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Concentrations of phthalate metabolites and phenolic substances in urine from first-time mothers in Uppsala, Sweden: temporal trends 2009-2018

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Sammanfattning

Sedan 1996 samlas blod- och modersmjölksprover regelbundet in från förstföderskor i Uppsala i den så kallade POPUP-studien. Sedan 2009 tas också ett urinprov. I denna rapport har tidstrender för ftalater och fenolära ämnen studerats i urinprov insamlade mellan 2009 och 2018. Ftalater och fenolära ämnen metaboliseras relativt snabbt i kroppen och för flertalet är det därför en metabolit till själva huvudsubstansen som har analyserats.

Totalt sett analyserades tolv metaboliter till sex ftalater, en metabolit till en ersättningskemikalie till ftalater, metaboliter till tre fosforbaserade flamskyddsmedel, två pesticidmetaboliter samt åtta fenolära ämnen, bland annat triclosan, bisfenol A, S och F. Analyserna utfördes av Lunds universitet. Syftet var att studera tidstrender för dessa olika ämnen under perioden 2009-2018.

Resultaten visade en nedåtgående tidstrend för de ftalater som håller på att fasas ut samtidigt som metaboliten för en ersättare till ftalaterna ökade. Det omdiskuterade ämnet bisfenol A och triclosan visade nedåtgående trender medan en ersättningssubstans till bisfenol A, bisfenol F, snarare hade en omvänd u-formad kurva. Även en metabolit till insekticiden klorpyrifos minskade under perioden, möjligen som en konsekvens av att strängare gränsvärden införts i EU.

Analyser av urin gör det möjligt att studera hur befolkningens exponering för snabbmetaboliserande substanser ser ut. Genom att analysera prover över tid kan man studera hur befolkningens exponering förändras efter att åtgärder för att begränsa vissa kemikalier satts in samt hur exponeringen för nya ersättningskemikalier utvecklas.

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INTRODUCTION

The Swedish Food Agency has conducted recurrent sampling of breastmilk and blood from primiparous women in Uppsala since 1996, in the so-called POPUP study (Persistent Organic Pollutants in Uppsala Primiparas). The Swedish Environmental Protection Agency has funded the study since year 2000. The main aim of the study is to investigate temporal trends of exposure to persistent organic pollutants (POP) among pregnant and nursing women. Since 2009, urine samples are collected from the women in POPUP three weeks after delivery for evaluation of temporal trends of less persistent, rapidly metabolized contaminants excreted in urine (e.g. phthalates and phenolic compounds, such as bisphenols). Many of these chemicals have been identified as potential endocrine disrupting chemicals (Dann and Hontela 2011, Peretz et al. 2014, Weatherly and Gosse 2017, Radke et al. 2018, Zamkowska et al. 2018), and there is a concern that human exposures to some of these chemicals are high enough to affect human health (Braun et al. 2013, Rochester 2013, Marie et al. 2015, Weatherly and Gosse 2017, Radke et al. 2018, Rochester et al. 2018).

Phtalates are widely used in industrial and consumer products such as plasticizers, solvents and additives, and are ubiquitous in the human environment. Four of these phthalates (di-ethylhexyl pthtalate [DEHP], di-n-butyl phthalate [DBP], butylbenzyl phthalate [BBzP], and diisobutyl phthalate [DIBP]) are classified as substances toxic for reproduction on EU´s candidate list of substances of very high concern. The use of these four phthalates was restricted in toys and childcare articles in EU in 2007 (EU commission 2006) and in 2020, their use will be further restricted to less than 0.1% by weight, individually or in combination, in plasticized materials (EU commission 2018b). The use of some phthalates has therefore been or are being phased out and substituted with new chemicals with similar function. For example, di-iso-nonyl cyclohexane-1,2-dicarboxylate (DiNCH) was introduced on the European market in 2002 to replace DEHP and other high-molecular weight phthalates in polyvinyl chloride (PVC) (Schutze et al. 2014).

Phenolic substances are a heterogeneous group including bisphenols used as monomers in the production of plastic, the antibacterial agent triclosan (TCS), the preservative butylated hydroxyanisole (3-tert-butyl-4-hydroxyanisole, BHA) and the UV filter benzophenone-3 (BP-3). Some chemicals are metabolized to phenolic compounds in the body, e.g. pesticides and the contaminants polycyclic aromatic hydrocarbons (PAH). Several of these substances are included on EU´s candidate list of substances of very high concern and their use is regulated

on the EU market, e.g. TCS (EU commission 2016a), bisphenol A (BPA) (Swedish Chemicals Agency 2019), and chlorpyrifos (EU commission 2018a).

This report describes temporal trends of twelve metabolites from sex different phthalates, one metabolite of a chemical replacing phthalates, three metabolites of organophosphate flame retardants, two pesticide metabolites and eight different phenolic substance in urine of first-time mothers between 2009 and 2018. The aim is to investigate if measures to decrease production and use of some of these chemicals have resulted in decreased human exposure, and to determine if exposures to replacement chemicals have increased. It covers an extended reporting period than what has been described previously, i.e. 2009-2018 vs 2009-2014 (Gyllenhammar et al. 2017).

MATERIALS AND METHODS

Recruitment and sampling

Participants were randomly recruited among first-time mothers who were Swedish by birth and delivered at Uppsala University Hospital. Thirty women were recruited every year between 2009 and 2018. The participation rate was 46%. Spot urine samples of the participating women were collected three weeks after delivery. Data on age, weight, length, lifestyle, medical history, food habits etc. of the mothers were obtained from questionnaires. The present study includes urine samples from 296 women.

Analysis

An overview of the analysed substances and their parent compounds are given in Table 1. Urine metabolites of di-ethyl phthalate (DEP, one metabolite), BBzP (one metabolite), DEHP (five metabolites), di-iso-nonyl phthalate (DiNP, three metabolites) and two metabolites of a mixture of di-iso-decyl phthalate (DiDP) and di-propylheptyl phthalate (DPHP) were analysed as well as one DiNCH metabolite. Analyses were also conducted for four organophosphate flame retardant metabolites (di-phenylphosphate [DPP], dibutyl phosphate [DBP], bis(2-butoxyethyl)phosphate [BBOEP], and bis(1,3-dichloro-2-propyl) phosphate [BDCIPP]) as well as for metabolites of the insecticides chlorpyrifos (trichloropyridinol [TCP]) and pyrethroids (3-phenoxybencoic acid [3PBA]). In addition, eight phenolic substances were analysed; four bisphenols (BPA, BPS, 2,2-BPF, 4,4-BPF), the antibacterial compound TCS,

two PAH metabolites (2-OH-phenantrene [2-OH-PH], 1-hydroxypyren [1-HP]), and 3-tert-butyl-4-hydroxyanisole (BHA), an antioxidant used as food additives. BDCIPP, the metabolite of tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) and 2,2-BFS were excluded from the present report due to non-valid data.

The samples were analysed in February-April 2019 at Lund University by a modified method for phthalate metabolites, as previously described (Bornehag et al. 2015). Briefly, urine was added to ammonium acetate (pH 6.5) and glucoronidase (E-coli), and incubated at 37°C in 30 minutes. Thereafter, a 50:50 (v:v) water and acetonitrile solution of labelled (^{3}H or ^{13}C) internal standards (IS) of all analysed compounds was added, with the exception of BHA and DBP. A C18 column was used prior to the injector to reduce the interferences of contaminants in the mobile phase. The substances in the samples were separated on a C18 column. The mobile phases were water and acetonitrile with 0.08% formic acid or water methanol with 0.1% ammonia. The samples were analysed on a Shimadzu UFLC system (Shimadzu Corporation, Kyoto, Japan) coupled to a QTRAP5500 triple quadrupole linear ion trap mass spectrometer equipped with a TurboIon Spray source (LC-MS/MS; AB Sciex, Foster City, CA, USA). All samples were analysed in a randomized order. For quality control of the analyses, chemical blanks and in-house prepared quality control samples were analysed in all sample batches. The limit of detections (LOD), defined as the concentration corresponding to a peak area ratio of three times the standard deviation of the chemical blanks, are shown in Table 1. The imprecisions of the method, reported as the coefficient of variation (CV) of the quality control sample, are also shown in Table 1. The laboratory at Lund University is reference laboratory for analyses of urinary phthalate metabolites and BPA in European biomonitoring projects (http://www.eu-hbm.info/cophes and https://www.hbm4eu.eu/). The laboratory participates in the ICI/EQUAS exercises for the analysis of BPA, BPS, 4,4-BPF 1-HP, monobenzyl phthalate (MBzP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxylhexyl) phthalate (5OH-MEHP), mono-(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP), mono-(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP), and are approved for these compounds in the HBM4EU project. Moreover, the laboratory participates in the Erlangen inter-laboratory comparison program for several phthalate metabolites, TCP, and 3-PBA. Urine concentrations adjusted to urine density were calculated according to Carnerup et al (Carnerup et al. 2006), using the average density of the current population, 1.016 kg/l. Sum of DEHP metabolites was calculated as molar sum and then converted to ng/ml (Zota et al. 2014).

Table 1. *Limit of detection (LOD) and the coefficient of variation (CV) for the analysed substances.*

Biomarker	**Abbreviation**	**Parent compound**	**LOD (ng/ml)**	**Low QC**		**High QC**	
				Mean (ng/ml)	**CV (%)**	**Mean (ng/ml)**	**CV (%)**
Phatalates and alternative plasticizer							
Monoethyl phthalate	MEP	DEP	0.20	131	7.0	264	7.7
Monobenzyl phthalate	MBzP	BBzP	0.20	8.1	15	18	14
Mono-(2-ethylhexyl) phthalate	MEHP	DEHP	0.30	0.9	14	11	10
Mono-(2-ethyl-5-hydroxylhexyl) phthalate	5OH-MEHP	DEHP	0.10	6.1	5.7	16	8.6
Mono-(2-ethyl-5-oxohexyl) phthalate	5oxo-MEHP	DEHP	0.20	4.3	10	16	9.3
Mono[2-(carboxymethyl)hexyl] phthalate	2cx-MEHP	DEHP	0.05	1.2	14	11	8.4
Mono-(2-ethyl-5-carboxypentyl)phthalate	5cx-MEPP	DEHP	0.07	4.9	5.5	16	5.7
Mono-(4-methyl-7-hydroxyloctyl)phthalate	OH-MiNP	DiNP	0.05	5.5	5.9	16	7.5
Mono-(4-methyl-7-oxo octyl)phthalate	oxo-MiNP	DiNP	0.05	2.4	9.2	13	6.6
Mono-(4-methyl-7-carboxyheptyl)phthalate	cx-MiNP	DiNP	0.05	8.6	8.4	20	8.6
Monocarboxyisononyl phthalate	cx-MiDP	DiDP/DPHP	0.10	0.6	27	11	6.8
6-Hydroxy monopropylheptylphthalate	OH-MPHP	DiDP/DPHP	0.08	1.5	13	12	6.8
Cyclohexane-1,2-dicarboxylate-mono(oxo-isononyl) ester	oxo-MINCH	DiNCH	0.08	1.1	13	12	11
Bisphenols							
Bisphenol A	BPA		0.20	2.2	9.3	7.8	5.8
Bisphenol S	BPS		0.03	0.8	25	6.6	8.7
4,4-Bisphenol F	4,4-BPF		0.03	<LOD	<LOD	5.7	7.0
Polycyclic aromatic hydrocarbons (PAH)							
2-OH-phenantrene	2-OH-PH	Phenanthrene	0.10	2.2	11	11	8.4
1-Hydroxypyren	1-HP	Pyrene	0.10	0.8	10	4.5	7.7
Pesticides							
Trichloropyridinol	TCP	Chlorpyrifos	0.07	3.0	7.7	8.2	7.4
3-Phenoxybencoic acid	3PBA	Pyrethroids	0.05	1.1	11	6.4	10

Biomarker	Abbreviation	Parent compound	LOD (ng/ml)	Low QC		High QC	
				Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)
Organophosphate flame retardants							
Di-phenylphosphate	DPP	TPP	0.07	1.0	13	2.3	13
Dibutyl phosphate	DBP	TBP	0.05	0.1	41	6.7	12
Bis(2-butoxyethyl)phosphate	BBOEP	TBOEP	0.05	<LOD	<LOD	5.0	8.0
Other phenolic substances							
Triclosan	TCS		0.10	8.8	14	12	17
3-Tert-butyl-4-hydroxyanisole	BHA		0.02	0.8	21	51	10
Benzophenone-3	BP-3		0.20	<LOD	<LOD	22	14

Calculations and statistics

Statistical analyses were performed using the software package STATA version 15.1. Mean concentrations were described by geometric means (GM) and medians with 95% confidence intervals (CI). When urine concentrations were below LOD, the reported urine concentrations were used (i.e. the blank concentration was subtracted from the measured concentration of the sample). Temporal trends were investigated for the study period 2009-2018. Linear regressions were used to analyse associations between logarithmically transformed density-adjusted urine concentrations and sampling year. Sampling date was used as predictor in the linear regressions and the slope (β) was converted to year by multiplying with 365 (i.e. to correspond to change in concentration per year). Multiple linear regression analyses including the covariates age, pre-pregnancy body mass index (BMI), weight gain during pregnancy (kg), weight loss from delivery to time of sampling (kg), education, and season of sampling were also conducted. Observations with standardized residuals ≥3 were excluded in these sensitivity tests.

RESULTS AND DISCUSSION

Characteristics of the first-time mothers with urine samples 2009-2018 are shown in Table 2.

Table 2. *Population characteristics (N=296).*

Variable		**Mean ± SD**	**(Min-Max)**
Age (year)		29 ± 4	(20-41)
Pre-pregnancy body mass index (BMI, kg/m^2)		23 ± 3	(17-37)
Weight gain during pregnancy (kg)		16 ± 6	(-6-38)
Weight reduction from delivery to sampling (kg)[a]		7 ± 3	(-1-19)
Urine density (kg/l)		1.016 ± 0.007	(1.002-1.038)
Variable		**N**	**(%)**
Education	Max 3-4 years of high school	48	(16%)
	1-3 years of higher education	60	(20%)
	>3 years of higher education	188	(64%)
Smoking[b]	Non-smoker	225	(76%)
	Former smoker	57	(19%)
	Smoker	14	(5%)
Season for sampling	Spring	81	(27%)
	Summer	38	(13%)
	Autumn	105	(35%)
	Winter	72	(24%)

[a]Defined as weight just before delivery minus weight at sampling time point and birth weight of the child.
[b]Women who stopped before pregnancy are considered to be former smoker. Women who smoked during pregnancy are defined as smoker even if they stopped during the first or second month of pregnancy.

Urine concentrations of the analysed phthalate metabolites are presented in ng/ml in Table 3. Urine concentrations of phenolic substances and other rapidly metabolised substances are shown in Table 4. Both reported concentrations and concentrations adjusted for urine density are included. Most substances had detectable concentrations in all samples or only a few samples with concentrations below LOD (Table 3 and Table 4). However, the number of samples with concentrations below LOD was relatively high for 2-OH-PH (42%), 1-HP (73%) and BBOEP (52%), which should be considered when interpreting these data.

Table 3. *Urine concentrations (ng/ml) of phthalate metabolites and one DiNCH metabolite in first-time mothers between 2009 and 2018. Both reported and density-adjusted concentrations are presented (N=296).*

Biomarker		Geometric mean (95% CI)	Median (95% CI)	95% percentile (95% CI)	Min-Max	N(%) <LOD	LOD (ng/ml)
MEP	raw	21.4 *(18.5-24.9)*	20.2 *(17.5-23.7)*	228 *(142-435)*	1.19-1356	0	0.20
	adj	24.4 *(21.5-27.8)*	21.4 *(17.9-25.5)*	228 *(142-351)*	1.78-1118		
MBzP	raw	4.79 *(4.19-5.47)*	5.20 *(4.28-6.02)*	28.2 *(22.9-42.2)*	0.21-145	0	0.20
	adj	5.45 *(4.87-6.11)*	5.58 *(4.76-6.45)*	27.2 *(23.0-46.8)*	0.39-110		
MEHP	raw	1.60 *(1.43-1.78)*	1.57 *(1.32-1.69)*	9.84 *(6.84-16.5)*	0.16[a]-33.9	8 (3)	0.30
	adj	1.82 *(1.65-2.00)*	1.69 *(1.51-1.92)*	9.13 *(6.44-15.0)*	0.21[a]-22.7		
5OH-MEHP	raw	7.76 *(6.88-8.74)*	7.83 *(6.73-9.00)*	45.4 *(32.6-59.0)*	0.54-213	0	0.10
	adj	8.84 *(8.03-9.72)*	9.03 *(7.78-9.68)*	37.1 *(27.5-53.9)*	1.23-125		
5oxo-MEHP	raw	5.06 *(4.49-5.69)*	5.11 *(4.46-5.79)*	29.7 *(20.3-39.9)*	0.34-135	0	0.20
	adj	5.76 *(5.24-6.34)*	5.63 *(5.10-6.15)*	22.6 *(18.6-35.9)*	0.54-78.3		
2cx-MEHP	raw	2.91 *(2.65-3.20)*	2.80 *(2.57-3.05)*	12.9 *(9.83-17.5)*	0.42-96.0	0	0.05
	adj	3.32 *(3.08-3.58)*	3.20 *(2.98-3.39)*	10.2 *(8.33-17.4)*	0.33-51.2		
5cx-MEPP	raw	7.50 *(6.67-8.44)*	7.27 *(6.43-8.39)*	45.8 *(34.5-60.6)*	0.42-212	0	0.07
	adj	8.55 *(7.78-9.40)*	8.28 *(7.55-9.18)*	34.1 *(26.8-60.0)*	0.76-118		
OH-MiNP	raw	5.11 *(4.35-6.01)*	4.56 *(4.01-5.22)*	82.5 *(43.0-185)*	0.20-1792	0	0.05
	adj	5.83 *(5.04-6.73)*	4.49 *(4.01-5.57)*	80.5 *(41.5-149)*	0.73-1792		
oxo-MiNP	raw	1.99 *(1.69-2.33)*	1.77 *(1.51-2.17)*	34.6 *(14.5-74.3)*	0.11-959	0	0.05
	adj	2.27 *(1.96-2.61)*	1.87 *(1.55-2.20)*	31.7 *(18.1-46.0)*	0.22-959		
cx-MiNP	raw	7.69 *(6.55-9.03)*	6.81 *(5.91-7.87)*	88.9 *(69.7-246)*	0.25-1258	0	0.05
	adj	8.77 *(7.57-10.1)*	6.90 *(5.91-7.98)*	110 *(80.9-184)*	0.89-1258		
cx-MiDP	raw	0.58 *(0.52-0.64)*	0.51 *(0.47-0.59)*	3.43 *(2.60-5.45)*	0.08[a]-14.4	3 (1)	0.10
	adj	0.66 *(0.60-0.72)*	0.56 *(0.51-0.65)*	3.55 *(2.33-4.97)*	0.15[a]-15.3		
OH-MPHP	raw	1.30 *(1.13-1.51)*	1.18 *(1.06-1.36)*	16.4 *(8.27-27.2)*	0.06[a]-611	1 (<1)	0.08
	adj	1.49 *(1.32-1.68)*	1.31 *(1.12-1.50)*	12.9 *(7.17-20.6)*	0.13[a]-376		
oxo-MiNCH	raw	0.55 *(0.47-0.64)*	0.46 *(0.39-0.53)*	6.09 *(4.11-14.1)*	0.03[a]-179	10 (3)	0.08
	adj	0.63 *(0.55-0.73)*	0.52 *(0.45-0.55)*	6.19 *(4.00-13.1)*	0.03[a]-220		

95% CI, 95% confidence interval; LOD, limit of detection.
[a]Reported concentration below LOD.

Table 4. *Urine concentrations (ng/ml) of phenolic substances and other rapidly metabolised substances in first-time mothers between 2009 and 2018. Both reported and density-adjusted concentrations are presented (N=296).*

Biomarker		Geometric mean (95% CI)	Median (95% CI)	95% percentile (95% CI)	Min-Max	N(%) <LOD	LOD (ng/ml)
Bisphenols							
BPA	raw	0.82 *(0.73-0.92)*	0.76 *(0.64-0.84)*	5.78 *(3.80-8.06)*	0.07[a]-16.7	13 (4)	0.20
	adj	0.93 *(0.85-1.03)*	0.86 *(0.75-0.99)*	4.99 *(3.50-7.07)*	0.15[a]-18.9		
BPS	raw	0.08 *(0.07-0.09)*	0.07 *(0.06-0.08)*	0.41 *(0.29-0.69)*	0.01[a]-2.00	28 (9)	0.03
	adj	0.09 *(0.08-0.10)*	0.09 *(0.08-0.10)*	0.38 *(0.30-0.62)*	0.01[a]-2.46		
4,4-BPF	raw	0.31 *(0.26-0.36)*	0.26 *(0.21-0.30)*	3.68 *(2.00-5.86)*	0.01[a]-23.9	7 (2)	0.03
	adj	0.35 *(0.30-0.41)*	0.30 *(0.24-0.34)*	4.65 *(2.85-7.85)*	0.00[a]-19.1		
Polycyclic aromatic hydrocarbons (PAH)							
2-OH-PH[b]	raw	0.11 *(0.10-0.12)*	0.12 *(0.10-0.13)*	0.48 *(0.39-0.67)*	0.01[a]-1.34	123	0.10
	adj	0.13 *(0.12-0.14)*	0.12 *(0.11-0.13)*	0.42 *(0.32-0.56)*	0.02[a]-1.02	(42)	
1-HP	raw	0.06 *(0.06-0.07)*	0.06 *(0.06-0.07)*	0.22 *(0.19-0.25)*	0.00[a]-0.97	215	0.10
	adj	0.07 *(0.06-0.08)*	0.07 *(0.07-0.08)*	0.19 *(0.17-0.24)*	0.00[a]-1.11	(73)	
Pesticides							
TCP[c]	raw	1.12 *(1.01-1.24)*	1.09 *(0.93-1.26)*	5.27 *(4.27-8.15)*	0.14-14.1	0	0.07
	adj	1.27 *(1.17-1.39)*	1.13 *(1.01-1.26)*	5.25 *(4.24-6.23)*	0.23-25.1		
3-PBA	raw	0.24 *(0.22-0.27)*	0.24 *(0.21-0.26)*	1.35 *(0.98-1.81)*	0.01[a]-6.84	18 (6)	0.05
	adj	0.28 *(0.25-0.30)*	0.25 *(0.23-0.29)*	1.29 *(0.89-2.23)*	0.01[a]-4.08		
Organophosphate flame retardants							
DPP	raw	0.73 *(0.66-0.80)*	0.73 *(0.65-0.80)*	2.97 *(2.34-4.03)*	0.06[a]-30.9	1 (<1)	0.07
	adj	0.83 *(0.77-0.89)*	0.77 *(0.72-0.83)*	2.76 *(2.16-3.70)*	0.18[a]-32.9		
DBP	raw	0.37 *(0.34-0.41)*	0.34 *(0.32-0.38)*	1.25 *(1.01-2.09)*	0.04[a]-54.1	2 (<1)	0.05
	adj	0.42 *(0.38-0.46)*	0.38 *(0.36-0.41)*	1.46 *(1.01-2.28)*	0.02[a]-108		
BBOEP	raw	0.05 *(0.04-0.05)*	0.05 *(0.04-0.05)*	0.18 *(0.14-0.24)*	0.00[a]-0.83	153	0.05
	adj	0.06 *(0.05-0.06)*	0.06 *(0.05-0.06)*	0.20 *(0.18-0.23)*	0.01[a]-0.51	(52)	
Other phenolic substances							
TCS	raw	0.31 *(0.26-0.37)*	0.26 *(0.22-0.31)*	3.63 *(1.69-26.0)*	0.02[a]-607	51	0.10
	adj	0.35 *(0.30-0.42)*	0.30 *(0.28-0.35)*	3.01 *(1.56-24.8)*	0.02[a]-546	(17)	
BHA	raw	0.45 *(0.36-0.55)*	0.46 *(0.35-0.57)*	8.32 *(5.00-13.9)*	0.00[a]-144	11 (4)	0.02
	adj	0.51 *(0.42-0.62)*	0.46 *(0.37-0.62)*	7.70 *(5.87-13.9)*	0.00[a]-121		
BP-3	raw	2.28 *(1.89-2.74)*	1.77 *(1.51-2.09)*	47.3 *(25.8-120)*	0.09[a]-511	14 (5)	0.20
	adj	2.59 *(2.18-3.09)*	1.92 *(1.56-2.32)*	46.5 *(28.6-125)*	0.14[a]-673		

95% CI, 95% confidence interval; LOD, limit of detection.
[a]Reported concentration below LOD.
[b]Sum of 2-OH-PH and 3-OH-PH.
[c]N=295.

Temporal trends

Temporal trends for the analysed substances are presented in Table 5. The linear regressions indicate that most of the analysed substances are declining. Adjustment for possible cofounders and exclusion of outliers did not have any major impact on the results. The inverse temporal associations seen for the two PAH metabolites should be interpreted with caution since 42-73%

of the samples had concentrations below LOD. No temporal trends were observed for the organophosphate flame retardant metabolites. The inverse univariate association for one of them, DPP, was biased by four outliers and no trend was observed when these were excluded. The only substances with increasing temporal trends were oxo-MiNCH and 3-PBA.

Table 5. *Regression coefficients for the associations between density-adjusted urine concentrations (ln-tranformed) and sampling year[a] in first-time mothers between 2009 and 2018 (N=296).*

	Univariate analysis		Multivariate analysis[b]			
Substance	**β**	**p**	**n**	**β**	**p**	**N(%) < LOD[c]**
Phtalates and alternative plasticizer						
MEP	-0.13	0.000	294	-0.12	0.000	0
MBzP	-0.17	0.000	295	-0.17	0.000	0
MEHP	-0.088	0.000	294	-0.086	0.000	8 (3)
5OH-MEHP	-0.16	0.000	294	-0.15	0.000	0
5oxo-MEHP	-0.16	0.000	294	-0.15	0.000	0
2cx-MEHP	-0.12	0.000	292	-0.13	0.000	0
5cx-MEPP	-0.15	0.000	292	-0.16	0.000	0
OH-MiNP	-0.094	0.000	290	-0.11	0.000	0
oxo-MiNP	-0.087	0.001	291	-0.10	0.000	0
cx-MiNP	-0.11	0.000	291	-0.13	0.000	0
cx-MiDP	-0.095	0.000	290	-0.10	0.000	3 (1)
OH-MPHP	-0.10	0.000	291	-0.11	0.000	1 (<1)
oxo-MiNCH	0.13	0.000	292	0.11	0.000	10 (3)
Bisphenols						
BPA	-0.12	0.000	293	-0.12	0.000	13 (4)
BPS	0.028	0.11	293	0.024	0.14	28 (9)
4,4-BPF	-0.092	0.001	294	-0.091	0.001	7 (2)
PAH						
2-OH-PH	-0.057	0.000	292	-0.059	0.000	123 (42)
1-HP	-0.052	0.000	295	-0.049	0.001	215 (73)
Pesticides						
TCP[d]	-0.070	0.000	293	-0.069	0.000	0
3-PBA	0.048	0.005	292	0.051	0.002	18 (6)
Organophosphate flame retardants						
DPP	-0.032	0.018	292	-0.012	0.32	1 (<1)
DBP	-0.021	0.21	291	-0.019	0.14	2 (<1)
BBOEP	0.0016	0.92	296	-0.0038	0.81	153 (52)
Other phenolic substances						
TCS	-0.15	0.000	288	-0.12	0.000	51 (17)
BHA	-0.082	0.017	295	-0.090	0.008	11 (4)
BP-3	-0.0087	0.78	292	0.014	0.65	14 (5)

[a]Sampling date was used in the analysis and β converted to per year by multiplying with 365.
[b]Adjusted for maternal age, education, pre-pregnancy BMI, weight gain during pregnancy, weight loss after delivery, and sampling season. Outliers were excluded.
[c]For values below LOD, reported values were used.
[d]N = 295

Phthalates and alternative plasticizer

Most phthalate metabolites had detectable urine concentrations in all women and only three metabolites had concentrations below LOD; MEHP (N=8), cx-MiDP (N=3), and OH-MPHP (N=1), see Table 3. MEP had by far the highest mean concentrations, followed by 5OH-MEHP, cx-MiNP, and 5cx-MEPP (Table 3).

The urine concentrations of MEP and the sum of three DEHP metabolites were lower than for other European mothers; unadjusted geometric means were 21 (19-25) ng/ml vs 48 (46–51) ng/ml and 15 (13-16) ng/ml vs 29 (28–30), respectively. The MBzP concentration was similar; 4.8 (4.2-5.5) ng/ml vs 4.5 (4.3–4.7) ng/ml (Den Hond et al. 2015). Considering the decreasing temporal trend, comparisons of concentrations during the same reporting period (2011-2012) were conducted with similar results. The MEP concentration during 2016-2018 in the present population was also lower than what has been reported among Swedish adolescents in 2017 (unadjusted medians were 13 ng/ml vs 29 ng/ml) whereas all other metabolite concentrations were in the same range (Norén et al. 2019).

For women of reproductive age, a HBM-I value of 300 µg/l has been calculated for the sum of the DEHP metabolites 5oxo-MEHP and 5OH-MEHP (Schulz et al. 2012). The HBM-I value is a health related value derived by the German Human Biomonitoring Commission, below which there is no risk of adverse health effects and no need for action according to the current knowledge (Apel et al. 2017). In the current population, only one woman had concentration above this value (348 µg/l, the urine density-adjusted concentration was 203 µg/l]). This sample was assessed in year 2011 and since 2013, all women have had concentration of these DEHP metabolites below 100 µg/l and thus without concern with regard to the HBM-I value.

Importantly, negative temporal trends were seen for all the analyzed phthalate metabolites (Table 5 and Figure 1). Hence, the efforts to phase out phthalates in Europe seem to have reduced the human exposure in Sweden, as previously reported (Gyllenhammar et al. 2017). Decreasing concentrations have also been reported in Swedish adolescents (Jönsson et al. 2014), other European countries and US (Koch et al. 2017, Wang et al. 2019). Sources for phthalate exposure are PVC and food packaging. DEP is widely used in cosmetics (Wang et al. 2019). This may partly explain the observed differences in MEP concentrations between the present population of newly delivered mothers and Swedish adolescents.

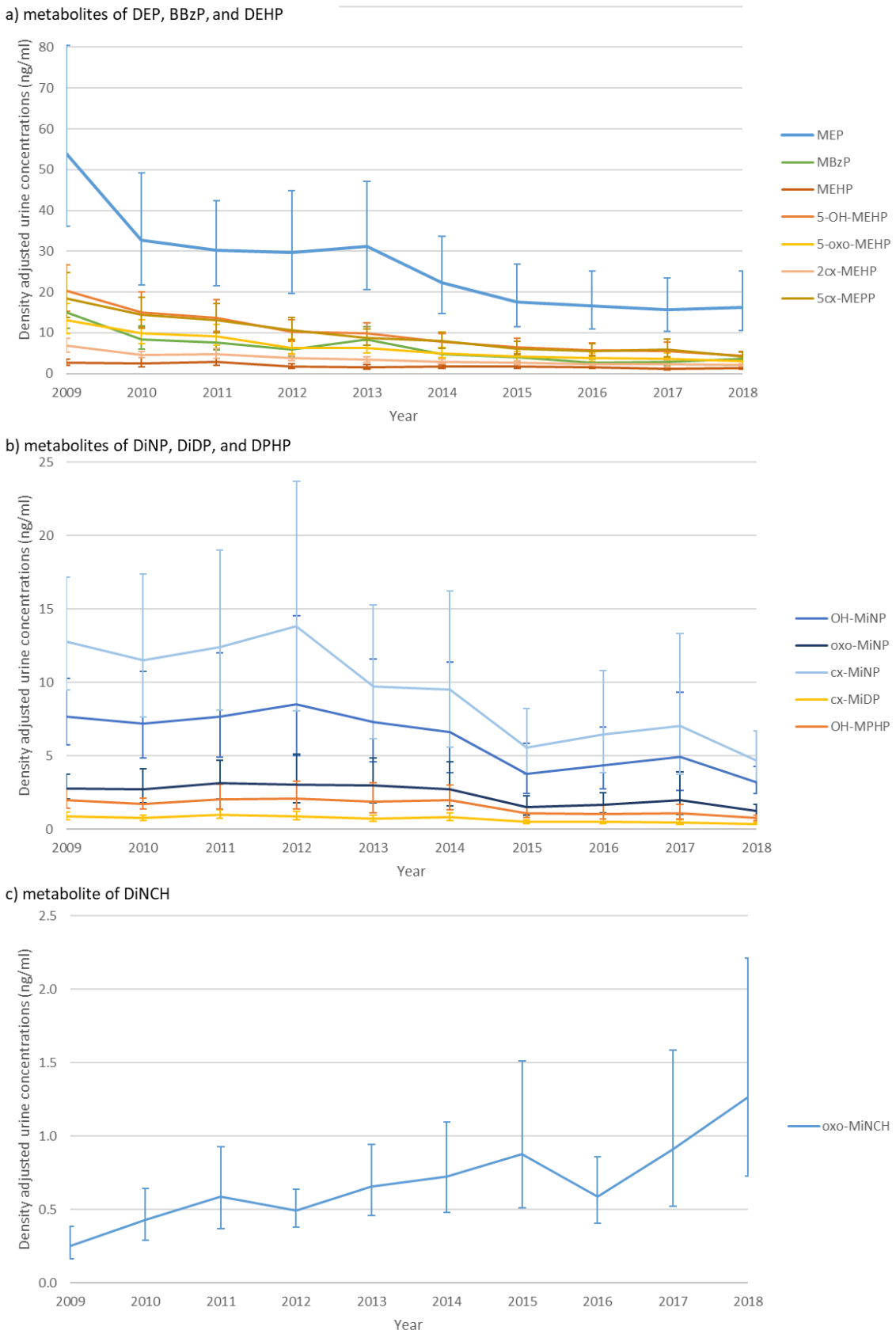

Figure 1. *Temporal trends in density-adjusted urine concentrations of phthalate metabolites and oxo-MiNCH between 2009 and 2018.*

Geometric means per sampling year. The error bars indicate the 95% confidence intervals. The lines connecting the geometric means are not referring to any statistics.

The alternative plasticizer, DiNCH, was introduced on the European market in 2002 to replace phthalates in products such as toys, food contact materials and medical devices. Since then, there has been a several fold increase in production volume (Schutze et al. 2014). As a consequence, the human exposure has increased, which could be detected in the present population (Figure 1) as well as in other populations (Schutze et al. 2014). The observed mean concentration of oxo-MiNCH was however still low compared to the phthalate metabolites (Table 3). The observed concentration was in line with Swedish adolescents (Norén et al. 2019).

Bisphenols

The majority of the women had detectable urine concentrations of all three bisphenols and only 2-9% had levels below LOD. The highest mean concentration was detected for BPA (Table 4), even though an inverse temporal trend and declining concentrations were observed (Table 5 and Figure 2). Other studies have also reported declining levels in Sweden (Jönsson et al. 2014) and U.S. (LaKind and Naiman 2015). However, one study has suggested increasing BPA intake worldwide from 2008 to 2011 among adults whereas there seemed to be a decreasing trend for children (Huang et al. 2018).

The highest BPA concentration in the present population was 19 ng/ml. Hence, there seems to be a marginal to the calculated HBM-I value of 200 ng/ml (Apel et al. 2017), even for those with the highest exposure in the present population. The observed BPA concentrations were comparable to Canadian (Haines et al. 2017) and U.S. (LaKind and Naiman 2015) data during their corresponding reporting periods, whereas they were lower than in an European study (Covaci et al. 2015) and in Swedish adolescents (Norén et al. 2019). The declining trend is in line with decreased exposure due to EU regulations of BPA use in baby bottles and lately also in thermal paper, such as receipts (EU commission 2016b).

The use of BPA has partly been substituted by other bisphenols like BPS and 4,4-BPF, even though possible potent reproductive toxic effects also have been suggested for these substances (Rochester and Bolden 2015, Siracusa et al. 2018). The urine levels of BPS were low (median: 0.09 ng/ml) and comparable to what has been reported in Swedish adolescents (Norén et al. 2019), whereas the 4,4-BPF concentration was higher among the adolescents compared to the present study (Norén et al. 2019). There was no temporal trend for BPS, which may be due to

that monitoring of BPS in thermal paper has been stressed in the phase-out process of BPA to avoid substitution (EU commission 2016b). Interestingly, an inverted u-shaped temporal trend was indicated for 4,4-BPF (Figure 2). By dividing the sampling period into 2009-2013 and 2013-2018, a positive association was observed for the first sampling period and a negative association for the latter (β=0.24, p=0.001 and β=-0.28, p<0.001, respectively). These trends suggest that 4,4-BPF initially was used as a replacement for BPA.

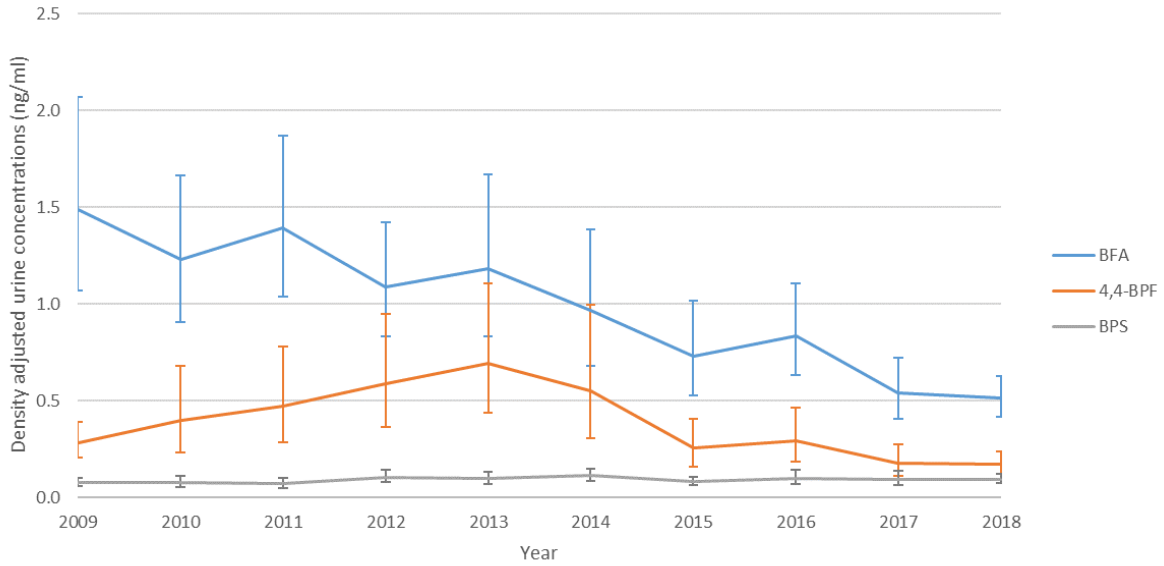

Figure 2. *Temporal trends in density-adjusted urine concentrations of bisphenols between 2009 and 2018.*
Geometric means per sampling year. The error bars indicate the 95% confidence intervals. The lines connecting the geometric means are not referring to any statistics.

Polycyclic aromatic hydrocarbons (PAH) metabolites

The concentrations of the PAH metabolites were low and many of the women had concentrations below LOD (42% for 2-OH-PH and 73% for 1-HP), see Table 4. Decreasing temporal trends were seen for both these metabolites in linear regression (Table 5), even though one should keep in mind that many of the concentrations were below LOD. Slightly lower geometric means (95% CI) were detected during the period 2016-2018 compared with the period 2009-2011 for both 2-OH-PH and 1-HP; 0.11 (0.10-0.12) ng/ml vs 0.15 (0.13-0.17) ng/ml), and 0.05 (0.05-0.06) ng/ml vs 0.08 (0.07-0.09) ng/ml, respectively. Similar concentrations have been observed in other Swedish populations (Jönsson et al. 2014, Norén et al. 2019).

Pesticide metabolites

Urine concentrations of the metabolites of the insecticides chlorpyrifos (TCP) and pyrethroids (3-PBA) were detectable in all and 94% of the women, respectively (Table 4). Divergent trends were seen for TCP and 3-PBA. Whereas TCP concentrations decreased between 2009 and 2018, there was a positive trend for 3-PBA, indicating an increased exposure to pyrethroids (Table 5, Figure 3). The concentration of TCP was lower than in Swedish adolescents (Norén et al. 2019) and Swedish middle-aged women (Littorin et al. 2013) whereas the 3-PBA concentrations were in the same range (Littorin et al. 2013, Norén et al. 2019).

Human exposure to these insecticides is probably mainly from residues in food. Use of chlorpyrifos is not allowed in Sweden, but the substance can be found in food from some parts of EU or outside of EU. The maximum residue levels were lowered in 2016, and levels of chlorpyrifos in food on the Swedish market has decreased during the last decade (Swedish Food Agency 2019). The decreasing trend seen in the present study could be an indication of a resulting lower exposure. It is also worth noting the narrowing of 95% confidence intervals for TCP in later years, indicating a reduction of the high exposure level.

3-PBA is the most frequently detected metabolite of the pyrethroids in urine, and similar concentrations as in the present study has been reported in other European countries (Saillenfait et al. 2015). The present study indicates a slight increase in pyrethroid exposure, which also has been suggested in U.S (Saillenfait et al. 2015, Jain 2016). A possible explanation may be substitution with pyrethorids as a consequence of reduced use of TCP and other similar substances.

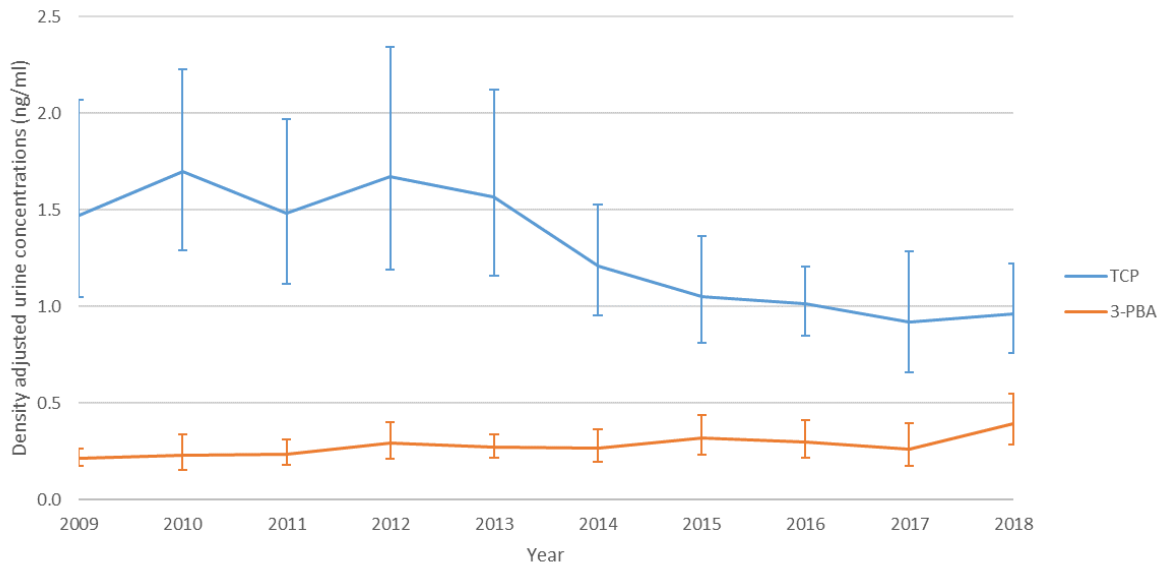

Figure 3. *Temporal trends in density-adjusted urine concentrations of pesticide metabolites between 2009 and 2018.*
Geometric means per sampling year. The error bars indicate the 95% confidence intervals. The lines connecting the geometric means are not referring to any statistics.

Metabolites of organophosphate flame retardants

Detectable levels of urinary DPP (triphenyl phosphate [TPP] metabolite) and DBP (tributyl phosphate [TBP] metabolite) were assessed in almost all women, whereas approximately half had concentrations of BBOEP (tris(2-butoxyethyl) phosphate [TBOEP] metabolite) below LOD (Table 4). The observed concentrations were in the same range as in Norwegian mothers (Cequier et al. 2015) and Swedish adolescents (Cequier et al. 2015, Norén et al. 2019). There were no temporal trends seen for DBP and BBOEP. Neither was there any trend for DPP after exclusion of four outliers (Table 5).

Other phenolic substances

TCS in an antibacterial compound that was detected in urine at concentrations above LOD in most of the women (83%), see Table 4. A decreasing time trend for TCS was seen in the present population (Table 5 and Figure 4), which also has been reported in U.S. (Han et al. 2016). This is in agreement with a decreased human exposure due to that the substance was banned in biocidal products in EU in 2016 (EU commission 2016a). A higher variability in the early sampling period, possibly due to use of e.g. TCS-containing toothpaste by some participants, may also had an impact on the results. Population mean (0.35 ng/ml) was far below the estimated HBM- I value (3000 ng/ml) (Apel et al. 2017). There was also a margin to HBM-I

for the highest observed concentration of 550 ng/ml. Median concentration of TCS was lower in the present study than in a previous of Swedish women (Jönsson et al. 2014) but comparable to another with Swedish adolescents (Norén et al. 2019). The observed concentrations were lower than those reported in U.S. (Ferguson et al. 2017) and Canada (Juric et al. 2019).

Almost all women also had concentrations of BHA and BP-3 above LOD (Table 4). The observed BP-3 levels were comparable to other European populations (Kim and Choi 2014). BP-3 is used for UV filters in sunscreens, and personal care products are believed to be the major exposure source (Han et al. 2016). Already in 2009, the EU commission decided that products with BP-3 needed to be labeled and that a maximum content of 10% was allowed (European parlament 2009), which may explain the observed similar exposure during 2009-2018 (Table 5). Increasing BP-3 levels have been reported in U.S. up to 2012 (Han et al. 2016).

BHA is used as an antioxidant in food, cosmetics and plastics (Wang and Kannan 2019). Low concentrations of BHA have been detected in the environment in Sweden (Rosqvist 2004) but biomonitoring data seem sparse. The median concentration was slightly higher in the present population compared to a diverse small sample of U.S. and Asian countries (Wang and Kannan 2019). The temporal changes of BHA did not seem to be linear. Instead, there was a tendency of increased exposure between 2009 and 2013 (β=0.27, p=0.005), followed by a reduction and no statistical trend between 2014 and 2018 (Figure 4). However, there seems to be a concomitant decrease in the variation of BHA levels.

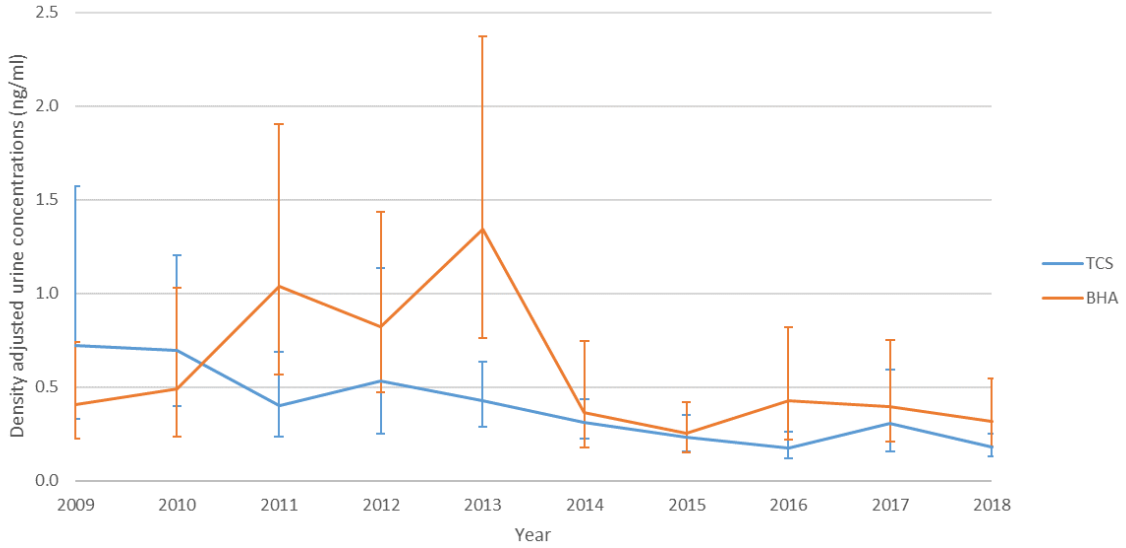

Figure 4. *Temporal trends in density-adjusted urine concentrations of TCS and BHA between 2009 and 2018.*
Geometric means per sampling year. The error bars indicate the 95% confidence intervals. The lines connecting the geometric means are not referring to any statistics.

CONCLUSION

Urine concentrations of phthalate metabolites have declined between 2009 and 2018 among first-time mothers in Uppsala. This is in line with reduced use of some phthalates such as DEP, BBzP, and DEHP. Concomitant with the reduced phthalate exposure, an increase in the metabolite of an alternative substance DiNCH was observed. Declining temporal trends of BPA, TCS and TCP were also seen during the reporting period, whereas there seemed to be an inverse u-shaped temporal trend of the BPA-substitute 4,4-BPF. Spot-urine samples, used in the present study, do not necessarily reflect the long-term exposure but can give an indication of temporal trends on group level.

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