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Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children



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ABSTRACT

Chemicals such as phthalates, parabens, bisphenol A (BPA) and triclosan (TCS), used in a wide variety of consumer products, are suspected endocrine disrupters although their level of toxicity is thought to be low. Combined exposure may occur through ingestion, inhalation and dermal exposure, and their toxic as well as combined effects are poorly understood.

The objective of the study was to estimate the exposure to these chemicals in Swedish mothers and their children (6–11 years old) and investigate potential predictors of the exposure. Urine samples from 98 mother–child couples living in either a rural or an urban area were analyzed for the concentrations of four metabolites of di-(2-ethylhexyl) phthalate (DEHP), three metabolites of di-iso-nonyl phthalate (DiNP), mono-ethyl phthalate (MEP), mono-benzyl phthalate (MBzP) and mono-n-butyl phthalate (MnBP), methylparaben (MetP), ethylparaben (EthP), propylparaben (ProP), butylparaben, benzylparaben, BPA, and TCS. Information on sociodemographics, food consumption habits and use of personal care products, obtained via a questionnaire, was used to investigate the associations between the urinary levels of chemicals and potential exposure factors. There were fairly good correlations of biomarker levels between the mothers and their children. The children had generally higher levels of phthalates (geometric mean Σ DEHP 65.5 $\mu\text{g/L}$; Σ DiNP 37.8 $\mu\text{g/L}$; MBzP 19.9 $\mu\text{g/L}$; MnBP 76.9 $\mu\text{g/L}$) than the mothers (Σ DEHP 38.4 $\mu\text{g/L}$; Σ DiNP 33.8 $\mu\text{g/L}$; MBzP 12.8 $\mu\text{g/L}$; MnBP 63.0 $\mu\text{g/L}$). Conversely, the mother's levels of parabens (MetP 37.8 $\mu\text{g/L}$; ProP 13.9 $\mu\text{g/L}$) and MEP (43.4 $\mu\text{g/L}$) were higher than the children's levels of parabens (MetP 6.8 $\mu\text{g/L}$; ProP 2.1 $\mu\text{g/L}$) and MEP (28.8 $\mu\text{g/L}$). The urinary levels of low molecular weight phthalates were higher among mothers and children in the rural area (MBzP $p = <0.001$; MnBP $p = 0.001$ – 0.002), which is probably due to higher presence of PVC in floorings and wall coverings in this area, whereas the levels of parabens were higher among the children in the urban area (MetP $p = 0.003$; ProP $p = 0.004$) than in the rural area. The levels of high molecular weight phthalates were associated with consumption of certain foods (i.e. chocolate and ice cream) whereas the levels of parabens were associated with use of cosmetics and personal care products.

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1. Introduction

Chemicals such as phthalates, parabens, bisphenol A (BPA) and triclosan (TCS), used in a wide variety of consumer products, are suspected endocrine disrupters although their level of toxicity is thought to be low. Combined exposure may occur through ingestion, inhalation and dermal exposure, and their toxic as well as combined effects are poorly understood.

Phthalates are industrial chemicals which are used for a wide range of applications. They are primarily used as plasticizers in PVC found in consumer products such as shoes, gloves and packing materials as well as in building materials, floorings and wall coverings. Some phthalates are

Abbreviations: BenP, benzylparaben; BPA, bisphenol A; BBzP, butylbenzyl phthalate; ButP, butylparaben; DEHP, di-(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DiNP, di-iso-nonyl phthalate; DnBP, di-n-butyl phthalate; EthP, ethylparaben; MetP, methylparaben; 5-cx-MEPP, mono(2-ethyl-5-carboxy-pentyl) phthalate; 5-OH-MEHP, mono(2-ethyl-5-hydroxy-hexyl) phthalate; 5-oxo-MEHP, mono(2-ethyl-5-oxo-hexyl) phthalate; cx-MiNP, mono-(carboxy-isooctyl) phthalate; OH-MiNP, mono-(hydroxyl-isononyl) phthalate; oxo-MiNP, mono-(oxo-isononyl) phthalate; MBzP, mono-benzyl phthalate; MEP, mono-ethyl phthalate; MEHP, mono(2-ethylhexyl) phthalate; MnBP, mono-n-butyl phthalate; ProP, propylparaben; TCS, triclosan.

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also used in non-plastic products such as pharmaceuticals, personal care products, paints and adhesives (Frederiksen et al., 2007; Wittassek et al., 2011). Phthalates can be released from products and exposure may occur in humans through food, dust, air and direct use of personal care products (Janjua et al., 2008; Wittassek and Angerer, 2008; Wormuth et al., 2006). After absorption, the parent phthalates are metabolized into respective monoesters, which can be further hydroxylated, oxidized and/or glucuronidated before excretion in urine as free or conjugated monoesters (Frederiksen et al., 2007). The presence of phthalate metabolites in urine indicates recent exposure to respective parent compound (Townsend et al., 2013). Some phthalates, such as di-(2-ethylhexyl) phthalate (DEHP), butylbenzyl phthalate (BBzP) and di-n-butyl phthalate (DnBP) are endocrine disruptors. These phthalates have been shown in animal studies to affect the development of the reproduction system in male offspring, referred to as the “phthalate syndrome” including e.g. shortened anogenital distance, hypospadias and cryptorchidism (Foster, 2006; Gray et al., 2000; Mylchreest et al., 2000). Similar effects have been observed after in utero exposure in humans (Suzuki et al., 2012; Swan et al., 2005). Due to their supposed toxic effects, DEHP, BBzP and DnBP have been prohibited within the EU from the production of toys, childcare articles (EC, 2005) and cosmetic products (EC, 2009) and the migration levels from food contact materials are regulated (EC, 2007). Di-iso-nonyl phthalate (DiNP) is prohibited only from toys which can be put in the mouth by the child (EC, 2005).

BPA (2,2-bis(4-hydroxyphenyl)propane) is a high production volume chemical used in polycarbonate plastics and epoxy resins, which are used in e.g. CDs and DVDs, tooth fillings, cash receipts, plastic bottles, inner coatings of cans, and relining of water pipes. Food is the main source of exposure in humans because BPA can migrate from cans coated with epoxy as well as other plastics in contact with food or beverages (Geens et al., 2012). In addition, BPA has been detected in indoor dust which may contribute to the exposure (Geens et al., 2009; Loganathan and Kannan, 2011). After ingestion, BPA is readily absorbed, glucuronidated or sulfated and subsequently excreted in urine with an elimination half-life of less than 6 h (Völkel et al., 2002). The levels of BPA in spot-urine samples reasonably reflect the ongoing average exposure on a population/group level (Christensen et al., 2012; Ye et al., 2011). BPA is a well-known endocrine disruptor with estrogenic potency. The toxicity of BPA shown in animal studies has mainly been attributed to effects on the development and function of the reproductive organs as well as the nervous system and behavior (Richter et al., 2007). However, the low-dose effects shown for BPA are debated (Beronius et al., 2010). Aiming to lower the exposure, the use of BPA in baby bottles and cosmetics has been banned within the EU (EC, 2009, 2011).

Parabens are used as antimicrobial preservatives in personal care products, cosmetics and pharmaceuticals. The maximum level of parabens in cosmetics is restricted by the European Cosmetic Directive to 0.4% for one ester and 0.8% for a mixture of esters (EC, 2009). Methylparaben (MetP), ethylparaben (EthP) and propylparaben (ProP) are also permitted as food preservatives in confectionary and dried meat (EC, 1995). Parabens are readily absorbed orally and to a lesser extent dermally. After absorption, parabens can be hydrolyzed to parahydroxybenzoic acid (PHBA) and/or conjugated and are then excreted in urine as free or conjugated parabens and PHBA within hours (Janjua et al., 2008; Ye et al., 2006a). Despite their short half-life, the levels of parabens in a spot urine sample reasonably represent an individual's exposure over several months (Smith et al., 2012). The use of parabens has raised concern due to their weak estrogenic activity confirmed in *in vivo* and *in vitro* studies. The potency seems to increase with the length of the alkyl chain, thus the long-chain parabens (e.g. ProP and butylparaben (ButP)) are of highest concern (Boberg et al., 2010; Routledge et al., 1998; Witorsch and Thomas, 2010). In 2010, the EU Scientific Committee on Consumer Safety (SCCS) evaluated the safety of parabens and concluded that the use of MetP and EthP below the maximum permitted levels is considered safe, whereas the safety

of ProP and ButP at the maximum levels is more uncertain due to lack of data (SCCS, 2011).

TCS (5-chloro-2-(2,4-dichlorophenoxy)phenol) is used as an antimicrobial agent in personal care products such as deodorants, toothpastes, mouth washes and shower gels, and also in consumer products such as cleaning products, plastics and toys (Bedoux et al., 2012). TCS is approved by the European Cosmetic Directive for use in cosmetic products in concentrations up to 0.3% (EC, 2009), but is no longer permitted for use in food contact materials (EC, 2010). TCS is readily absorbed by the gastrointestinal tract, whereas the uptake via the oral cavity and skin is lower (SCCP, 2009). After absorption, TCS is almost completely converted to glucuronic and sulphuric acid conjugates and is subsequently excreted predominately in urine as glucuronide conjugates. The elimination half-life in humans after oral administration is estimated to be 13–29 h (SCCP, 2009). Serial measurements of TCS in morning urine have shown relatively high consistency over time (ICC = 0.56; (Lassen et al., 2013)). TCS has been shown in animal studies to cause endocrine effects, especially on the levels of thyroid hormones (Crofton et al., 2007; Dann and Hontela, 2011; Kumar et al., 2009; Zorrilla et al., 2009). The Scientific Committee on Consumer Products (SCCP) has concluded that the current maximum concentration of 0.3% is not safe when the aggregate exposure from all cosmetic products is considered. However, the maximum concentration is considered safe for individual products such as toothpastes, soaps and deodorants, but not in products that stay on the skin (e.g. body lotions) or mouth wash (SCCP, 2009).

The objectives of the present study were to evaluate the levels of 10 phthalate metabolites, 5 parabens, BPA and TCS in urine from Swedish children (6–11 years old) and their mothers, in relation to demographics, lifestyle, housing and different potential sources of exposure to these chemicals. The study is part of a harmonized approach for biomonitoring on the European level; the COPHES (Consortium to Perform Human biomonitoring on a European Scale) and DEMOCOPHES (DEMONstration of a study to COordinate and Perform Human biomonitoring on a European Scale) twin projects.

2. Materials and methods

2.1. Recruitment and sampling

The participants were selected via inhabitant registers, based on the age of the child (6–11 years) and the living area. The mother–child couples were either from the urban area of Uppsala with a population of 140,000 inhabitants, or a sparsely populated area in the county of Västerbotten in northern Sweden. Inclusion criteria included that the mother was under 45 years of age, had lived in the study area for at least 3 years, that the child lived more than half of the time at the mother's address, and that the mother or child had no chronic kidney or liver disease. The sampling was performed according to the harmonized approach developed within the COPHES/DEMOCOPHES projects (Becker et al., 2014). First morning urine samples were collected in polypropylene tubes. The urine samples were frozen at $-20\text{ }^{\circ}\text{C}$ and transported to the analyzing laboratories for analysis. Ethical permission was granted by the regional ethical review board in Stockholm (Dnr 2011/1024-31/1).

2.2. Questionnaires

The mothers answered an extensive questionnaire (developed by the COPHES/DEMOCOPHES consortium) covering questions about living environment, food consumption, use of personal care products, smoking, lifestyle and sociodemographics. The questionnaires were answered through face-to-face interviews with field workers or online. The Computer Assisted Personal Interviewing system SOCRATOS (Ivox, Belgium) was used for interviews and self-administered questionnaires. The information reported through questionnaires was

checked for unreasonable answers and errors and cleaned before further analysis. Also, a non-responder questionnaire was answered by 65 mothers who chose to not participate in the full study.

2.3. Chemical analysis

Urine samples from 98 mother–child couples were analyzed for phthalates and BPA and 79 samples from mothers and 80 samples from children were analyzed for parabens and TCS. Creatinine was analyzed by the Jaffe method (Larsen, 1972). We participated in the extensive analytical quality control program implemented by COPHES/DEMOCOPHES for phthalates and BPA, with excellent results (Schindler et al., 2013).

2.3.1. Phthalate metabolites

The urine samples were prepared with an automated solid-phase extraction technique and analyzed by liquid chromatography tandem mass spectrometry (LC/MS/MS) as previously described by Toft et al. (2012), but with addition of DiNP metabolites. Moreover, in order to reduce the contamination from the mobile phase a column was placed in the flow before the auto-samples. Briefly, the samples were spiked with internal standards for all analyzed metabolites, treated with glucuronidase to hydrolyze glucuronic acid and acidified. The metabolites were extracted using Oasis HLB 3 mL (60 mg) on an Aspec XL4 automated solid phase extraction equipment (Gilson; Middleton, WI, USA). The samples were then evaporated and dissolved in a water:acetonitrile solution (50:50) containing acetic acid and analyzed by LC/MS/MS (Perkin-Elmer series 200; API 3000; Sciex, Framingham, MA, USA). The limit of detection (LOD) was ≤ 0.1 $\mu\text{g/L}$ for most of the compounds but for MEP and MnBP it was 0.4 and 0.6, respectively. The limit of quantification (LOQ) was set to three times the detection limit. The relative standard deviations (RSD) determined from analyses of an in-house prepared chemical quality control sample, made by addition of small amounts of the metabolites to human urine and analyzed two times within a sample batch of 50 samples, were $<20\%$ for all metabolites analyzed; mono-ethyl phthalate (MEP; 460 $\mu\text{g/L}$) 15%, mono-n-butyl phthalate (MnBP; 17 $\mu\text{g/L}$) 13%, mono-benzyl phthalate (MBzP; 54 $\mu\text{g/L}$) 15%, mono(2-ethylhexyl)phthalate (MEHP; 41 $\mu\text{g/L}$) 11%, mono(2-ethyl-5-hydroxy-hexyl)phthalate (5-OH-MEHP; 84 $\mu\text{g/L}$) 16%, mono(2-ethyl-5-oxo-hexyl)phthalate (5-oxo-MEHP; 38 $\mu\text{g/L}$) 12%, mono(2-ethyl-5-carboxy-pentyl)phthalate (5-cx-MEPP; 61 $\mu\text{g/L}$) 14%, mono-(hydroxyl-isononyl)phthalate (OH-MiNP; 27 $\mu\text{g/L}$) 15%, mono-(oxo-isononyl)phthalate (oxo-MiNP; 20 $\mu\text{g/L}$) 19%, and mono-(carboxy-isoctyl)phthalate (cx-MiNP; 21 $\mu\text{g/L}$) 9%. All sample batches were analyzed during a period of a month. The samples were analyzed in duplicates and four chemical blank samples were included in all analytical batches containing about 50 samples each.

2.3.2. BPA

The analysis of BPA in urine was performed by LC/MS/MS according to a modified method by Kuklenyik et al. (2003) and Völkel et al. (2005). Briefly, urine was spiked with D_{16} -labeled BPA as internal standard and treated with glucuronidase (*E. coli*) to hydrolyze glucuronic acid. The BPA was extracted using 3 mL SPE columns (EC) 221-0020-BPS (Sorbent) on the Aspec XL4. The analysis was performed on a LC/MS/MS (Perkin-Elmer; series 200 LC and a Sciex API 3000 MS). The LOD was 0.05 $\mu\text{g/L}$ and the LOQ was 0.15 $\mu\text{g/L}$. The RSD for the in-house prepared quality control sample, made by addition of a small amounts of BPA to human urine and analyzed two times within a sample batch of 50 samples, were 7% at 2 $\mu\text{g/L}$. All sample batches were analyzed during a period of a month. The samples were analyzed in duplicates and two chemical blank samples were included in all analytical batches containing about 50 samples each.

2.3.3. Parabens and TCS

An on-line SPE-HPLC-MS/MS method (Ye et al., 2006b) was adapted for offline use. An internal standard solution containing 500 ng/mL $^{13}\text{C}_6$ -propylparaben (Sigma-Aldrich, Steinheim, Germany), and 500 ng/mL $^{13}\text{C}_{12}$ -triclosan (Wellington Laboratories, Ontario, Canada) was prepared in methanol (MeOH, Rathburn, Scotland). 20 mg sulfatase (*Helix pomatia*, 15,000 U/g solid, Sigma-Aldrich) was dissolved in 10 mL 1 M ammonium acetate buffer, pH 5. β -Glucuronidase, type H-3AF (*Helix pomatia* 101,700 U/mL, Sigma-Aldrich) was diluted ten times with water (MilliQ academic purifier, Millipore).

To 500 μL urine sample (or water for blanks), 10 μL internal standard solution, 50 μL sulfatase solution and 50 μL glucuronidase solution were added. After 4 h in 37 °C, 800 μL 0.1 M formic acid was added. A SPE column (Isolute C18 100 mg, 3 mL, Biotage) was conditioned with 5 mL MeOH and 5 mL water. The urine solution was added to the SPE column and allowed to pass followed by 2 mL water. The column was dried by applying suction for 5 min. The column was then eluted using 3 mL MeOH. The volume of the eluate was reduced to approximately 0.5 mL under a stream of nitrogen. A mixed calibration standard (5 $\mu\text{g/mL}$ of each compound in MeOH) was prepared from MetP (Supelco, Bellefonte, PA, USA), EthP, ProP, ButP, and benzylparaben (BenP) (Sigma-Aldrich), all with a declared purity of $\geq 99\%$, and TCS (Ciba). Calibration solutions containing 10 μL internal standard solution and 0.01, 0.03, 0.1, 0.3, 1, 3, 10 ng calibration standard per mL were prepared in MeOH. Calibration curves were run at the beginning, middle and end of all sample batches. The calibration curves were linear including the highest point corresponding to a maximum sample concentration of 20 ng/mL (500 μL urine used). Samples with higher concentrations were re-run after dilution (maximum 1:20) or re-analyzed using a smaller sample volume.

Liquid chromatography was performed on a Prominence UFLC system (Shimadzu) with two pumps LC-20AD, degasser DGU-20A5, autosampler SIL-20A8, analytical column (Thermo HyPurity C8 50 mm \times 3 mm, particle size 5 μm ; Dalco Chromtech) and column oven CTO-20AC. The mobile phase A was 2 mM ammonium acetate in water, and the mobile phase B was MeOH. The column temperature was 35 °C and the flow rate was 0.4 mL/min. The injection volume was 10 μL and a gradient from 15% to 95% B was run for a total runtime of 17 min. The effluent was directed to an API 4000 triple quadrupole mass spectrometer (Applied Biosystems) using electrospray ionization in negative mode. Two different MRM transitions for each compound were recorded and used as quantifier and qualifier, respectively. One duplicate and one blank sample were analyzed for every eight urine sample. The variation coefficients (quadratic means for five samples analyzed in duplicate) were 3.3%, 1.7%, 2.0%, 14%, 8.8% and 4.7% for MetP, EthP, ProP, ButP, BenP and TCS, respectively. The samples were analyzed during two sessions within a period of two months. For MetP, the LOD was 1/1.4 $\mu\text{g/L}$ (in two separate analytical runs) and the LOQ was 3.3/4.6 $\mu\text{g/L}$. For ProP, the LOD was 0.4/1.6 $\mu\text{g/L}$ (in two separate analytical runs) and the LOQ was 1.3/5.3 $\mu\text{g/L}$. For EthP, ButP, BenP and TCS, the LOD and LOQ were 0.4 $\mu\text{g/L}$ and 1.3 $\mu\text{g/L}$, respectively.

2.4. Statistical analysis

Urine samples with creatinine levels lower than 30 mg/dL or higher than 300 mg/dL were excluded from the analysis (WHO, 1996). Biomarker levels below the respective LOD were substituted by half the value of LOD.

The statistical software IBM SPSS version 20 was used for the statistical analyses. The levels of biomarkers in urine were not normally distributed and therefore logarithmic (ln)-transformed values were used for the univariate and multiple analyses. Questionnaire variables with multiple answer alternatives were categorized into two or three subgroups. Variables were excluded from the analysis if any subgroup contained less than 5 participants. The studied variables were age,

gender (only children), time since last urination (hours), living area (urban/rural), education (highest in the family), recent renovation or redecoration at home (within the last 2 years), PVC in floorings or wall coverings, food consumption within the last 4 weeks (frequencies of meat, fish, fast food, milk, cheese, chocolate, ice cream, chewing gum, canteen food and canned food consumption), consumption of fast food within the last 24 h, drinking water source (private well/public water supply), use of personal care products (frequencies of lotion, skin make-up, eye make-up, sunscreen, hair styling products, deodorant, fragrance, shampoo, mouth wash and hand or body disinfectant), playing with rubber-like plastic toys (frequency, only children) and use of rubber gloves (frequency, only mothers).

The univariate comparisons between subgroups for each variable were performed with analysis of variance (ANOVA) with a significance level of 0.05. Univariate analyses were performed with both raw and creatinine-adjusted concentrations using ANOVA as well as with raw values adjusted for creatinine and/or age using ANCOVA. In this article, the results from the ANOVA with creatinine-adjusted levels of biomarkers are presented. Multiple regression models for unadjusted levels of each biomarker were created by forcing creatinine and age into the models and applying stepwise selection of variables which were correlated with respective biomarker below a significance level of 0.25 in the ANOVA analysis. Variables with a significance level below 0.05 were allowed to stay in the final model. The variable describing the overall use of personal care products was not included in the multiple models due to high correlation with individual products. Univariate and multiple analyses were not performed if the levels of the biomarker were lower than the LOD in more than 50% of the samples.

The sum of DEHP metabolites (MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP) as well as the sum of DiNP metabolites (OH-MiNP, oxo-MiNP and cx-MiNP) were calculated and used in the univariate

and multiple analyses. Analyses of the correlation between different metabolites in the same sample as well as the correlation of biomarkers between the mothers and their children were performed using the non-parametric Spearman's correlation (r_s) test.

A non-responder analysis was performed based on the 98 mothers who participated in the study and 65 mothers who had answered the non-responder questionnaire, but did not participate in the study. Pearson Chi-square test was used to evaluate significant ($p < 0.05$) differences in civil status, smoking status, education and work status.

3. Results

In total, 98 mother–child pairs were recruited. After exclusion of samples with creatinine levels below 30 mg/dL or above 300 mg/dL and one sample that was not first morning urine, 95 mothers and 97 children were included in the analyses. Among the children there were 47 boys and 50 girls, 47 were living in the urban area and 50 were living in the rural area. The response rate was 22%. However, the non-responder analysis did not show any significant differences between participating and non-participating mothers regarding civil status, smoking status, education and work status.

The creatinine levels were significantly lower in the children (94 mg/dL) than in the mothers (114 mg/dL) and the levels of creatinine in urine were significantly positively correlated with the children's age (Spearman's correlation coefficient; $r_s = 0.27$; $p = 0.006$).

3.1. Phthalates

The phthalate metabolites were detected at levels above the LOD in all urine samples, except for MEHP which was detected in 98% of the urine samples from the mothers (Table 1). The children generally

Table 1
Levels of phthalate metabolites, BPA, parabens and TCS in urine from Swedish mothers and children. Geometric mean (GM) with 95% confidence interval (95% CI) and percentiles P25, P50 and P95 are given for unadjusted and creatinine-adjusted levels of biomarkers. GM, P25 and P50 are not given if more than 50% < LOD.

Parent compound	Measured biomarker	Unit	Mothers						Children					
			n	>LOD	GM (95% CI)	P25	P50	P95	n	>LOD	GM (95% CI)	P25	P50	P95
DEHP	MEHP	µg/L	95	97.9%	2.32 (1.85–2.92)	1.34	2.64	8.05	97	100%	2.74 (2.30–3.26)	1.44	2.87	12.81
		µg/g creatinine			2.22 (1.85–2.68)	1.41	2.40	9.11			3.08 (2.60–3.64)*	1.72	3.19	11.47
	5-OH-MEHP	µg/L	95	100%	14.94 (12.66–17.64)	9.65	13.40	50.62	97	100%	24.56 (21.34–28.28)*	14.27	24.50	125.05
		µg/g creatinine			14.08 (12.25–16.18)	9.37	13.17	39.00			27.75 (24.36–31.60)*	17.00	26.69	93.50
	5-oxo-MEHP	µg/L	95	100%	8.68 (7.34–10.28)	6.07	8.04	28.73	97	100%	15.68 (13.57–18.11)*	9.25	16.34	72.65
		µg/g creatinine			8.18 (7.11–9.42)	5.27	7.34	28.54			17.71 (15.51–20.21)*	10.58	17.74	60.54
BBzP	5-cx-MEPP	µg/L	95	100%	11.53 (9.79–13.59)	6.93	10.69	50.30	97	100%	21.54 (18.77–24.71)*	13.24	22.77	78.07
		µg/g creatinine			10.87 (9.50–12.42)	6.79	10.04	36.11			24.33 (21.31–27.78)*	14.10	23.12	82.01
	MBzP	µg/L	95	100%	12.81 (10.23–16.04)	5.72	12.56	86.02	97	100%	19.91 (16.79–23.61)*	10.00	22.17	80.51
		µg/g creatinine			12.07 (9.99–14.58)	6.28	10.83	74.16			22.49 (18.80–26.89)*	11.53	22.37	96.58
	MnBP	µg/L	95	100%	63.01 (53.63–74.04)	36.69	59.19	296.27	97	100%	76.87 (68.11–86.75)*	52.36	79.25	192.67
		µg/g creatinine			59.36 (52.58–67.03)	37.79	58.49	161.19			86.83 (76.72–98.26)*	65.80	83.24	236.58
DEP	MEP	µg/L	95	100%	43.40 (34.60–54.46)*	18.09	42.40	328.55	97	100%	28.83 (23.73–35.01)	15.62	24.68	201.55
		µg/g creatinine			40.89 (33.17–50.41)	18.85	36.97	320.82			32.56 (27.12–39.10)	19.44	27.36	179.08
DiNP	cx-MiNP	µg/L	95	100%	19.74 (14.89–26.17)	6.79	15.55	332.68	97	100%	21.66 (17.55–26.72)	11.34	19.89	215.67
		µg/g creatinine			18.60 (14.20–24.37)	7.30	13.51	290.09			24.46 (19.54–30.63)*	12.14	21.41	231.59
	OH-MiNP	µg/L	95	100%	8.33 (6.22–11.15)	3.32	6.54	148.04	97	100%	9.72 (7.89–11.97)	4.95	8.95	56.67
		µg/g creatinine			7.85 (5.93–10.37)	3.02	5.61	180.74			10.98 (8.81–13.69)*	5.05	9.73	73.23
	oxo-MiNP	µg/L	95	100%	4.85 (3.68–6.40)	1.89	3.87	59.11	97	100%	5.63 (4.61–6.89)	2.91	5.19	41.25
		µg/g creatinine			4.57 (3.52–5.93)	1.77	3.35	74.61			6.36 (5.15–7.86)*	3.06	5.46	44.27
BPA	BPA	µg/L	95	100%	1.31 (1.13–1.52)	0.80	1.29	5.02	97	100%	1.48 (1.27–1.73)	0.90	1.31	6.24
		µg/g creatinine			1.23 (1.09–1.41)	0.79	1.20	3.95			1.67 (1.43–1.95)*	1.00	1.46	6.30
MetP	MetP	µg/L	76	100%	38 (26–55)*	11	40	680	80	86.2%	6.8 (4.6–10)	1.9	5.3	220
		µg/g creatinine			36 (25–53)*	11	40	625			7.5 (5.1–11)	2.6	5.5	240
EthP	EthP	µg/L	76	94.7%	3.1 (2.1–4.6)*	0.89	2.4	84	80	77.5%	0.77 (0.59–1.0)	0.42	0.66	8.6
		µg/g creatinine			3.0 (2.0–4.4)*	0.79	2.4	70			0.85 (0.64–1.1)	0.41	0.77	8.8
ProP	ProP	µg/L	76	88.2%	14 (8.8–22)*	3.5	18	280	80	62.5%	2.1 (1.4–3.1)	–	1.9	49
		µg/g creatinine			13 (8.5–21)*	2.5	14	220			2.3 (1.6–3.4)	–	2.1	50
ButP	ButP	µg/L	76	36.8%	–	–	–	11	80	13.8%	–	–	–	0.84
		µg/g creatinine			–	–	–	9.7			–	–	–	0.87
TCS	TCS	µg/L	76	36.8%	–	–	–	7.3	80	36.3%	–	–	–	4.5
		µg/g creatinine			–	–	–	16			–	–	–	3.7

* Mothers/children have statistically significant ($p < 0.05$) higher levels of the biomarker.

Table 2

Correlations between creatinine-adjusted levels of phthalate metabolites, BPA, parabens and TCS in samples from mothers (gray) and children (white). Spearman's correlation coefficient is presented.

	ΣDEHP	ΣDiNP	MEP	MBzP	MnBP	BPA	MetP	EthP	ProP	TCS
ΣDEHP		0.37**	−0.07	0.33**	0.22*	0.35**	0.03	0.08	−0.05	0.13
ΣDiNP	0.51**		−0.12	0.00	−0.08	0.05	0.00	−0.05	0.02	−0.04
MEP	0.10	0.09		0.06	0.06	0.03	0.09	0.03	0.22	0.21
MBzP	0.45**	0.32**	0.16		0.53**	0.17	−0.03	0.06	−0.07	0.09
MnBP	0.29**	0.16	0.34**	0.48**		0.06	0.03	0.17	−0.00	−0.02
BPA	0.45**	0.16	0.13	0.18	0.13		0.10	−0.01	−0.04	0.14
MetP	0.14	0.06	0.11	−0.07	0.18	0.13		0.38**	0.81**	0.11
EthP	0.16	0.14	0.02	0.03	0.13	0.14	0.45**		0.24*	0.10
ProP	0.21	0.11	0.12	0.04	0.12	0.17	0.69**	0.40**		0.04
TCS	0.15	0.03	0.11	0.19	0.27*	0.14	0.01	0.23*	0.08	

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

had higher concentrations than the mothers of phthalate metabolites, except for MEP which was higher in the mothers. There were strong correlations between the levels of individual DEHP metabolites ($r_s = 0.60–0.96$; $p < 0.001$) as well as between individual DiNP metabolites ($0.88–0.96$; $p < 0.001$) in urine (Table 2). There

was also a significant correlation between the sum of DEHP metabolites and the sum of DiNP metabolites. Also, the levels MnBP and MBzP were well correlated, whereas MEP had the weakest correlation to the other phthalate metabolites. There were statistically significant correlations of all phthalate metabolites in urine from the mothers and their children ($r_s = 0.24–0.62$; $p = <0.001–0.03$), except for cx-MiNP ($r_s = 0.17$; $p = 0.10$), both for unadjusted (r_s within parentheses) and creatinine adjusted concentrations (data not shown). The strongest mother–child correlation was seen for MBzP ($r_s = 0.62$).

Significant exposure variables, as evaluated by the univariate analysis, in mothers and children are presented in Tables 3 and 4, respectively. Living in the rural area was associated with significantly higher levels of MBzP, MnBP and MEP in mothers and children compared to living in the urban area. Living in a house with PVC in floorings or wall coverings was associated with higher levels of MBzP in both mothers and children, and also MnBP in children. Children and mothers from families with low education had higher levels of MBzP and children from these families also had higher levels of MnBP and MEP. Younger children (6–8 years) had higher levels of MnBP, DEHP and DiNP metabolites than older children (9–11 years). However, if raw levels of phthalate metabolites were used in the analysis instead of creatinine-adjusted levels, only DiNP remained significantly associated with age (data not

Table 3

Geometric mean levels ($\mu\text{g/g}$ creatinine) of biomarkers in mothers categorized by population characteristics and potential exposure sources. Statistically significant differences are indicated by bold script and asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Variables which were not significantly correlated with any biomarker are not included in the table.

Variable	N ^a	N ^b	Category	DEHP ^c	MEP	MBzP	MnBP	DiNP ^d	BPA	MetP	EthP	ProP
Age	21	17	<37 years	36.63	44.04	15.88*	58.95	34.15	1.01	35.64	3.13	16.31
	43	31	38–40 years	32.02	39.08	11.79	66.99	32.01	1.23	28.38	2.57	8.45
	31	28	>41 years	40.52	39.69	9.32	52.78	29.57	1.52*	45.27	3.29	16.61
Area	46	39	Urban	37.26	31.45	6.74	46.03	41.03	1.31	45.75	3.03	17.50
	49	37	Rural	35.20	52.33*	20.85***	75.37***	25.15	1.17	28.14	2.94	9.85
Education	24	17	High school/college	33.95	50.57	19.06**	67.02	33.58	1.11	40.32	5.99	10.56
	70	59	University/PhD	37.04	38.68	10.18	56.17	31.82	1.27	34.98	2.44	14.11
House renovation/redecoration last 2 yrs	58	45	Yes	35.16	48.62*	12.72	58.52	34.39	1.27	30.81	2.10	12.63
	37	31	No	37.83	31.17	11.12	60.70	28.31	1.19	45.48	4.97*	14.14
PVC in floorings or wall coverings at home	36	30	Yes	34.99	41.73	17.47***	63.65	27.28	1.28	31.24	1.65	13.26
	31	24	No	39.65	50.66	7.49	53.43	33.17	1.33	53.67	3.90	16.80
Meat consumption	77	63	Several times per week	34.71	39.88	11.77	58.78	27.42	1.13	33.20	3.02	12.26
	18	13	Once a week or less	43.16	45.51	13.42	61.93	60.76*	1.81**	54.29	2.83	19.08
Fish consumption	35	31	Several times per week	39.45	38.06	10.94	56.65	38.50	1.52*	40.32	3.68	13.83
	60	45	Once a week or less	34.40	42.64	12.78	61.00	28.56	1.10	33.47	2.58	12.82
Chocolate consumption	41	35	Several times per week	44.52**	35.09	12.17	59.00	33.39	1.28	27.98	2.48	9.88
	53	40	Once a week or less	30.85	46.34	11.98	59.34	30.25	1.21	42.09	3.77	15.79
Fast food consumption	8	7	Several times per week	38.63	36.44	11.36	67.79	39.68	2.02*	52.74	1.06	14.98
	87	69	Once a week or less	35.95	41.33	12.14	58.64	31.24	1.18	34.75	3.32	13.06
Chewing gum consumption	34	30	Several times per week	34.30	52.40	10.05	56.44	39.35	1.15	65.24*	4.42	24.69*
	60	46	Once a week or less	37.37	36.25	13.18	60.11	28.82	1.28	24.55	2.31	8.80
Canteen food consumption	38	32	Several times per week	32.10	38.45	8.52	51.79	39.15	1.12	37.64	2.80	15.18
	55	42	Once a week or less	38.21	43.60	15.20**	65.29	27.54	1.28	39.71	3.51	13.21
Drinking water	87	71	Public water supply	36.31	38.40	11.53	57.10	30.30	1.25	34.81	2.75	12.68
	8	5	Well/private water	34.88	80.99	19.91	90.61*	55.40	1.12	60.77	9.71	24.07
Use of rubber gloves	25	21	Daily or sometimes	34.74	51.08	13.70	59.82	43.63	1.39	63.36	2.32	32.87*
	68	55	Never	36.93	37.83	11.35	58.39	28.68	1.20	29.13	3.29	9.34
Number of personal care products	63	50	High amount	33.05	43.95	11.13	57.44	32.72	1.24	50.10**	3.11	19.42**
	27	22	Moderate amount	43.47	30.66	14.14	58.98	31.34	1.24	14.95	3.44	4.81
Lotion	78	65	Every second day or more	36.31	41.39	12.08	60.95	29.69	1.25	46.12***	2.97	17.57**
	16	10	Once a week or less	33.52	40.00	12.06	53.18	39.01	1.07	6.59	3.53	2.26
Skin Make-up	62	50	Daily use	34.30	42.05	10.41	56.80	36.00	1.23	56.73***	3.15	24.64***
	33	26	Every second day or less	40.00	38.81	15.94*	64.50	25.38	1.24	15.15	2.70	4.00
Eye make-up	70	56	Daily use	32.82	41.88	10.47	56.94	32.73	1.17	43.16	2.97	19.54**
	25	20	Every second day or less	47.51*	38.24	17.94*	66.71	29.63	1.42	21.92	3.03	4.43
Sunscreen	12	7	Once a week or more	43.40	86.21**	10.45	72.76	66.44	1.34	66.59	14.43*	27.17
	79	65	Seldom/never	34.70	35.39	12.03	57.30	29.77	1.22	35.80	2.59	12.75
Mouth wash	12	11	Every second day or more	35.09	25.62	7.05	52.16	64.16	1.01	93.70*	4.37	42.88*
	83	65	Once a week or less	36.34	43.75	13.04*	60.48	28.81	1.27	30.73	2.80	10.84

^a Number of samples analyzed for phthalates and BPA.

^b Number of samples analyzed for parabens.

^c Sum of MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP.

^d Sum of OH-MiNP, oxo-MiNP and cx-MiNP.

Table 4
Geometric mean levels of biomarkers ($\mu\text{g/g}$ creatinine) in children categorized by population characteristics and potential exposure sources. Statistically significant differences are indicated by bold script and asterisks (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Variables which were not significantly correlated with any biomarker are not included in the table.

Variable	N ^a	N ^b	Category	DEHP ^c	MEP	MBzP	MnBP	DiNP ^d	BPA	MetP	ProP
Age	49	40	6–8 years	91.20***	32.42	25.23	101.79**	57.37**	2.01*	11.35*	2.87
	48	40	9–11 years	59.74	32.71	19.99	73.82	31.53	1.39	4.96	1.90
Area	47	40	Urban	75.09	25.18	13.72	67.63	41.41	1.77	13.01**	4.29**
	50	40	Rural	72.94	41.46**	35.78***	109.81***	43.88	1.58	4.32	1.27
Education	24	19	High school/college	73.89	51.06**	33.77**	111.06*	47.26	1.78	6.76	1.24
	72	61	University/PhD	74.00	27.92	19.41	78.88	40.42	1.64	7.75	2.85
PVC in floorings or wall coverings at home	35	30	Yes	73.08	37.96	27.90**	99.34*	39.93	1.71	7.89	1.89
	32	26	No	77.24	28.72	16.46	67.67	43.36	1.63	7.82	2.57
Fast food consumption	9	8	Several times per week	81.06	25.36	32.05	69.43	89.38*	2.09	5.16	3.13
	87	71	Once a week or less	72.70	33.47	21.73	89.31	39.56	1.63	7.78	2.26
Cheese consumption	66	56	Several times per week	72.96	33.89	25.01*	92.44	40.46	1.67	8.92	2.76
	28	21	Once a week or less	72.53	28.52	16.64	74.86	46.86	1.66	4.64	1.43
Ice cream consumption	14	13	Several times per week	103.07*	25.73	24.58	66.36	74.53*	2.20	4.47	2.13
	80	64	Once a week or less	69.77	33.78	22.42	92.29	38.94	1.60	8.42	2.41
Canteen food consumption	50	40	Daily	75.97	31.20	24.59	94.90	45.88	1.78	5.91	1.60*
	46	40	Less than daily	72.66	34.56	19.93	79.37	40.69	1.55	9.51	3.42
Drinking water	88	74	Public water supply	73.90	31.45	21.23	83.34	41.72	1.64	7.02	2.43
	9	6	Well/private water	74.70	45.74	39.51*	129.67*	53.08	2.04	17.04	1.47
Play with plastic toys	24	18	Daily	82.90	22.96*	28.60	97.65	38.26	1.69	5.31	1.77
	53	45	Less than daily/never	66.67	35.76	19.88	82.52	42.65	1.64	8.58	2.61
Lotion	44	36	Once a week or more	76.22	30.10	20.05	90.78	39.59	1.69	13.54**	4.22**
	52	43	Seldom/never	72.21	34.90	24.13	83.40	45.73	1.67	4.45	1.35
Eye make-up	6	5	Once a week or more	46.24	88.95**	18.77	92.43	16.26	2.14	11.06	5.91
	90	74	Seldom/never	76.38	30.50	22.41	86.34	45.65*	1.65	7.19	2.13
Hair styling products	10	10	Once a week or more	81.78	22.17	17.17	51.98	52.07	1.83	4.99	3.29
	86	69	Seldom/never	73.17	34.11	22.83	92.02**	41.84	1.66	7.82	2.15
Nail polish	8	8	Once a week or more	47.53	35.18	14.97	76.31	22.13	1.42	7.78	3.24
	88	71	Seldom/never	77.06*	32.39	22.97	87.72	45.45	1.71	7.34	2.18
Deodorant	11	10	Every second day or more	64.28	46.04	16.13	57.98	29.34	1.57	13.68	3.81
	85	69	Once a week or less	75.38	31.19	23.10	91.34*	44.95	1.69	6.76	2.20
Fragrance	5	5	Once a week or more	80.92	28.92	13.84	45.25	60.17	1.69	5.90	3.53
	91	74	Seldom/never	73.66	32.83	22.75	89.86*	42.01	1.68	7.50	2.21

^a Number of samples analyzed for phthalates and BPA.

^b Number of samples analyzed for parabens.

^c Sum of MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP.

^d Sum of OH-MiNP, oxo-MiNP and cx-MiNP.

shown). The urinary levels of phthalates did not significantly differ between boys and girls.

In children, the univariate analysis of phthalates showed significant correlations with several dietary variables. DEHP and DiNP metabolites were correlated with ice cream, DiNP metabolites with fast food and MBzP with cheese. Among the mothers, DEHP metabolites were correlated with chocolate consumption. Drinking water from a well was correlated with higher levels of MnBP in mothers and children, and also MBzP in children compared to drinking water from a public water supply.

The univariate analysis of personal care products showed significant correlations between urinary levels of MEP and the use of sunscreen among mothers and the use of eye make-up among children (Tables 3 and 4). Negative correlations were found between the use of several personal care products and levels of MnBP, MBzP and DEHP metabolites.

The multiple regression models for the children showed significant correlations between ice cream consumption and levels of DiNP metabolites and between use of eye make-up and levels of MEP (Table 5). Living in the rural area was correlated to higher levels of MBzP and MnBP in children. In the multiple regression models for the mothers, living in the rural area was correlated with higher levels of MBzP, MnBP and MEP and mothers living in houses with PVC in floorings or wall coverings had higher levels of MBzP. Use of sunscreen was correlated to higher urinary levels of MEP and use of fragrance was correlated to higher levels of DiNP metabolites in the mothers (Table 5). Mothers who frequently consumed chocolate had higher levels of DEHP metabolites, whereas negative correlations were found between meat consumption and

levels of DiNP metabolites and between canteen food consumption and levels of MBzP.

3.2. Bisphenol A

Urinary BPA was detected in levels above the LOD in all urine samples (Table 1). The levels of BPA were significantly correlated between the mothers and their children ($r_s = 0.35$; $p = 0.001$).

In the univariate analysis, mothers who often ate fish or fast food had higher levels of BPA (Table 3). In the multiple models, there was a negative correlation between mother's meat consumption and BPA, whereas there was a positive correlation between children's chocolate consumption and BPA (Table 5). Age was correlated to the BPA levels in mothers and children in both the univariate and multiple analyses. Younger children (6–8 years) had higher levels compared to older children (9–11 years), whereas the oldest mothers (>41 years) had higher levels than the youngest mothers (<37 years).

3.3. Parabens

Among the parabens, MetP was detected in concentrations above the LOD in 100% of the urine samples from mothers and in 86% of the samples from children. EthP was detected in levels above the LOD in 95% of the samples from mothers and in 77% of the samples from children. ProP was detected in concentrations above the LOD in 88% of the samples from mothers and in 62% of the samples from children. ButP was found in levels above the LOD only in 37% of the samples from

Table 5

Multiple regression models using ln-transformed levels of biomarkers, with creatinine (g/L) and age forced into the models. For individual variables, B-values are given with 95% confidence interval (95% CI) and p-value. For the full models, adjusted R² and p-values are given.

	Variable	B (95% CI)	p-Value	Adjusted R ² (p-value)	Variable	B (95% CI)	p-Value	Adjusted R ² (p-value)
Mothers					Children			
DEHP ^a	Intercept	2.55 (2.15–2.95)	–	0.33 (<0.001)	Intercept	3.00 (2.49–3.50)	–	0.22 (<0.001)
	Creatinine	0.91 (0.63–1.19)	<0.001		Creatinine	1.03 (0.58–1.48)	<0.001	
DiNP ^b	<37 years ^c	–0.13 (–0.47–0.21)	0.458	0.14 (0.003)	6–8 years ^d	0.43 (0.14–0.73)	0.004	0.06 (0.032)
	38–40 years ^c	–0.20 (–0.54–0.14)	0.252		Intercept	3.14 (2.39–3.88)	–	
	Chocolate	0.31 (0.04–0.59)	0.028		Creatinine	0.20 (–0.46–0.86)	0.546	
	Intercept	2.74 (1.75–3.73)	–		6–8 years ^d	0.43 (0.00–0.86)	0.048	
	Creatinine	0.86 (0.31–1.41)	0.002		Ice cream	0.63 (0.05–1.21)	0.034	
	<37 years ^c	0.14 (–0.53–0.81)	0.681					
	38–40 years ^c	0.16 (–0.52–0.83)	0.642					
MBzP	Meat	–0.74 (–1.44 to –0.04)	0.040	0.58 (<0.001)	Intercept	2.84 (2.10–3.58)	–	0.23 (<0.001)
	Fragrance	0.56 (0.02–1.10)	0.042		Creatinine	0.53 (–0.14–1.21)	0.117	
	Intercept	1.61 (0.95–2.26)	–		6–8 years ^d	0.18 (–0.25–0.60)	0.406	
	Creatinine	1.12 (0.76–1.48)	<0.001		Urban area	–0.90 (–1.31 to –0.48)	<0.001	
	<37 years ^c	0.07 (–0.38–0.52)	0.750					
	38–40 years ^c	–0.17 (–0.63–0.28)	0.448					
	Urban area	–0.78 (–1.21 to –0.35)	<0.001					
MnBP	Canteen food	–0.47 (–0.84 to –0.11)	0.012	0.47 (<0.001)	Intercept	3.70 (3.21–4.18)	–	0.21 (<0.001)
	PVC	0.48 (0.04–0.91)	0.031		Creatinine	0.77 (0.33–1.21)	<0.001	
	Intercept	3.27 (2.81–3.72)	–		6–8 years ^d	0.30 (0.02–0.58)	0.036	
	Creatinine	0.93 (0.65–1.22)	<0.001		Urban area	–0.46 (–0.73 to –0.19)	0.001	
	<37 years ^c	–0.06 (–0.42–0.30)	0.734					
MEP	38–40 years ^c	0.12 (–0.24–0.47)	0.519	0.29 (<0.001)	Intercept	2.37 (1.49–3.25)	–	0.15 (0.009)
	Urban area	–0.47 (–0.77 to –0.17)	0.002		Creatinine	0.91 (0.12–1.70)	0.025	
	Intercept	2.96 (2.32–3.59)	–		6–8 years ^d	0.13 (–0.39–0.64)	0.626	
	Creatinine	0.81 (0.41–1.21)	<0.001		Eye make-up	1.19 (0.14–2.25)	0.028	
	<37 years ^c	–0.14 (–0.64–0.36)	0.574					
	38–40 years ^c	–0.25 (–0.76–0.25)	0.316					
	Sunscreen	1.07 (0.47–1.67)	<0.001					
BPA	Urban area	–0.68 (–1.10 to –0.26)	0.002	0.29 (<0.001)	Intercept	–0.53 (–1.08–0.03)	–	0.10 (0.005)
	>8 h since urination	0.47 (0.07–0.88)	0.023		Creatinine	0.73 (0.24–1.22)	0.004	
	Intercept	–0.07 (–0.52–0.38)	–		6–8 years ^d	0.32 (0.00–0.63)	0.050	
	Creatinine	0.73 (0.47–0.99)	<0.001		Chocolate	0.41 (0.01–0.81)	0.047	
	<37 years ^c	–0.37 (–0.69 to –0.05)	0.023					
	38–40 years ^c	–0.12 (–0.45–0.20)	0.445					
	Meat	–0.42 (–0.76 to –0.08)	0.014					
MetP	Intercept	1.86 (0.72–3.01)	–	0.23 (<0.001)	Intercept	–0.67 (–1.96–0.63)	–	0.28 (<0.001)
	Creatinine	0.22 (–0.50–0.93)	0.546		Creatinine	1.00 (–0.14–2.13)	0.085	
	<37 years ^c	–0.05 (–0.89–0.79)	0.909		6–8 years ^d	0.77 (0.05–1.50)	0.037	
	38–40 years ^c	–0.34 (–1.18–0.51)	0.430		Lotion	1.19 (0.49–1.89)	0.001	
	Skin make-up	1.19 (0.48–1.91)	0.001		Urban area	1.13 (0.39–1.88)	0.003	
	Lotion	1.01 (0.30–1.72)	0.006		Well water	1.69 (0.42–2.95)	0.010	
	Plastic gloves	0.83 (0.03–1.63)	0.042					
EthP	Intercept	0.41 (–0.64–1.47)	–	0.10 (0.030)	–			
	Creatinine	0.28 (–0.48–1.04)	0.466					
	<37 years ^c	0.00 (–0.93–0.94)	0.994					
	38–40 years ^c	–0.23 (–1.17–0.71)	0.626					
	Sunscreen	1.65 (0.50–2.79)	0.005					
ProP	Education low	1.01 (0.14–1.87)	0.023	0.26 (<0.001)	Intercept	–1.78 (–3.06 to –0.51)	–	0.28 (<0.001)
	Intercept	0.76 (–0.49–2.01)	–		Creatinine	1.17 (0.02–2.33)	0.047	
	Creatinine	0.36 (–0.47–1.20)	0.387		6–8 years ^d	0.62 (–0.11–1.36)	0.096	
	<37 years ^c	0.24 (–0.75–1.22)	0.633		Lotion	1.06 (0.36–1.76)	0.004	
	38–40 years ^c	–0.46 (–1.44–0.52)	0.354		Urban area	1.08 (1.80–0.37)	0.004	
	Skin make-up	1.76 (0.92–2.60)	<0.001		Eye make-up	1.61 (0.08–3.14)	0.039	
	Plastic gloves	1.36 (0.43–2.30)	0.005					

^a Sum of MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP.

^b Sum of cx-MiNP, oxo-MiNP and OH-MiNP.

^c Compared to age group >41 years.

^d Compared to age group 9–11 years.

mothers and in 14% of the samples from children. BenP was not detected in any of the samples. The mothers had significantly higher levels of parabens than the children (Table 1). Due to the low number of samples with concentrations of ButP and BenP above the respective LOD, univariate and multiple analyses were not performed for these compounds. Also, the levels of EthP in children were not normally distributed even after ln-transformation, thus no further analysis of EthP among children was performed. Among the parabens, the correlation between MetP and ProP was the strongest, whereas the correlations between EthP and MetP as well as between EthP and ProP were weaker (Table 2). There

were significant correlations between the levels in mothers and their children of MetP ($r_s = 0.36$; $p = 0.002$) and ProP ($r_s = 0.55$; $p = <0.001$), but not EthP ($r_s = 0.19$; $p = 0.09$).

In the univariate analysis, mothers who used a high number of personal care products (make-up, shampoo, hair styling products, lotion, fragrance, deodorant, massage oil and nail polish) had significantly higher levels of MetP and ProP (Table 3). Higher levels of MetP and ProP were especially associated to the use of make-up, lotion and mouth wash. The levels of EthP were higher in mothers who more frequently used sunscreen. Among the children, the combined number of

personal care products used was not significantly correlated with the levels of parabens. However, when the personal care products were studied separately, significant positive correlations were found between the use of lotion and levels of MetP and ProP (Table 4). In mothers, frequent chewing gum consumption was associated with higher levels of MetP and ProP, and regular use of plastic gloves was associated with higher levels of ProP (Table 3). Children living in the urban area had higher levels of MetP and ProP than children living in the rural area (Table 4).

In the multiple analysis among the mothers, the use of skin make-up was correlated to higher levels of MetP and ProP, lotion was correlated with MetP and sunscreen with EthP (Table 5). Regular use of plastic gloves was correlated with higher levels of both MetP and ProP. Among the children, the multiple analyses showed significant correlations between the use of lotion and higher levels of MetP and ProP, and between the use of eye make-up and levels of ProP. Living in an urban area was correlated to higher levels of MetP and ProP and younger children had higher levels of MetP than older children. Also, drinking water from a well was correlated with higher levels of MetP (Table 5).

3.4. Triclosan

TCS was detected in levels above the LOD in 37% of the samples from mothers and 36% of the samples from children (Table 1). Due to the low number of samples with TCS levels above the LOD, no univariate or multiple analyses were performed. However, it can be noted that no obvious differences in TCS levels were detected between users and non-users of products which may contain TCS, such as mouth-wash, hand disinfectants or deodorants (data not shown). The levels of TCS were significantly correlated between the mothers and their children ($r_s = 0.35$; $p = 0.001$).

4. Discussion

We have evaluated the significance of potential exposure sources of phthalates, BPA, parabens as well as TCS in mothers and their children (6–11 years old) in a rural and an urban area of Sweden. We measured metabolites of these compounds in first morning urine and used a questionnaire to obtain information on potential exposure sources and factors. In general, children had higher levels of phthalate metabolites in urine than the mothers, except for a phthalate metabolite associated with the use of cosmetics (MEP). The mothers had higher levels of parabens associated with a frequent use of cosmetic products. We found comparatively low levels of BPA and TCS in urine.

PVC in the home environment is a strong predictor for exposure to phthalates. Previous studies have shown that dust in houses with PVC flooring contains higher levels of BBzP and DEHP (Bornehag et al., 2005) and that individuals living in houses with PVC in flooring or wall coverings have higher urinary levels of MBzP, the corresponding metabolite to BBzP (Carlstedt et al., 2013). In the current study, PVC in the home environment was associated with higher urinary levels of MBzP and MnBP. Families living in the rural area and having lower education were more likely to have PVC in their homes. Therefore, the effect of PVC may explain why mother–child couples in the rural area and with low education had higher levels of MnBP and MBzP.

Besides PVC in the home environment, phthalate exposure is associated with consumption of certain foods. Phthalates can be found in a wide range of food groups on the retail market and previous studies have shown that food is the main exposure source for high molecular weight phthalates, whereas humans are exposed to low molecular weight phthalates, such as BBzP, DnBP and diethyl phthalate (DEP), from other sources than food, i.e. PVC plastics, paints and cosmetics (Fierens et al., 2012; Fromme et al., 2007; Koch et al., 2013; Schecter et al., 2013; Wittassek et al., 2011). In the present study, consumption

of ice cream among children and chocolate among mothers was significantly correlated with higher levels of urinary phthalate metabolites originating from high molecular weight phthalates (DEHP and DiNP), indicating migration of these phthalates into the food through the production or packaging of food. Few studies have investigated the importance of specific foods for the dietary intake of phthalates. An American study combining urinary levels of phthalates and 24 hour dietary recalls of meat, poultry, fish, dairy and vegetable consumption found the strongest correlations between urinary DEHP metabolites and consumption of poultry as well as between urinary MEP and vegetable consumption (Colacino et al., 2010). Sioen et al. (2012) performed an intake assessment of phthalates in the Belgian population, using food consumption data and phthalate concentrations in foods. The assessment showed that bread was the major contributor to the DEHP intake in both adults and children. Dietary intakes of phthalates in UK children and adults have also been assessed in the UK Total Diet Study with food samples collected in 2007 (Committee on Toxicity, 2011). The results showed that the main contributors to the intake of DEHP were fish, meat, poultry and dairy products.

Food is the main source of BPA exposure and associations between BPA levels in urine and certain food habits were therefore expected. In the current study, higher levels of BPA were found in children who often ate chocolate, probably reflecting a more frequent consumption of foods contaminated from food wrapping materials. The dietary BPA exposure may depend more on the food packaging than the food item per se, and especially canned foods are known to contain high levels of BPA (Cao et al., 2011; Schecter et al., 2010). In the current study, there was a tendency but no significant association between consumption of canned foods and BPA among women. However, the number of mothers who reported frequent consumption of canned foods was low ($n = 8$). The elevated levels of BPA in mothers who seldom or never ate meat may be due to their relatively higher consumption of other foods containing BPA. For example, the current study showed a positive correlation between fish consumption and levels of BPA in mothers. This association may be explained by consumption of canned tuna, often used in sandwiches and salads, and which is common among Swedish women. An association between urinary levels of BPA in women of childbearing age and canned fish has previously been demonstrated in a Spanish study by Casas et al. (2013).

DEHP, BBzP, DnBP and BPA, but not DiNP, are banned from personal care products and cosmetics in the EU (EC, 2009) whereas DEP, the parent compound of MEP, is the phthalate most commonly used in these products. Also, plastic containers used for personal care products may contain phthalates and BPA with ability to migrate to the products. Several studies have investigated the association between use of personal care products and urinary phthalate levels. These studies have found associations between urinary levels of MEP and use of perfume in women (Just et al., 2010; Parlett et al., 2013), cologne and aftershave in men (Duty et al., 2005) and lotions in infants (Sathyanarayana et al., 2008). In the present study, urinary MEP was associated with the use of sunscreen and eye make-up. Furthermore, we found a correlation between mother's frequent use of fragrance and higher levels of DiNP metabolites, which was not studied in the previous studies.

Parabens are widely used in cosmetics, thus it is not surprising that urinary levels of MetP, EthP and ProP were associated with the use of personal care products (lotion, sunscreen and make-up). Also previous studies have shown significant associations between self-reported use of lotions and elevated plasma and urinary levels of parabens (Den Hond et al., 2013; Sandanger et al., 2011). The reason for these particular associations is probably that lotions and other products that are applied to a large area of the skin and not washed off are more likely to be absorbed than products that are washed off, such as shampoo. Another interesting observation in the current study was that mothers who regularly used plastic gloves had higher levels of MetP and ProP which is not due to the plastic per se, but possibly lotion or powder used as inner coating of gloves.

The phthalates DEHP, DnBP and BBzP are prohibited from the production of toys within the EU, but they may still be detected in some of these products (KEMI, 2013). In the current study, the levels of DEHP metabolites, MnBP and MBzP were elevated in children playing with plastic toys, but the associations were not statistically significant. We could not identify any previous study investigating the possible association between toys and exposure to phthalates in Europe.

Most metabolites were detected above the LOD in urine of both mothers and their children. There were generally fairly good correlations between the metabolite concentrations in urine between mothers and their children, indicating similar exposure patterns in mother–child couples. Especially the correlation of MBzP was strong, probably reflecting common exposure sources, such as PVC in the home environment. Children had generally higher levels of phthalates reflecting their higher consumption of food per kg bodyweight, but lower levels of parabens and MEP reflecting mother's more frequent use of personal care products and cosmetics. This pattern is consistent with other studies of children and adults (CDC, 2013; Frederiksen et al., 2013b; Health Canada, 2013). The creatinine-adjusted levels of DEHP, DiNP, MnBP, BPA and MetP were higher in younger than in older children. However, age was significantly correlated with creatinine, and if unadjusted levels were used for the analysis, only DiNP remained significantly associated with age. Also in the German GerES IV study, higher urinary levels of phthalates, and to some extent BPA, were found in younger than in older children (Becker et al., 2009). The levels of ButP and TCS were below the LOD in most urine samples and BenP was not detected in any sample, indicating a low exposure to these compounds in the general Swedish population. Decreasing levels of TCS have been reported in sewage from Swedish waste water treatment plants, indicating a decreased usage of TCS in products (Haglund and Olofsson, 2011).

The quality of the data gathering and chemical analyses in the current study were strengthened by applying a harmonized methodological approach elaborated by a consortium with representatives from several European countries. The harmonized approach also enables comparison of urinary levels of contaminants on the European level. Compared to 13–16 other European countries participating in the same harmonization program, the Swedish levels of DEHP metabolites and MEP in urine were close to the average levels in Europe, whereas the levels of MBzP and MnBP were higher than in the other countries (Den Hond et al., *in press*). The levels of BPA in Sweden were among the lowest compared to the levels in the other five participating countries that analyzed BPA (Covaci et al., *in press*). When compared to studies of children and women of childbearing age outside the harmonization program, the urinary levels of phthalates and BPA in the current study were in the same magnitude as levels found in studies from US, Canada, Netherlands and Norway (CDC, 2009; CDC, 2013; Health Canada, 2013; Ye et al., 2008; Ye et al., 2009). The levels of DEHP metabolites and MEP in the current study were generally among the lowest, whereas the levels of MnBP were among the highest compared to these studies. The levels of parabens in the current study were among the lowest and the levels of TCS were remarkably lower compared with studies from Spain, US and Denmark (Calafat et al., 2010; Casas et al., 2011; Frederiksen et al., 2013b).

The analyses of determinants of exposure based on questionnaire data should be interpreted with caution and the results should be regarded as indications of potentially important exposure sources for these compounds. The number of participants was fairly low, thus the statistical power was limited and a few random high values may get unbalanced importance in subgroups containing few participants. The number of exposure sources covered by the questionnaire was limited and some questions may serve as dummies for other related source–exposure relationships than the ones covered here.

Given the frequent use of products containing the studied compounds, recurrent exposure over time is likely to occur. A single urine sample may therefore reasonably represent an individual's ongoing

exposure (Christensen et al., 2012; Frederiksen et al., 2013a; Mouritsen et al., 2013; Smith et al., 2012). In the current study, first morning urine sampling was applied, which has been shown to reasonably reflect the individual exposure (except for BPA). Adjustment for creatinine is used to correct for dilution in individual urine samples. However, the creatinine excretion varies with factors such as age, gender and ethnicity (Barr et al., 2005). Therefore, direct comparisons of creatinine-adjusted levels between different groups of the population, e.g. mothers and children or children of various ages, should be interpreted with caution.

5. Conclusions

To our knowledge this is the first study examining exposure determinants for phthalates, BPA, parabens and TCS in Swedish mother–child couples. Phthalates, BPA and parabens were significantly correlated to certain foods and personal care products which were expected to be relevant exposure sources for these contaminants. The levels were fairly well correlated between the mothers and their children. For both mothers and children, urinary levels of phthalates were generally associated with food consumption whereas the levels of parabens were associated with use of cosmetics and personal care products. The urinary levels of the studied chemicals were in the same magnitude as in previous studies from other countries, although the levels of TCS were much lower.

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