Livsmedelsverket
Swedish Food Agency

NATUR VÅRDS VERKET
SWEDISH ENVIRONMENTAL PROTECTION AGENCY

NATIONAL ENVIRONMENTAL MONITORING COMMISSIONED BY THE SWEDISH EPA

Report to the Swedish EPA (the Health-Related Environmental Monitoring Program)

Concentrations of phthalate metabolites and phenolic substances in urine from first-time mothers in Uppsala, Sweden, sampled 2019-2021 and temporal trends for the period 2009-2021

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2023-03-31

NATIONELL
MILJÖÖVERVAKNING
PÅ UPPDRAG AV
NATURVÅRDSVERKET

ÄRENDENNUMMER NV-00791-21
AVTALSNUMMER 215-21-003
PROGRAMOMRÅDE Hälsorelaterad MÖ
DELPROGRAM Biologiska mätdata – organiska ämnen

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Rapporttitel
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Beställare
Naturvårdsverket
106 48 Stockholm

Finansiering
Nationell hälsorelaterad miljöövervakning

Nyckelord för plats
Uppsala, Sverige

Nyckelord för ämne
Ftalater, bisfenol, alkylfenoler, fosforbaserade flamskyddsmedel, pesticider, urin

Tidpunkt för insamling av underlagsdata
2019-2021

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 redovisas halter av ftalater och fenolära ämnen i urin från förstföderskor provtagna 2019-2021 samt tidstrender för perioden 2009-2021. 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 tio metaboliter till sex ftalater, två metaboliter till en ersättningskemikalie till ftalater, tre bisfenoler, metaboliter till fyra fosforbaserade flamskyddsmedel (PFR), två pesticidmetaboliter, fyra metaboliter till Polycykliska aromatiska kolväten (PAH) samt de fenolära ämnena triklosan och bensofenon-3 (BP-3) i urin. Analyserna utfördes av Lunds universitet.

Resultaten visade att en metabolit till ftalaten dietylftalat (DEP) förekom i högst halter i urin, följt av sex andra metaboliter till olika ftalater och BP-3. För samtliga ämnen låg halterna i urin från mammor provtagna 2019-2021 under de föreslagna vägledande nivåer (HBM-GV) som bedöms att inte innebär en risk för människor. Tidstrenderna för perioden 2009-2021 visade nedåtgående trender för de flesta av substanserna, t ex för ftalater, bisfenol A, en metabolit till insekticiden klorpyrifos och triklosan. För bisfenol S, som är en ersättare till bisfenol A, och för en metabolit till pyretroider (insekticider) sågs istället ökande trender.

Analyser av urin gör det möjligt att studera befolkningens exponering för snabbmetaboliserade substanser. 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).

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 (DEHP (di-ethylhexyl pthtalate), DBP (di-n-butyl phthalate), BBzP (butylbenzyl phthalate) and DIBP (diisobutyl phthalate)) 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 was further restricted within REACH, to less than 0.1% by weight, individually or in combination, in plasticized materials (EU commission 2018a). The use of some phthalates has therefore been 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) and the UV filter benzophenone-3 (BP-3). Some chemicals are metabolized to phenolic compounds in the body, e.g. some 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) (EU commission 2016b), and chlorpyrifos (EU commission 2018b).

This report describes levels of ten metabolites from sex different phthalates, two metabolites of DINCH, three bisphenols, four metabolites of organophosphate flame retardants (PFR), two pesticide metabolites, four metabolites of PAH and the phenolic substances TCS and BP-3 in urine from first-time mothers sampled between 2019 and 2021 (according to agreement 215-21-003). Temporal trends for the period 2009-2018 have been published earlier (Bjermo et al. 2019) and the new data were used to establish updated temporal trends for the period 2009-2021.

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. In total, 110 women were recruited between 2019 and 2021 and the participation rate was 44%. Spot urine samples of the participating women were collected three weeks after delivery and stored at the Swedish Food Agency at -20^{o}C. Data on age, weight, length, lifestyle, food habits etc. of the mothers were obtained from questionnaires. The temporal trend study includes urine samples from in total 406 women sampled 2009-2021.

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 (three 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 two 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 [3-PBA]). In addition, eight phenolic substances were analysed; three bisphenols (BPA, BPS, BPF), the antibacterial compound TCS, four PAH metabolites (2 and 3-OH-phenantrene [2,3-PHE], 1-hydroxyphenanthrene, [1-PHE], Σ2-,3-hydroxyfluorene [2,3-FLU], 1-hydroxypyren [1-PYR]), the UV filter Benzophenone-3 [BP-3].

The samples were analysed in February-April 2019 at Lund University by a modified method, as previously described (Gyllenhammar et al. 2017 Alhamdow et al. 2020). Briefly, urine was added to an ammonium acetate buffer (pH 6.5) and b-glucoronidase (E-coli), and incubated at

37°C in 30 minutes. Thereafter, a solution of labelled (^{3}H or ^{13}C) internal standards (IS) of all analysed compounds was added. Quantitative analysis was conducted using a triple quadrupole linear ion trap mass spectrometer equipped with TurboIonSpray sources (QTRAP® 5500+, AB Sciex, Framingham, MA, USA) coupled to a liquid chromatography system (UFLCXR, Shimadzu Corporation, Kyoto, Japan; LC-MS/MS).

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 is a reference laboratory for BPA and participates in the G-EQUAS inter-laboratory comparison program for several phthalate metabolites, TCP, and 3-PBA coordinated by the University of Erlangen-Nuremberg, Germany. The laboratory participated in the ICI/EQUAS exercises in the HBM4EU project for the analysis of BPA, BPS, BPF, 1-OH-Pyr, MBzP, three DEHP metabolites, three DINP metabolites and two DINCH metabolites.
Urine concentrations adjusted to urine density were calculated according to Carnerup et al (2006), using the average density of the current population, 1.015 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	11	645	13
Monobenzyl phthalate	MBzP	BBzP	0.05	9.4	9.6	47	5.7
Mono-(2-ethyl-5-oxohexyl) phthalate	5-oxo-MEHP	DEHP	0.08	10	7.5	50	6.8
Mono-(2-ethyl-5-hydroxylhexyl) phthalate	5-OH-MEHP	DEHP	0.04	11	5.4	51	5.9
Mono-(2-ethyl-5-carboxypentyl)phthalate	5-cx-MEPP	DEHP	0.03	11	9.2	48	8.1
Mono-(4-methyl-7-oxooctyl)phthalate	oxo-MiNP	DiNP	0.03	12	3.7	49	7.1
Mono-(4-methyl-7-hydroxyloctyl)phthalate	OH-MiNP	DiNP	0.03	17	5.7	58	5.5
Mono-(4-methyl-7-carboxyheptyl)phthalate	cx-MinP	DiNP	0.05	36	5.3	73	5.1
Monocarboxyisononyl phthalate	cx-MiDP	DiDP/DPHP	0.13	9.7	6.8	49	5.8
6-Hydroxy monopropylheptylphthalate	OH-MPHP	DiDP/DPHP	0.05	7.4	32	40	29
1,2-Cyclohexanedicarboxylic Acid Mono 4-Methyl-7-carboxy-heptyl Ester	cx-MINCH	DINCH	0.04	10	4.6	51	5.1
2-(((Hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic Acid	OH-MINCH	DINCH	0.03	8.5	26	45	18
Bisphenols							
Bisphenol A	BPA		0.20	4.9	6.6	24	5.4
Bisphenol S	BPS		0.03	4.9	4.7	25	4.3
4,4-Bisphenol F	BPF		0.03	4.5	7.0	23	6.5
Organophosphate flame retardants (PFR)							
Di-phenylphosphate	DPP	TPP	0.04	1.2	7.7	4.7	11
Dibutylphosphate	DBP	TBP	0.05	0.9	7.1	4.1	9.0
Bis(2-butoxyethyl)phosphate	BBOEP	TBOEP	0.05	0.9	6.6	4.8	6.1
Bis(1,3-dichloro-2-propyl)phosphate	BDCIPP	TDCIPP	0.40	1.3	13	5.4	5.8

Biomarker	Abbreviation	Parent compound	LOD (ng/ml)	Low QC		High QC	
				Mean (ng/ml)	CV (%)	Mean (ng/ml)	CV (%)
Pesticides							
Trichloropyridinol	TCP	Chlorpyrifos	0.07	5.1	5.6	25	5.1
3-Phenoxybencoic acid	3-PBA	Pyrethroids	0.07	4.9	4.5	25	5.2
Polycyclic aromatic hydrocarbons (PAH)							
Σ2-,3-hydroxyphenanthrene	Σ2,3-PHE	Phenantrene	0.05	0.8	17	4.1	5.1
1-Hydroxypyrene	1-PYR	Pyren	0.05	0.5	20	2.7	15
Σ2-,3-hydroxyfluorene	2,3-FLU	Fluorene	0.05	0.8	5.5	4.4	3.8
1-hydroxyphenanthrene,	1-PHE	Phenantrene	0.05	0.7	8.7	3.7	6.2
Other phenolic substances							
Triclosan	TCS		0.25	3.9	16	25	11
Benzophenone-3	BP-3		0.50	66	3.4	80	3.7

Calculations and statistics

Statistical analyses were performed using the software package STATA version 15.1. 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). For 1-PYR, three reported values were zero and therefore replaced with the lowest value reported for this substance (0.003 ng/ml) in the statistical analysis. Temporal trends were investigated for the study period 2009-2021. Linear regressions were used to analyse associations between ln-transformed density-adjusted urine concentrations and sampling year. Multiple linear regression analyses including the covariates age, pre-pregnancy body mass index (BMI), weight gain during pregnancy (%), weight loss from delivery to time of sampling (%), education, smoking and season of sampling were also conducted. Observations with standardized residuals ≥3 were regarded as outlier and omitted in these tests. As a consequence of the logarithmic transformation, the associations between sampling year and urine concentrations are presented as percent change of concentrations per year, and not as change in absolute levels.

Table 2. *Population characteristics of women sampled 2019-2021 (n=110).*

Variable		**Mean ± SD**	**(Min-Max)**
Age (year)		31 ± 4	(22-45)
Pre-pregnancy BMI (kg/m^2)[a]		24 ± 4	(18-44)
Weight gain during pregnancy (%)[a]		23 ± 9	(-1-57)
Weight reduction from delivery to sampling (%)[a]		9 ± 3	(2-15)
Urine density (kg/l)		1.014 ± 0.006	(1.002-1.028)
Variable		**n**	**(%)**
Education	Max 3-4 years of high school	13	(12%)
	1-3 years of higher education	34	(31%)
	>3 years of higher education	63	(57%)
Smoking[b]	Non-smoker	93	(85%)
	Former smoker	15	(14%)
	Smoker	2	(2%)
Season for sampling	Spring	33	(30%)
	Summer	7	(6%)
	Autumn	60	(55%)
	Winter	10	(9%)

[a]Body mass index, n=108
[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.

RESULTS AND DISCUSSION

Characteristics of the first-time mothers sampled 2019-2021 are shown in Table 2.

Urine concentrations of the analysed phthalate metabolites and the two DINCH metabolites are presented 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 were included. In total, 23 substances had urine concentration data for the whole period 2009-2021 and the temporal trends for these substances are presented in Table 5.

Table 3. *Urine concentrations (ng/ml) of phthalate metabolites and two DINCH metabolites in first-time mothers sampled 2019, 2020 and 2021. Both raw and density-adjusted concentrations are presented (n=110). When urine concentrations were below LOD, the reported urine concentrations (adjusted for levels in blank samples) were used.*

Biomarker		Mean (SD)	Median	Min-Max	n (%) <LOD	LOD (ng/ml)
MEP	raw	47.6 *(223)*	9.23	0.48-1950	0	0.20
	adj	46.8 *(212)*	13.2	0.42-2089		
MBzP	raw	3.34 *(3.58)*	2.02	0.08-20.6	0	0.05
	adj	3.82 *(4.18)*	2.11	0.16-25.8		
5-oxo-MEHP	raw	2.12 *(1.80)*	1.63	0.24-9.38	0	0.08
	adj	2.37 *(2.02)*	1.89	0.38-15.8		
5-OH-MEHP	raw	3.32 *(3.14)*	2.52	0.44-15.9	0	0.04
	adj	3.67 *(3.67)*	2.87	0.49-28.6		
5-cx-MEPP	raw	3.67 *(3.45)*	2.63	0.29-20.4	0	0.03
	adj	4.01 *(3.63)*	3.08	0.41-27.3		
oxo-MiNP	raw	2.26 *(7.30)*	0.85	0.10-65.7	0	0.03
	adj	3.19 *(13.5)*	0.98	0.20-123		
OH-MiNP	raw	6.84 *(28.8)*	2.06	0.23-283	0	0.03
	adj	10.0 *(52.9)*	2.31	0.66-531		
cx-MiNP	raw	6.59 *(20.4)*	2.15	0.14-147	0	0.05
	adj	9.26 *(37.9)*	2.44	0.48-290		
cx-MiDP	raw	0.44 *(0.26)*	0.35	0.10[a]-1.37	1 (0.9)	0.13
	adj	0.54 *(0.35)*	0.46	0.08[a]-2.58		
OH-MPHP	raw	0.76 *(5.35)*	0.16	0.002[a]-56.5	14 (13)	0.05
	adj	0.72 *(4.71)*	0.19	0.002[a]-49.9		
cx-MINCH	raw	1.57 *(1.60)*	1.14	0.14-9.81	0	0.04
	adj	1.71 *(1.39)*	1.24	0.15-6.56		
OH-MINCH	raw	2.18 *(2.70)*	1.24	0.12-20.1	0	0.03
	adj	2.32 *(2.26)*	1.56	0.13-11.4		

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, sampled 2019, 2020 and 2021. Both raw and density-adjusted concentrations are presented (n=110). When urine concentrations were below LOD, the reported urine concentrations (adjusted for levels in blank samples) were used.*

Biomarker		**Mean (SD)**	**Median**	**Min-Max**	**n (%) <LOD**	**LOD (ng/ml)**
Bisphenols						
BPA	raw	0.51 *(0.47)*	0.35	0.07[a]-3.22	18 (16)	0.20
	adj	0.58 *(0.42)*	0.46	0.05[a]-3.22		
BPS	raw	0.16 (*0.16)*	0.11	0.01[a]-1.04	8 (7)	0.03
	adj	0.18 (*0.13)*	0.14	0.02[a]-0.68		
BPF	raw	0.36 *(0.89)*	0.12	0.02[a]-5.47	5 (5)	0.03
	adj	0.40 *(0.90)*	0.17	0.01[a]-6.25		
Organophosphate flame retardants						
DPP	raw	0.85 *(0.96)*	0.55	0.10-6.57	0	0.04
	adj	0.88 *(0.76)*	0.67	0.30-6.16		
DBP	raw	0.20 *(0.23)*	0.13	0.03[a]-1.58	8 (7)	0.05
	adj	0.21 *(0.18)*	0.17	0.06[a]-1.48		
BBOEP	raw	0.02 *(0.03)*	0.02[a]	0.004[a]-0.30	107 (97)	0.05
	adj	0.03 *(0.04)*	0.02[a]	0.01[a]-0.37		
BDCIPP	raw	0.59 *(0.70)*	0.44	0.10[a]-6.57	51 (46)	0.40
	adj	0.65 *(0.53)*	0.55	0.08[a]-4.29		
Pesticides						
TCP	raw	0.65 *(0.63)*	0.46	0.13-4.65	0	0.07
	adj	0.74 *(0.65)*	0.58	0.15-5.36		
3-PBA	raw	0.51 *(0.94)*	0.25	0.07[a]-5.74	3 (3)	0.07
	adj	0.55 *(0.97)*	0.29	0.08[a]-6.62		
Polycyclic aromatic hydrocarbons (PAH)						
2,3-PHE	raw	0.11 *(0.10)*	0.07	0.01[a]-0.65	29 (26)	0.05
	adj	0.12 *(0.13)*	0.08	0.03[a]-0.85		
1-PYR	raw	0.05 *(0.04)*	0.03[a]	0.00[a]-0.23	71 (65)	0.05
	adj	0.05 *(0.05)*	0.04[a]	0.00[a]-0.34		
1-PHE	raw	0.12 *(0.12)*	0.09	0.02[a]-0.97	22 (20)	0.05
	adj	0.14 *(0.15)*	0.10	0.03[a]-1.10		
2,3-FLU	raw	0.10 *(0.09)*	0.07	0.01[a]-0.51	36 (33)	0.05
	adj	0.11 *(0.08)*	0.08	0.02[a]-0.48		
Other phenolic substances						
TCS	raw	0.36 *(0.74)*	0.27	0.01[a]-7.77	51 (46)	0.25
	adj	0.89 *(5.50)*	0.30	0.02[a]-58.3		
BP-3	raw	8.79 *(36.8)*	1.32	0.11[a]-349	26 (24)	0.50
	adj	9.27 *(40.4)*	1.80	0.15[a]-403		

LOD = limit of detection.
[a]Reported concentration below LOD.

Table 5. *Regression coefficients for the associations between density-adjusted urine concentrations (ln-tranformed) and sampling year in first-time mothers between 2009 and 2021 (n=406). When urine concentrations were below LOD, the reported urine concentrations (adjusted for levels in blank samples) were used.*

	Univariate analysis		**Multivariate analysis**[a]				
	Change per year (%)		**Change per year (%)**				
Substance	**Mean (SE)**	**p**	**n**	**Mean (SE)**	**p**	**R^2**	**n (%) < LOD**[b]
Phtalates							
MEP	-10 (1.4)	<0.001	399	-10 (1.3)	<0.001	0.17	0
MBzP	-12 (1.0)	<0.001	404	-12 (1.1)	<0.001	0.26	0
5-oxo-MEHP	-15 (0.8)	<0.001	404	-14 (0.8)	<0.001	0.45	0
5-OH-MEHP	-15 (0.8)	<0.001	404	-14 (0.8)	<0.001	0.46	0
5-cx-MEPP	-14 (0.8)	<0.001	404	-14 (0.9)	<0.001	0.42	0
oxo-MiNP	-9.2 (1.4)	<0.001	393	-9.6 (1.2)	<0.001	0.16	0
OH-MiNP	-9.7 (1.4)	<0.001	393	-10 (1.2)	<0.001	0.18	0
cx-MiNP	-13 (1.4)	<0.001	394	-13 (1.2)	<0.001	0.27	0
cx-MiDP	-6.7 (0.9)	<0.001	404	-6.7 (0.9)	<0.001	0.15	4 (1)
OH-MPHP	-20 (1.2)	<0.001	393	-19 (1.0)	<0.001	0.46	15 (4)
Bisphenols							
BPA	-9.9 (0.9)	<0.001	403	-9.6 (0.9)	<0.001	0.26	31 (8)
BPS	5.9 (1.1)	<0.001	402	6.0 (1.2)	<0.001	0.09	36 (9)
BPF	-8.7 (1.5)	<0.001	393	-8.8 (1.4)	<0.001	0.10	12 (3)
Organophosphate flame retardants							
DPP	-1.8 (0.8)	0.027	403	-1.1 (0.8)	0.20	0.05	1 (0.2)
DBP	-7.5 (1.0)	<0.001	400	-7.0 (0.9)	<0.001	0.17	10 (2)
BBOEP	-7.9 (1.0)	<0.001	403	-8.0 (1.0)	<0.001	0.19	260 (64)
Pesticides							
TCP[c]	-9.0 (0.9)	<0.001	403	-8.4 (0.9)	<0.001	0.22	0
3-PBA	5.0 (1.1)	<0.001	403	6.1 (1.2)	<0.001	0.10	21 (5)
PAH							
2,3-PHE	-4.6 (0.8)	<0.001	404	-4.5 (0.8)	<0.001	0.12	152 (37)
1-PYR	-6.1 (0.9)	<0.001	403	-6.1 (1.0)	<0.001	0.11	286 (70)
Other phenolic substances							
TCS	-7.4 (1.6)	<0.001	393	-4.8 (1.3)	<0.001	0.07	102 (25)
BP-3	-2.4 (2.0)	0.23	386	-1.2 (1.8)	0.52	0.03	40 (10)

[a]Adjusted for maternal age, education, pre-pregnancy BMI, weight gain during pregnancy, weight loss after delivery, education, smoking and sampling season. Outliers were excluded.
[b]For values below LOD, reported values were used.
[c]n = 405

Phthalates and alternative plasticizer metabolites

Most phthalate metabolites had detectable urine concentrations in all women and only two metabolites had concentrations below LOD, cx-MiDP (n=1), OH-MPHP (n=14) (Table 3). MEP had by far the highest mean concentrations, followed by OH-MiNP, cx-MiNP, 5-cx-MEPP and MBzP (Table 3). The urine concentrations of phthalate metabolites were lower for all substances in the present study compared to Swedish young adult women sampled in 2016-2019 (Zettergren et al. 2020) and Swedish adolecents sampled 2016-2017 in the national dietary survey Riksmaten Adolescents (RMA) (Livsmedelsverket Naturvårdsverket 2020). Considering the decreasing temporal trend, comparisons of concentrations have to be made during the same reporting period and as most European studies and studies from the rest of the world were performed before 2015 (Zhang et al 2021, Vogel et al. 2023a) comparisons were difficult. Levels in teenagers from the HBM4EU Aligned Studies (2014-2021) showed higher geometric means for all metabolites except MBzP compared to the present study (Govarts et al. 2023).

Human-Biomonitoring guidance values (HBM-GV), below which there is no risk of adverse health effects and no need for action according to the current knowledge, has been derived by the Human Biomonitoring Commission of the German Environment Agency for several chemicals (UBA 2020). For phthalates several HBM-GVs has been derived such as 500 ng/ml for the sum of 5-oxo-MEHP and 5-OH-MEHP, 3 000 ng/mL for MBzP and 220 ng/mL for OH-MPHP (Lange et al. 2021). All women in the present study had much lower levels than the HBM-GVs.

Decreasing temporal trends were seen for all the analyzed phthalate metabolites, ranging from 7 to 19% per year (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 children, adolescents and pregnant women (Jönsson et al. 2014, Larsson et al. 2017, Shu et al. 2018) and in other European countries and US (Koch et al. 2017, Wang et al. 2019, Voget et al. 2023b).

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 as an increasing trend of the metabolite oxo-MINCH in POPUP-mothers in 2008-2018 (Figure 1) (Bjermo et al. 2019) as well as in other populations (Schutze et al. 2014, Vogel et al. 2023b). Oxo-MINCH was not analysed in the samples from 2019-2021, but replaced by cx-MINCH and OH-MINCH. The concentrations of these metabolites were in line with Swedish adolescents (mean 3.1 and median 0.8 ng/ml for cx-MINCH and mean 3.5 and median 0.8 ng/ml for OH-MINCH) sampled 2016-2017 (Livsmedelsverket Naturvårdsverket 2020). However, the concentrations in POPUP were higher compared to the HBM4EU Aligned Studies of teenagers (2014-2021) with a geometric mean for the sum cx-MINCH and OH-MINCH 1.88 µg/g creatinine compared to 2.68 µg/g creatinine in the present study (Govarts et al. 2023). The HBM-GV for adults for the sum of OH-MINCH and cx-MINCH are 4 500 ng/ml (Lange et al. 2021) and the highest urine concentration in the present study was 15 ng/ml showing that levels are of no health concern

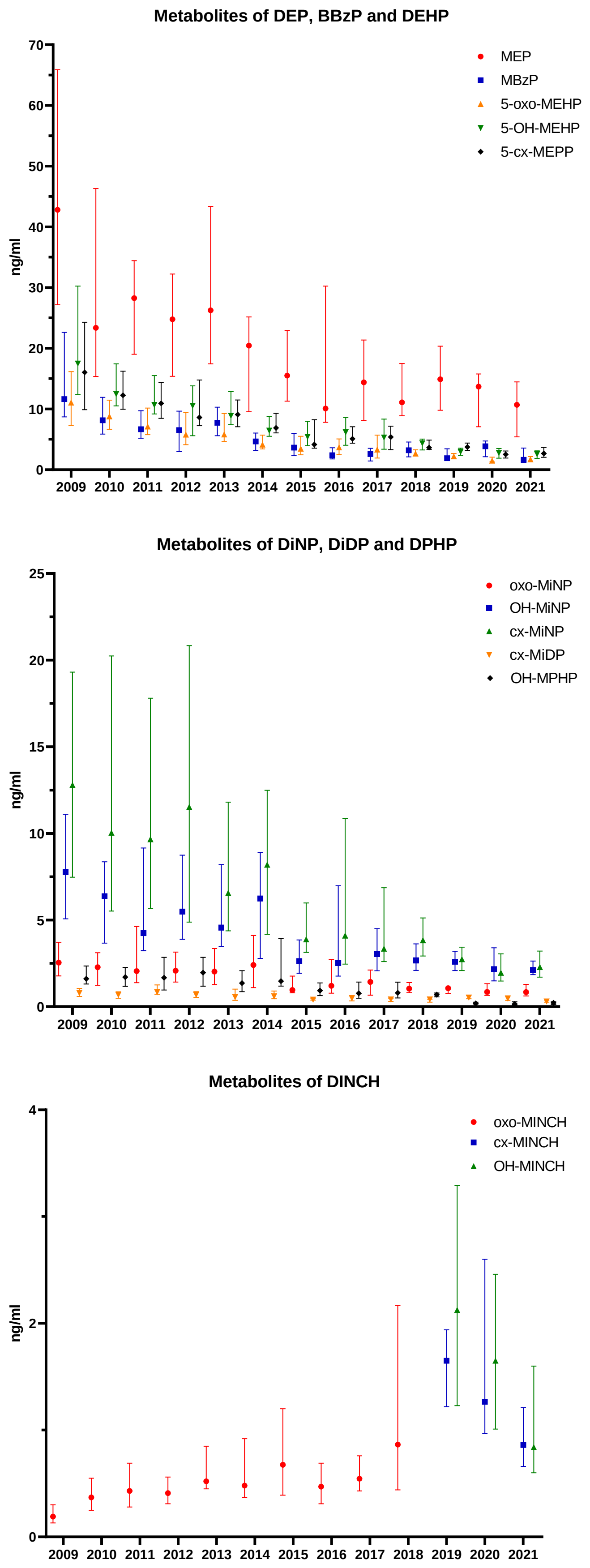

Figure 1. *Medians and 95% confidence intervals of density-adjusted urine concentrations of phthalate metabolites and metabolites of DINCH, between 2009 and 2021(n=406).*

Bisphenols

The majority of the women had detectable urine concentrations of all three bisphenols and about 5-16% had levels below LOD. The highest mean concentration was detected for BPA (Table 4). Concentrations of BPA were lower in the present study but BPS and BPF were in the same range as levels in Swedish young adult women sampled in 2016-2019 (Zettergren et al. 2020) and Swedish adolecents sampled 2016-2017 in the RMA (Livsmedelsverket Naturvårdsverket 2020). In the HBM4EU Aligned Studies (2014-2021) geometric means of 1.13 µg BPA/g creatinine, 0.072 for BPS total and 0.094 BPF total were reported for adults (Govarts et al. 2023), which could be compared to the corresponding geometric means in the present study of 0.45 µg BPA/g creatinine, 0.13 µg BPS/g creatinine and 0.17 µg BPF/g creatinine.

The highest BPA concentration measured in urine from participants in POPUP during 2019-2021 was 3 ng/ml and there seems to be a large marginal to the calculated HBM-GV of 230 ng/ml (Ougier et al 2021). The use of BPA has partly been substituted by other bisphenols like BPS and BPF, even though possible potent reproductive toxic effects also have been suggested for these substances (Rochester and Bolden 2015, Siracusa et al. 2018). A HBM-GV of 1 ng/ml was derived for BPS in urine (Meslin et al. 2022) and in the present report the mean concentration was 0.2 ng/ml and the highest adjusted urine concentration was 0.7 ng/ml (unadjusted 1.04 ng/ml).

The temporal trend for BPA showed decreasing urine concentrations at the same rate as previously reported, around 10% per year (Gyllenhammar et al. 2017) (Table 5, Figure 2). On the contrary to the last report, an increasing temporal trend for BPS was now observed with an increase of about 6% per year (Bjermo et al. 2019). An increasing temporal trend for BPF has also been reported from the POPUP-mothers sampled 2009-2014 (Gyllenhammar et al. 2017), however when more data were added to the trend, instead a significantly decrease was seen over the period 2009-2021 (Table 5, Figure 2). The present report also shows that the ratio between BPA, BPS and BPF has changed during the study period. During the time period 2009-2013, the ratios between the median concentrations were 15:4.4:1 (BPA:BPF:BPS), whereas the ratios in 2019-2021 were 3.3:1.2:1. Other studies have also reported declining urine levels of BPA in Sweden (Jönsson et al. 2014) and U.S. (LaKind and Naiman 2015). The declining trend is in line with decreased exposure due to EU regulations of BPA use in baby bottles since

2011 and also in thermal paper, such as receipts, since 2020 (EU commission 2016b). In Sweden, BPA is not allowed in food packaging intended for children up to three years of age (since 2012) and was also banned for use in the renovation (relining) of drinking water pipes in 2016.

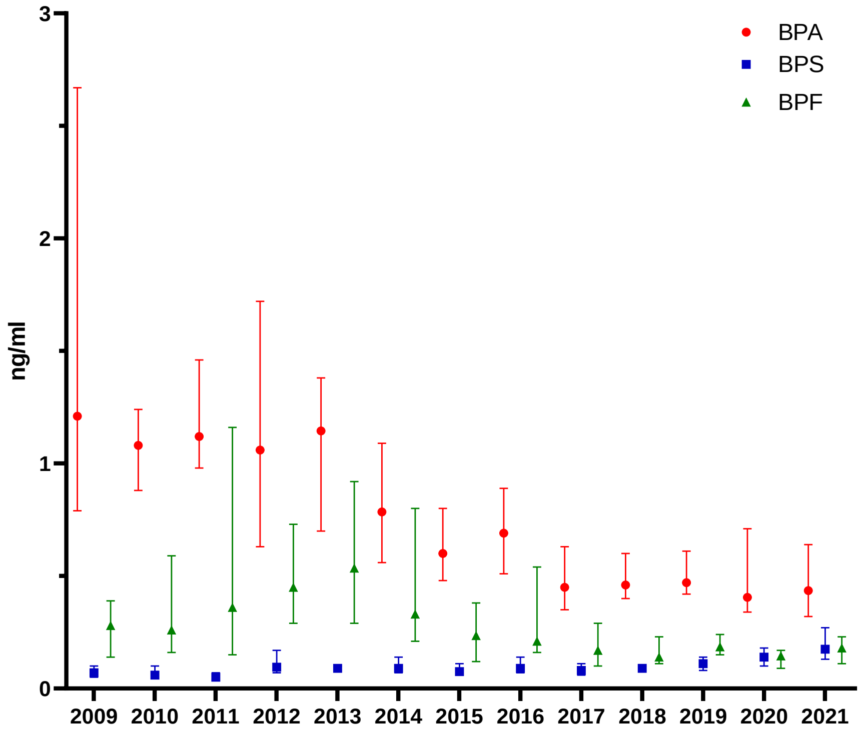

Figure 2. *Medians and 95% confidence intervals of density-adjusted urine concentrations of bisphenols, between 2009 and 2021 (n=406).*

Organophosphate flame retardants (PFR) metabolites

Detectable concentrations of urinary DPP and DBP were assessed in almost all women sampled 2019-2021, whereas approximately half had concentrations of BDCIPP and only 3% of BBOEP above LOD (Table 4). The observed concentrations were in the same range or slightly lower than in Swedish young women and Swedish adolescents (RMA) (Zettergren et al. 2020, Livsmedelsverket Naturvårdsverket 2020).

A decrease in concentrations was observed for DPP in the univariate analysis but in the adjusted model when four outliers were excluded the association was not significant (Table 5), as shown also in the previous report from the POPUP-mothers (Bjermo et al. 2019). Significantly decreasing temporal trends were observed for DBP and BBOEP, however the associations seen for BBOEP should be interpreted with caution since 64% of the samples had concentrations below LOD. The previous report showed no temporal trends from DBP and BBOEP, and the levels in urine were noticeably lower 2019-2021 (Figure 3) (Bjermo et al. 2019).

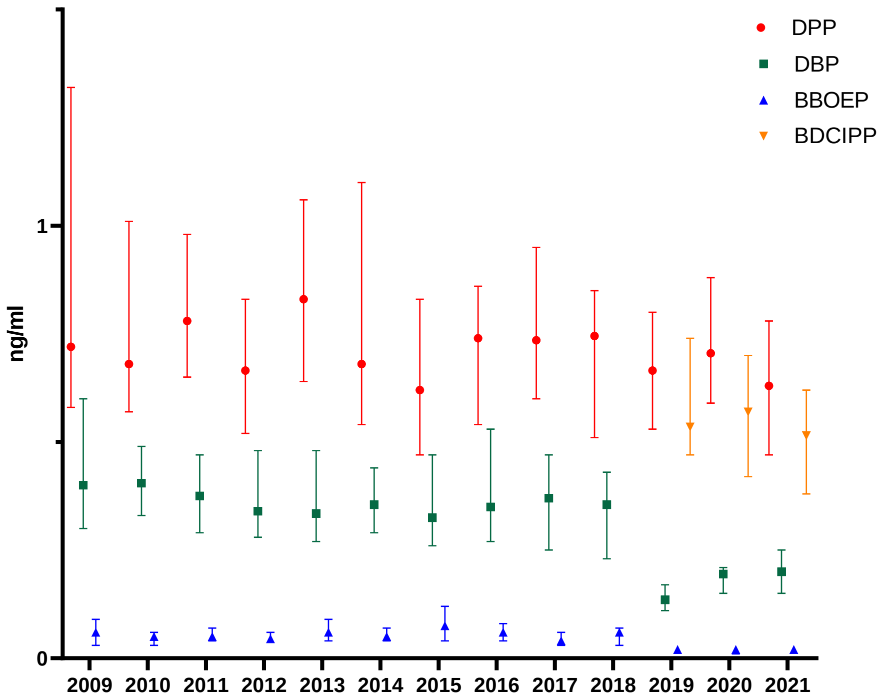

Figure 3. *Medians and 95% confidence intervals of density-adjusted urine concentrations of PFR, between 2009 and 2021 (n=406).*

Pesticide metabolites

Urine concentrations of the metabolites of the insecticides chlorpyrifos (TCP) and pyrethroids (3-PBA) were detectable in all and 97%, respectively, in the women sampled 2019-2021 (Table 4). 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 and in adults from the HBM4EU Alinged Studies (Saillenfait et al. 2015, Govarts et al. 2023). The urine concentrations of TCP were a little lower in the present study compared to Swedish young adult women sampled in 2016-2019 (median 0.98 ng/ml) and Swedish adolescents sampled 2017 (median 0.92 ng/ml) whereas the 3-PBA concentrations were in the same range (median 0.21 ng/ml in both studies) (Norén et al. 2020, Zettergren et al. 2020). Also Swedish adolescents sampled 2016-2017 in the RMA had higher median TCP concentration (1.2 ng/ml), but the median 3-PBA concentrations were lower (0.1 ng/ml) (Livsmedelsverket Naturvårdsverket 2020). A HBM-GV is set for TCP in urine at 2 100 ng/ml (Arnold et al. 2015) and the maximum level in the present study were about 300 times lower than that.

Divergent trends were seen for TCP and 3-PBA. Whereas TCP concentrations decreased between 2009 and 2021 with around 8% per year, there was a positive trend for 3-PBA, indicating an increased exposure to pyrethroids around 6% per year (Table 5, Figure 4). Temporal trends of TCP and 3-PBA in Swedish adolescents sampled 2000-2017 showed increasing urine levels around 1.7% and 3.7% per year respectively (Norén et al 2020), however after 2009 a suggested decrease of TCP was observed. Human exposure to these insecticides is probably mainly from residues in food. Use of chlorpyrifos as a plant protection product has never been allowed in Sweden and from year 2020 the use is not approved within EU and the maximum residue level (MRL) is 0.01 mg/kg for all food products. As a consequence of restricted uses and lowered MRLs, the levels of chlorpyrifos in food on the Swedish market should have decreased during the last decade (Widenfalk and Mie 2018). 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 pyrethroids as a consequence of reduced use of chlorpyriphos and other types of insecticides.

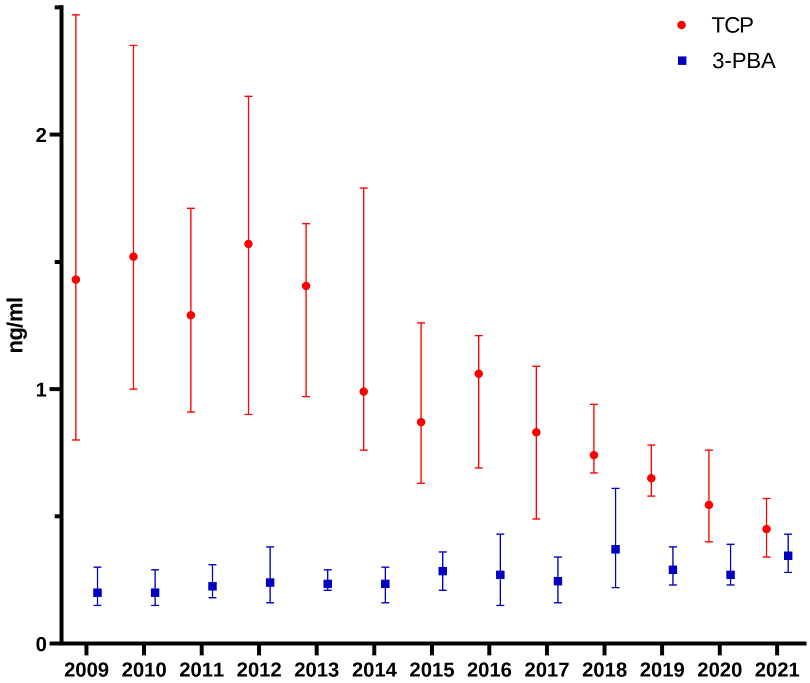

Figure 4. *Medians and 95% confidence intervals of density-adjusted urine concentrations of pesticide metabolites between 2009 and 2021(TCP n=405, 3-PBA n=406).*

Polycyclic aromatic hydrocarbons (PAH) metabolites

The concentrations of the PAH metabolites were low and 20-65% of the women sampled 2019-2021 had concentrations below LOD (Table 4). Levels in the present study were lower compared to Swedish young adult women sampled in 2016-2019 (Alhamdow et al. 2021) and compared to 2,3-PHE and 1-PYR in Swedish adolecents sampled 2016-2017 in the RMA (Livsmedelsverket Naturvårdsverket 2020) but in the same range as adults in the HBM4EU Aligned Studies (2014-2021) (Govarts et al. 2023). 2,3-PHE and 1-PYR showed decreasing temporal trends (Table 5) which also have been shown previous in the POPUP study (Bjermo et al. 2019). However, the results for 1-PYR should be interpreted with caution since 70% of the samples had concentrations below LOD.

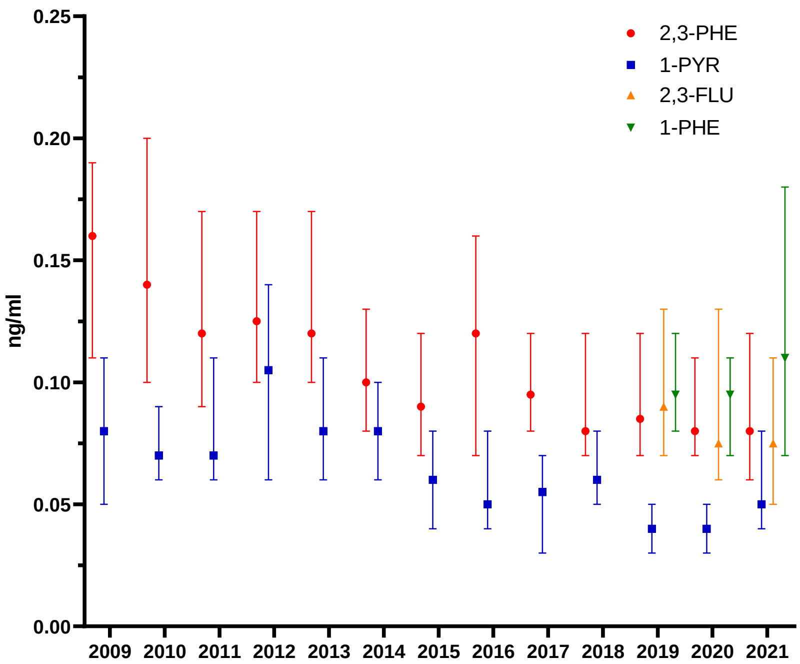

Figure 5. *Medians and 95% confidence intervals of density-adjusted urine concentrations of PAH metabolites between 2009 and 2021 (n=406).*

Other phenolic substances

TCS is an antibacterial compound that was detected in urine at concentrations above LOD in 54% of the women sampled 2019-2021 (Table 4). Concentration of TCS were in the same range as in Swedish young adult women sampled in 2016-2019 and in Swedish adolescents in the RMA-study (Zettergren et al. 2020, Livsmedelsverket Naturvårdsverket 2020). But the observed concentrations were lower than those reported in U.S. (Ferguson et al. 2017) and Canada (Juric et al. 2019) and it has been concluded that exposure to BP-3 is higher in North Americans than in European and Asian populations (Mustieles et al. 2023). The maximum concentration of TCS of 58 ng/ml was far below the estimated HBM-GV value of 3000 ng/ml (Apel et al. 2017). A decreasing temporal trend for TCS was seen in the present population (Table 5), which also has been reported in U.S. (Han et al. 2016). This is in agreement with a decreased human exposure since thethe ban of TCS in biocidal products within EU in 2016 (EU commission 2016a).

In total, 76% of the women had BP-3 concentrations above LOD (Table 5). The observed BP-3 levels were comparable to other European populations and were lower than the provisional HBM-GV of 340 µg/g creatinine (Kim and Choi 2014, Rousselle et al. 2022, Govarts et al. 2023). BP-3 is used as UV filter in sunscreens, in personal care products and in plastic surfaces as UV stabilizer for food packaging material and other consumer products. 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 non-trend and similar exposure during 2009-2021 (Table 5, Figure 6).

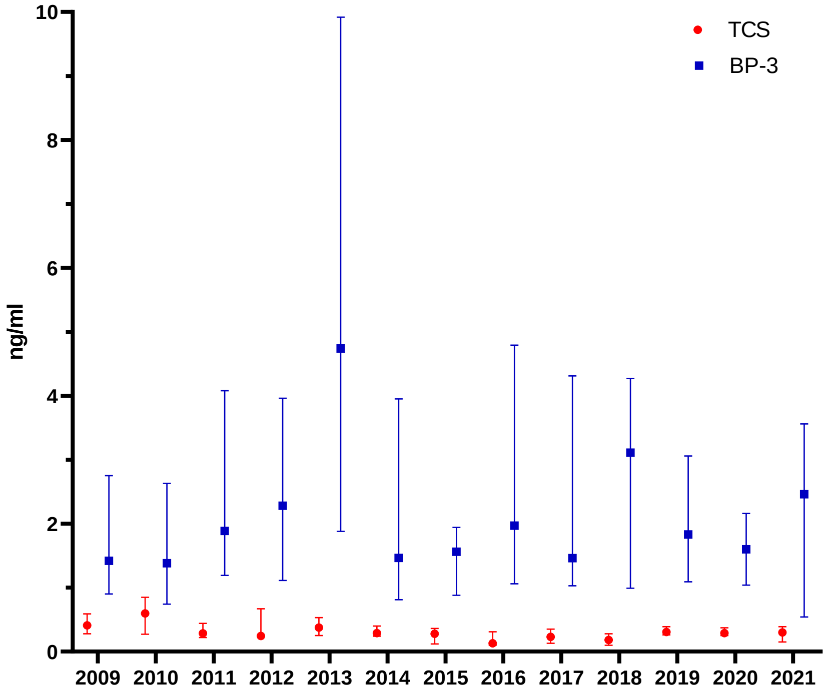

Figure 6. *Medians and 95% confidence intervals of density-adjusted urine concentrations of TCS and BP-3 between 2009 and 2021 (n=406).*

CONCLUSION

Urine concentrations of phthalate metabolites have declined between 2009 and 2021 among first-time mothers in Uppsala. This is in line with reduced use of some phthalates such as DEP, BBzP and DEHP. Declining temporal trends of BPA, TCP and TCS were also seen during the reporting period, whereas there seemed to be a slight increase of the BPA-substitute BPS and the insecticide metabolite 3-PBA in urine during the same time. Spot-urine samples, used in the present study, do not necessarily reflect the long-term exposure in individuals but give an indication of exposure and temporal trends on group level.

ACKNOWLEDGEMENT

We thank the Swedish Environmental Protection Agency for financial support. Appreciation is expressed to the participating women and to Marianne Leimar who assisted in recruitment, interviewing, and sample collection. The laboratory technicians at Livsmedelsverket are acknowledged for their assistance. We also acknowledge Anna Rönnholm for the excellent work with the chemical analysis.

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