0.10	42	0.18	0.11	< LOD	< LOD	< LOD	< LOD	0.26	0.44	0.59	< LOD	0.75
	BPF	0.07	15	0.80	0.08	< LOD	< LOD	< LOD	< LOD	< LOD	4.33	7.18	< LOD	7.67
Other environmental phenols	BP-3	0.04	99	45.5	6.64	0.41	0.58	1.15	9.44	26.7	115	440	0.24	589
	TCS	0.04	96	51.4	0.39	0.08	0.11	0.14	0.21	0.42	3.47	404	0.07	1706
	TCC	0.04	19	0.03	< LOD	< LOD	< LOD	< LOD	< LOD	0.04	0.09	0.13	< LOD	0.15
Children (n = 54)														
Parabens	MeP	0.04	100	136	14.9	1.72	2.19	4.10	9.55	41.2	312	1248	1.07	2061
	EtP	0.04	100	13.1	0.91	0.25	0.33	0.47	0.60	1.10	4.09	24.9	0.18	605
	PrP	0.04	100	30.1	1.50	0.11	0.17	0.25	0.70	7.27	48.6	320	0.06	529
	BuP	0.07	21	0.80	< LOD	< LOD	< LOD	< LOD	< LOD	0.07	0.79	4.18	< LOD	24.3
Bisphenols	BPA	0.04	100	4.54	3.70	1.61	1.95	2.62	3.67	4.85	6.92	9.95	1.46	36.4
	BPS	0.10	48	0.45	0.16	< LOD	< LOD	< LOD	0.13	0.39	0.95	1.68	< LOD	8.09
	BPF	0.07	4	0.89	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	1.88	< LOD	39.2
Other environmental phenols	BP-3	0.04	100	157	4.24	0.15	0.45	1.36	4.29	10.9	27.3	126	0.14	7884
	TCS	0.04	99	53.7	0.47	0.10	0.11	0.16	0.30	0.54	3.09	243	0.08	1919
	TCC	0.04	23	0.03	< LOD	< LOD	< LOD	< LOD	< LOD	0.04	0.06	0.08	< LOD	0.09

BPB and BPAF were not detected in the urine samples.

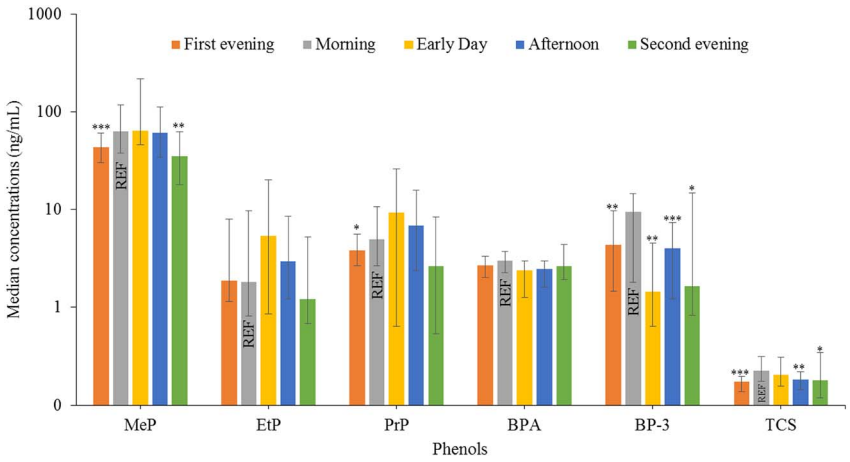

Fig. 1. Median concentrations and diurnal variation of different environmental phenols in mothers during one day. Morning urine samples are reference (REF) and Wilcoxon test was used to show if other time-periods during the day were significantly different from morning urine sample. Number of participants in time-periods (first evening: 45, morning: 48, early day: 24, afternoon: 35 and second evening: 23).
*p-Value ≤ 0.05, **p-value ≤ 0.01, ***p-value ≤ 0.001.

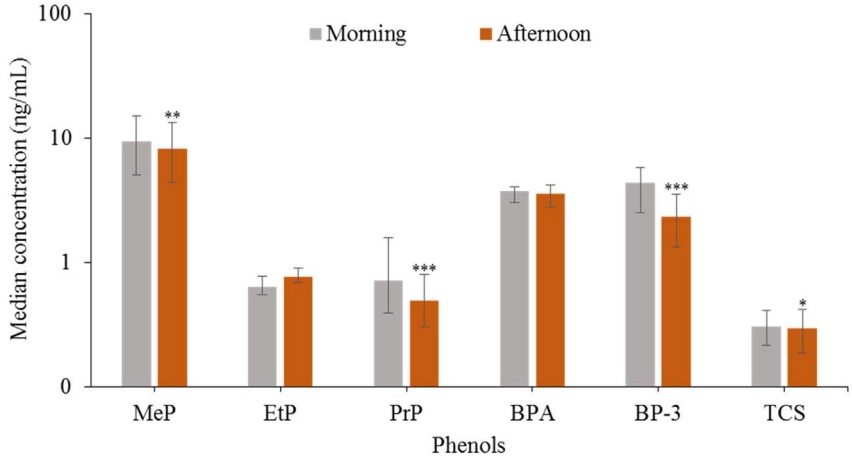

Fig. 2. Median concentrations of different environmental phenols in children for morning (grey bars, n = 54) and afternoon/evening (orange bars, n = 53) urine samples. Wilcoxon test was used to show if afternoon/evening urine samples were significantly different from morning urine samples.
*p-Value ≤ 0.05, **p-value ≤ 0.01, ***p-value ≤ 0.001.

concentrations in children. However, median concentration of BPA was higher than median concentration of PrP in children. For MeP, PrP, BP-3 and TCS, the morning urine samples were significantly higher compared to afternoon/evening urine samples. As for mothers, BPA and EtP in morning urine samples were not significantly different compared to afternoon/evening urine samples.

The concentrations of MeP, EtP and BP-3 in morning urine samples were significantly higher in mothers compared to children (Fig. 3). Median concentration of MeP was 6 times higher (63 and 10 ng/mL), whereas median concentrations of EtP and BP-3 were 2–3 times higher in mothers compared to children, (EtP: 2 and 0.6 ng/mL and BP-3: 9 and 4 ng/mL) (Table 1). Similar results were observed if only one of the siblings was included in the statistical analysis (data not shown).

In both mothers and children, parabens were significantly correlated to each other. BPA was not correlated to any other environmental phenol (Table 2). In mothers, BP-3 and TCS were significantly correlated to each other, while in children, BP-3 was correlated to two parabens (MeP and PrP) (Table 2).

Significant correlations were found between mothers and children in morning urine samples for two parabens (EtP and PrP), BP-3 and TCS (Table 3). Similar results were observed if only one of the siblings was included in the statistical analysis (data not shown).

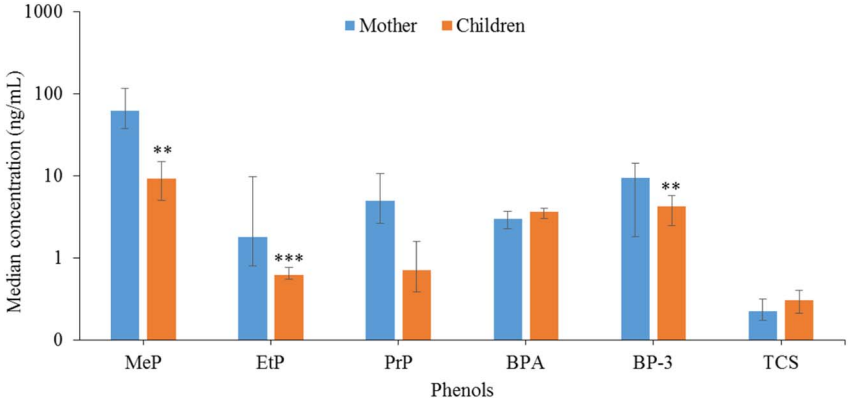

Fig. 3. Median concentrations of different environmental phenols in mother (blue bars, n = 48) and children (orange bars, n = 54) in morning urine samples. Wilcoxon test was used to show if phenols concentrations in mothers were significantly different from children. **p-value ≤ 0.01, ***p-value ≤ 0.001. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Spearman rank correlations between different environmental phenols in mothers (n = 48) and children (n = 54) in the morning urine samples.

Environmental phenols	MeP	EtP	PrP	BPA	BP-3	TCS
Mothers						
MeP	1.000					
EtP	0.655***	1.000				
PrP	0.544***	0.276	1.000			
BPA	0.101	0.038	−0.093	1.000		
BP-3	−0.039	−0.248	−0.031	−0.043	1.000	
TCS	0.024	−0.042	0.094	0.238	0.449***	1.000
Children						
MeP	1.000					
EtP	0.242	1.000				
PrP	0.726***	0.326*	1.000			
BPA	−0.022	0.079	−0.053	1.000		
BP-3	0.304*	0.040	0.367*	−0.040	1.000	
TCS	−0.077	−0.087	−0.065	0.236	0.207	1.000

* p-Value ≤ 0.05.
*** p-Value ≤ 0.001.

Table 3
Spearman correlations of urinary environmental phenols between mothers and children in morning samples.

Environmental phenols	Correlation coefficient	p-Value
MeP	0.148	0.287
EtP	0.546	< 0.001
PrP	0.576	< 0.001
BPA	0.160	0.247
BP-3	0.693	< 0.001
TCS	0.644	< 0.001

Table 4
ICCs of environmental phenols (SG adjusted and ln transformed) in mothers during one day.

Environmental phenols	Within-person variance	Between-person variance	ICC (95% confidence interval)
MeP	0.41	0.95	0.70 (0.65–0.75)
EtP	0.46	2.82	0.86 (0.83–0.88)
PrP	0.92	2.67	0.74 (0.70–0.79)
BPA	0.20	0.46	0.70 (0.64–0.75)
BP-3	0.23	4.34	0.95 (0.94–0.96)
TCS	0.12	3.75	0.97 (0.96–0.98)

The ICCs calculated for concentrations in spot urines sampled during 24 h were moderate for MeP, PrP and BPA and high for BP-3, TCS and EtP (ICC > 0.80) (Table 4).

Table 5 shows the estimated daily intakes of different environmental phenols in mothers and children. Although the median estimated intakes were higher in mothers compared to children for all the environmental phenols, the 95th percentile was 2 times higher in children for MeP and PrP. Both median and 95th percentile were lower than the available TDI/ADI of environmental phenols. None of the participants exceeded the TDI/ADI for BPA, MeP and EtP as established by EFSA (EFSA, 2004; EFSA Panel on Food Contact Materials, 2015). For BP-3 and TCS, SCCP has published only no observed adverse effect level (NOAEL) values of 200 mg/kg bw/day and 12 mg/kg bw/day, respectively (SCCP, 2008, 2009). After taking into account the uncertainty factor of 100 due to intra- and inter species differences (based on general risk assessment), the estimated TDIs for BP-3 and TCS would be 2 mg/kg bw/day and 0.12 mg/kg bw/day, respectively. None of the participants exceeded these estimated TDIs for BP-3 and TCS.

3.2. Determinants of environmental phenols in mothers and children

Both the use of PCPs and consumption of food were used in separate mixed-effect multivariable linear regression models to find out the important determinants of environmental phenols in the present study. For the PCPs (Table 6), we found positive associations between use of hand and face cream and concentrations of most environmental phenols in mothers and children. The use of face cream increased the EtP concentration by 24% and 10% in mothers and children, respectively, compared to no use. The use of hand soap decreased BPA in mothers and children by 60% and 30% respectively, compared to no use. The use of hair products was associated with increased parabens in both mothers and children up to 5–7 times.

When exploring dietary determinants, few food groups were significantly associated with urinary environmental phenols and a specific exposure pattern or trend was not identified (Supplementary information, Table S11).

4. Discussion

4.1. Environmental phenol concentrations and estimated daily intakes in mothers and children

This is the first study reporting concentrations of 12 different environmental phenols in Norwegian women and children. Guidry et al. (2015) and Bertelsen et al. (2014) have earlier reported the levels of

Table 5
Estimated daily intakes (μg/kg bw) of different environmental phenols in mothers (n = 48) and children (n = 54) using unadjusted morning urinary concentrations.

Environmental phenols	Mean	Percentiles							Min	Max	TDI/ADI
		5	10	25	50	75	90	95			
Mothers											
MeP	17	0.84	1.8	3.6	6.6	21	46	56	0.28	171	0–10,000
EtP	3.3	0.03	0.05	0.12	0.29	2.8	11	24	0.03	35	
PrP	6.2	0.03	0.11	0.39	1.1	4.1	19	32	0.01	104	
BPA	0.09	0.02	0.02	0.03	0.07	0.11	0.22	0.27	0.01	0.54	4
BP-3	1.4	0.01	0.01	0.03	0.15	0.43	1.9	16	0.01	22	2[a]
TCS	1.6	0.00	0.00	0.00	0.00	0.01	0.04	7.6	0.00	63	0.12[a]
Children											
MeP	18	0.14	0.32	0.55	1.0	7.0	38	114	0.10	368	0–10,000
EtP	3.0	0.03	0.04	0.08	0.14	0.22	0.44	2.8	0.02	143	
PrP	6.6	0.02	0.03	0.07	0.22	2.0	9.5	51	0.01	167	
BPA	0.12	0.02	0.04	0.06	0.09	0.13	0.21	0.31	0.02	0.86	4
BP-3	1.8	0.00	0.01	0.04	0.08	0.27	0.91	2.1	0.00	85	2[a]
TCS	1.3	0.00	0.00	0.00	0.01	0.02	0.09	4.4	0.00	54	0.12[a]

[a] TDIs for BP-3 and TCS are estimated by dividing NOAEL values established by SCCP (SCCP, 2008, 2009) with an uncertainty factor of 100.

Table 6
Multivariable linear mixed-model regression analysis showing ratios of environmental phenol concentrations in PCPs users compared to non-users in mothers and children.

PCPs	Users (%)	MeP	EtP	PrP	BPA	BP-3	TCS
MOTHERS[a]							
BODY and FACE CREAMS							
Hand cream use	67	**2.4**	**3.0**	1.6	1.3	**4.1**	2.5
Body lotion use	58	1.5	1.5	1.0	1.4	0.6	1.1
Face cream use	96	2.7	**23.9**	3.2	0.5	1.7	1.8
SOAPS							
High hand soap[c]	92	1.1	1.3	0.5	**0.4**	0.4	**0.2**
Shower soap use	85	1.6	1.2	**4.3**	1.5	1.0	1.0
Shampoo use	63	0.8	1.2	0.8	0.8	1.0	**3.3**
OTHERS							
Deodorant use	94	1.6	**9.2**	0.7	**1.0**	4.6	2.5
Perfume use	50	**0.5**	**0.3**	1.6	1.1	0.4	1.3
Any hair product	38	1.3	**2.6**	**4.6**	1.0	2.5	2.4
Any nail product	6	1.0	0.3	3.5	0.5	8.5	0.4
CHILDREN[b]							
BODY and FACE CREAMS							
Hand cream use	9	1.9	0.4	3.3	1.2	2.4	3.7
Body lotion use	13	1.7	1.5	2.6	1.1	0.6	0.6
Face cream use	9	2.5	**9.6**	1.5	1.0	2.2	0.7
SOAPS							
High hand soap[c]	75	1.1	**0.5**	0.5	**0.7**	**0.2**	1.0
Shower soap use	48	0.7	0.7	0.5	0.9	1.0	0.6
Shampoo use	27	2.0	1.2	**3.2**	**1.1**	**2.8**	1.8
OTHERS							
Deodorant use	16	0.6	0.8	0.4	0.8	0.7	3.7
Perfume use	2	0.2	0.4	2.2	2.3	0.0	1.5
Any hair product	11	**5.9**	1.8	**7.2**	1.6	4.8	0.4
Any nail product	7	0.4	0.7	0.6	1.5	3.4	0.9

[a]Models are adjusted for women's age, weight and education level.
[b]Models are adjusted for child's gender, age and weight.
[c]For hand soap, the category is high and low users since almost all participants (mothers 100% users and children 96% users) used soap. High users' category comprises of > 3 times use per day.
Bold represents ratios with p-value ≤ 0.05.

Ratio range
0 to 0.5
0.5 to 1
1 to 1.5
1.5-2
>2

some environmental phenols (MeP, PrP, BuP, BPA, BP-3 and TCS) in 45 pregnant women from the Norwegian Mother and Child Cohort study (MoBa) and levels of TCS in children (median age: 11 years, range: 8.8–13 years). The levels of MeP in the present study were 20 times lower than the MoBa participants' (MoBa GM: 1236 ng/mL, present study GM: 62 ng/mL). One of the reasons could be that parabens have been in negative focus in media for the past 10 years and many manufactures have deliberately removed parabens from their products. Thus, the difference in MeP concentrations could be explained by the different time of surveys between the two studies (MoBa: 2007–2008 vs present study: 2012). The levels of BPA, PrP and BuP in the present study were 3–40 times lower than the MoBa study (BPA: MoBa GM 8 ng/mL, present study GM: 3 ng/mL, PrP: MoBa GM 32 ng/mL, present study GM: 5 ng/mL, BuP: MoBa GM 6 ng/mL, present study GM: 0.15 ng/mL). The high concentrations of these urinary phenols in MoBa samples could be due to the different time of surveys as mentioned above, or due to sample contamination during collection or in laboratory (Guidry et al., 2015; Longnecker et al., 2013).

When comparing the levels of environmental phenols in both adults and children with the studies worldwide during similar time-period (Table 7), the levels in the present study were in the same range compared to other European countries, but slightly lower than levels observed in the USA. In line with our results, it has consistently been reported that mothers have significant higher levels of most of the parabens and BP-3 compared to children (Table 7). Use of PCPs is one of the major sources of exposure to parabens (Guo and Kannan, 2013; Guo et al., 2014). Thus, the higher levels in mothers can probably be explained by their more frequent use of PCPs. We observed similar mother-child differences in the same study group for the phthalate metabolite monoethyl phthalate (MEP) for which the use of PCPs is known to be one of the main sources of exposure (Sakhi et al., 2017).

Due to restrictions in use of BPA in children's products (EFSA Panel on Food Contact Materials, 2015), several bisphenol analogs (i.e., BPS, BPF, BPB and BPAF) are available as BPA substitutes. Among these

Table 7
Median unadjusted urinary concentrations (ng/mL) of different environmental phenols in adults and children worldwide.

Environmental phenols	Norway	Denmark	Sweden	USA	Germany	China	Greece
	Present study	Frederiksen et al. (2013)	Larsson et al. (2014)	NHANES report (Centers for Disease Control and Prevention, 2017)	Moos et al. (2015)	Wang et al. (2013)	Asimakopoulos et al. (2014)
	2012	2011	2011	2011–2012	2012	2012	2012
Adults							
MeP	56	14	40	77	43	20	12
EtP	1.8	0.89	2.4	1.6	1	0.09	2.0
PrP	5.0	1.7	18	13.8	2.2	4.3	5.3
BPA	2.6	2.1	1.3	1.3			
BP-3	6.6	3.7		22.2			
TCS	0.19	0.64		7.6			5.8
Children							
MeP	8.1	3	5.3	13.8		3.7	
EtP	0.71	0.4	0.66	< 1		0.62	
PrP	0.84	< LOD	1.9	1.4		1.5	
BPA	3.6	1.7	1.3	1.5			
BP-3	3.2	1.8		13.2			
TCS	0.27	0.46		5			

emerging bisphenols, only BPS and BPF were detected in urine samples in our study (detection frequency: BPS 42–48% (LOD: 0.1 ng/mL) and BPF 4–15% (LOD: 0.07 ng/mL). In a study from Brazil, BPS (LOD: 0.01 ng/mL) and BPF (LOD: 0.2 ng/mL) were detected in 10% and 2% of the urine samples, respectively (Rocha et al., 2016). Higher detection frequencies (42–100%) were observed for BPS in different Asian populations and US (LOD: 0.01 ng/mL) (Liao et al., 2012). Ye et al. (2015) have determined BPA, BPS and BPF in urine samples at eight time points during time-period 2000–2014 in US adults and found increasing exposure trends for BPS and decreasing exposure to BPA. A systematic review (25 in vitro and 7 in vivo studies) by Rochester and Bolden (2015) has concluded that both BPS and BPF possess similar hormonal activities as BPA, and may therefore pose similar health hazards as BPA. However, there is still a large knowledge gap regarding human exposure in different populations and the associated health risk for these bisphenols (Chen et al., 2016). Thus, it is important to monitor the emerging bisphenols that possess similar hormonal activities as BPA, have increasing trends of exposures and are still not regulated by authorities.

Strong correlations among the parabens in both mothers and children indicate that parabens are used in combination and have common sources of exposures. For mothers only, BP-3 and TCS were significantly correlated. BP-3 (UV filters) and TCS (antimicrobial agent) possess different chemical properties and are used in different PCPs and cosmetics although some PCPs like soaps, body wash and shampoos may contain both of these chemicals (Dann and Hontela, 2011; Kim and Choi, 2014). The observed correlation between BP-3 and TCS only in mothers may indicate that the use of PCPs pattern and frequency in mothers is much more diverse compared to children. Another hypothesis could be that the use of chemicals in combinations is limited in the PCPs available for children compared to PCPs available for adults, but we have no evidence to support this hypothesis. We also observed strong correlations between mothers and children for parabens, BP-3 and TCS, indicating that mothers and children have some similar sources of exposure. As expected, BPA was not correlated to any of the environmental phenols. For BPA, the major source of exposure is food and not PCPs (EFSA Panel on Food Contact Materials, 2015). In the present study, no correlation was observed between mothers and children for BPA. Myridakis et al. (2015) studied exposure to non-persistent chemicals including BPA in 239 mother-child pairs in Crete and found no correlations between mothers and children for BPA. However, weak but significant correlation were observed for BPA between mother and children (621 mother-child pairs) in a harmonized biomonitoring study conducted in Europe (DEMOCOPHES, Demonstration of a study to Coordinate and Perform Human biomonitoring on a European Scale) (Covaci et al., 2015). The estimated daily intakes for BPA and parabens in the present study were lower than the TDI and ADI established by EFSA (EFSA, 2004; EFSA Panel on Food Contact Materials, 2015). Although the intakes are below the ADI/TDI of some environmental phenols, adverse effects on immune systems were observed in levels below TDI for BPA and reconsideration of TDI for BPA is warranted (Hessel et al., 2016). Further, the cumulative effect with other less studied chemicals, which might have similar negative mode of action, is still of concern (Howdeshell et al., 2017; Kortenkamp and Faust, 2010; Orton et al., 2014). Therefore, it is important to biomonitor the levels of as many as possible environmental chemicals in different populations. One important consideration in back calculating intakes from urinary concentrations is the F_{ue} values. Although we have used urinary F_{ue} values based on the available pharmacokinetic studies (Moos et al., 2016a; Teeguarden et al., 2015; Thayer et al., 2015; Volkel et al., 2002), some new studies have shown levels of parabens, BPA, BP-3 and TCS in human adipose tissues (Artacho-Cordon et al., 2017; Wang et al., 2015). It is early to predict how this may affect the intake estimates based on urinary concentrations and needs to be explored in future studies.

Diurnal variation in mothers and children showed that morning urine samples had higher concentrations of BP-3 and TCS than urine collected at other time-periods. For MeP and PrP only the evening urine samples were significantly lower than the morning urine samples. Similar results have been observed by Lassen et al. (2013) for BP-3 that morning urine samples were higher compared to any spot or 24-hour urine samples. Weiss et al. (2015) showed that urine collection time was a significant determinant of the urinary TCS concentrations, although the time of the day was not specified. The short-term ICCs (1 day) in the present study were moderate for parabens and BPA, but high for BP-3 and TCS. Similar ICCs have been observed in other studies with time span between urine samples < 1 week as shown in Table 8. For parabens, BP-3 and TCS, ICCs decrease with time span between urine samples but are still moderate. Moderate to high ICCs suggest that one single spot urine sample can be used to estimate exposure to these environmental phenols. However, the standardization of time of urine collection during the day is advisable since Figs. 1 and 2 show that levels in morning urine samples were significantly different from other time points for BP-3, TCS and MeP. For BPA, the ICCs decrease below 0.4 even for urine samples taken within one week (Table 8). Consequently, for BPA, a single spot urine may be used for estimating a short–term exposure, but not a long-term exposure. The findings that

Table 8
Overview of short-term and long-term ICCs calculated in other studies worldwide.

Study	Time span between urine samples	ICCs of different environmental phenols					
		MeP	EtP	PrP	BPA	BP-3	TCS
Present study	1 day	0.70	0.86	0.74	0.70	0.95	0.97
Heffernan et al. (2014)	2 days				0.51		
Lassen et al. (2013)	4 days				0.40	0.80	0.93
Koch et al. (2014)	6 days	0.71	0.82	0.54	0.26	0.92	0.96
Cox et al. (2016)	28 days				0.18		
Pollack et al. (2016)	2 months	0.59	0.38	0.46	0.04	0.63	0.57
Bertelsen et al. (2014)	3 months						0.49
Dewalque et al. (2015)	4 months	0.59	0.66	0.68		0.59	
Smith et al. (2012)	9 months	0.46		0.44			
Braun et al. (2011)	9 months				0.11		
Sun et al. (2017)	1 year				0.39		

the concentration of BPA in the morning urine samples was not significantly different compared to concentrations at other time-points may indicate that the BPA exposure is spread throughout the day.

4.2. Determinants of environmental phenols in mothers and children

In the present study, we investigated both food consumption and use of PCPs as separate determinants of exposure. Use of body and face creams, deodorants and hair products were associated with higher concentrations of most parabens in both mothers and children. This is in accordance with studies analyzing parabens in PCPs where highest concentrations were found in different creams and other leave-on products (Guo and Kannan, 2013; Guo et al., 2014). Other studies have also shown positive associations between the use of lotions and urinary concentration of parabens (Fisher et al., 2017; Meeker et al., 2013). Positive though weak associations were found between BP-3 and creams, deodorant and hair products. BP-3 is mainly used as UV stabilizer in PCPs and is more likely to be used in hair products, body and face creams (Liao and Kannan, 2014). None of the environmental phenols showed a clear pattern with any of the food groups consumed in the present study. Nevertheless, some studies have shown that consumption of canned foods is important predictors of urinary BPA (Casas et al., 2013; Covaci et al., 2015; Hartle et al., 2016).

5. Strengths and limitations

The main strength of the present study is that 44% of the mothers provided all spot urine samples. Thus, we could study both diurnal variations and calculate short-term (24 h) ICCs of environmental phenol concentrations in urine. Another strength of the present study is the paired samples from mother and children, making it possible to study similar sources of exposure. In addition to the determination of eight common environmental phenols, we have also determined four emerging bisphenols. Finally, the 24-h food recall and PCPs registration gave us the opportunity to explore possible associations between urinary concentrations, and exposures occurring simultaneously as the urine collection. One limitation of the study is that the exact time point for use, brand and amount of PCPs use were not registered, as the participants only were asked to report the use of PCPs the last 24 h. Since two similar products from different brands may contain different environmental phenols, it may cause exposure misclassification. Furthermore, we did not collect the information on canned food consumption (reported as an important source of BPA) during the 24 h recall for a more exhaustive assessment of BPA. Finally, a limitation due to the study sources is the low number of participants and therefore, some of the findings must be taken with caution and should be further investigated.

6. Conclusion

Twelve different environmental phenols (4 parabens, 5 bisphenols, BP-3, TCS and TCC) were measured in urine from healthy Norwegian mother and child pairs. The urinary levels of most of environmental phenols except for BPA and TCS were higher in mothers compared to children. For future biomonitoring studies, it is important to include emerging bisphenols, especially BPS that was detected in near to 50% of the urine samples in both mothers and children. The short-term ICCs were moderate to high for all the environmental phenols indicating that a single spot urine may be used to estimate short-term exposure. Body and face creams, deodorants and hair products were the main determinants of urinary parabens and BP-3.

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Appendix A. Supplementary data

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