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Exposure to Phthalates and Phenols during Pregnancy and Offspring Size at Birth

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Abbreviations:

BP: butyl paraben
BPA: bisphenol A
BP3: benzophenone 3
CI: confidence interval
DEHP: molecular sum of di(2-ethylhexyl) phthalate metabolites
EP: ethyl paraben
LOD: limit of detection
MBP: mono-n-butyl phthalate
MBzP: monobenzyl phthalate
MCNP: monocarboxy-isononyl phthalate
MCOP: monocarboxy-isooctyl phthalate
MCPP: mono(3-carboxypropyl) phthalate
MECPP: mono(2-ethyl-5-carboxypentyl) phthalate
MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate
MEHP: mono(2-ethylhexyl) phthalate
MEOHP: mono(2-ethyl-5-oxohexyl) phthalate
MEP: monoethyl phthalate
MiBP: mono-isobutyl phthalate
MP: methyl paraben
MW: molecular weight
PP: propyl paraben
TCS: Triclosan
2,4-DCP: 2,4-dichlorophenol
2,5-DCP: 2,5-dichlorophenol
∑HMW: molecular sum of high molecular weight phthalates
∑LMW: molecular sum of low molecular weight phthalates
∑PB: molecular sum of parabens

Abstract

Background: Data concerning the effects of prenatal exposures to phthalates and phenols on fetal growth are limited in humans. Previous findings suggest possible effects of some phenols on male birthweight.

Objectives: Our aim was to assess the relationships between prenatal exposures to phthalates and phenols and fetal growth among male newborns.

Methods: We conducted a case-control study on male malformations of the genitalia nested in two French mother-child cohorts with recruitment between 2002 and 2006. We measured, in maternal urinary samples collected between 6 and 30 gestational weeks, the concentrations (µg/l) of 9 phenol (n=191 pregnant women) and 11 phthalate metabolites (n=287). Weight, length and head circumference at birth were collected from maternity records. Statistical analyses were corrected for the over-sampling of malformation cases.

Results: Adjusted birthweight decreased by 77 g (95% confidence interval (CI), -129; -25) and by 49 g (95% CI, -86; -13) in association with a 1-unit increase ln-transformed 2,4-dichlorophenol (DCP) and 2,5-DCP urinary concentrations, respectively. Benzophenone-3 (BP3) ln-transformed concentrations were positively associated with weight (+ 26 g, 95% CI, -2; 54) and head circumference at birth (+ 0.1 cm, 95% CI, 0.0; 0.2). Head circumference increased by 0.3 cm (95% CI, 0.0; 0.7) in association with a 1-unit increase in ln-transformed BPA concentration. For phthalate metabolites there was no evidence of monotonic associations with birthweight.

Conclusions: Consistent with findings of a previous study, we observed evidence of an inverse association of 2,5-DCP and a positive association of BP3 with male birthweight.

Introduction

Diesters of phthalic acid (phthalates) and phenols are found in many consumer products. Low molecular weight (MW) phthalates (MW < 250 g/mol) are used in personal care products (perfumes, cosmetics) or as coating for pharmaceutical products; high MW phthalates (MW > 250 g/mol) tend to be used in polyvinylchloride floor and wall covering, food packaging and medical devices (Calafat et al. 2006; Hauser and Calafat 2005). Phenols are used in food packaging (bisphenol A, BPA), polycarbonates (BPA), cosmetics (parabens, PB), soap (triclosan, (TCS)) and sunscreen (benzophenone 3, BP3) (Calafat et al. 2008). Precursors of dichlorophenols (DCPs) are used as intermediates in the production of several herbicides or insecticides (Agency for Toxic Substances and Disease 2006).

Widespread exposure to phthalates and phenols has been documented for pregnant women in several industrialized countries (Adibi et al. 2008; Braun et al. 2011; Cantonwine et al. 2010; Wolff et al. 2008; Ye et al. 2009; Ye et al. 2008). Some of these compounds can cross the placenta in humans (Balakrishnan et al. 2010; Mose et al. 2007), and phthalates have been detected in cord blood (Latini et al. 2003), amniotic fluid (Huang et al. 2009; Silva et al. 2004) and meconium (Zhang et al. 2009).

Little is known about the consequences of prenatal exposures to phthalates and phenols on fetal growth; an American cohort study of 404 mother-infant pairs reported an inverse association for 2,5-DCP maternal urinary concentrations and a positive association for BP3 urinary concentrations with birthweight in male but not in female newborns (Wolff et al. 2008).

Our aim was to study the relationships between prenatal exposures to phthalates and phenols and weight, length and head circumference at birth among male newborns.

Population and Methods

Study population

We conducted a case-control study of male malformations of the genitalia nested in the Eden and Pélagie mother-child cohorts. These cohorts are described elsewhere (Drouillet et al. 2009; Garlantezec et al. 2009). Briefly, the Eden cohort consists of 2002 pregnant women recruited before the end of the 28th gestational week from April 2003 to March 2006 in the obstetrical departments of the University Hospitals of Nancy and Poitiers, France. The Pélagie cohort consists of 3421 pregnant women enrolled before 19 weeks of gestation from April 2002 to February 2006 in three districts of Brittany: Ille et Vilaine, Finistère and Côtes d'Armor, France. The present study includes all of the male newborns with undescended testis or hypospadias (identified at birth by pediatricians, n=48 in Eden and 24 in Pélagie). In addition, 3 male newborns without congenital malformation of the genitalia (controls) were matched to each case by recruitment center, date of recruitment (+/- 6 months), day of week (week-end yes/no) and gestational week when the maternal urine sample was collected, for a total of 288 mother–newborn pairs (72 cases and 216 controls). Participants provided informed consent for data and biological sample collection for themselves and their offspring. These cohorts received the approvals of the appropriate ethical committees. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was limited and determined not to constitute engagement in human subjects research.

Outcomes

We extracted from hospital maternity records weight, length and head circumference assessed at birth.

Exposure assessment

Urine was collected between 6 and 19 gestational weeks in the Pélagie cohort and between 24 and 30 gestational weeks in the Eden cohort. Assessment of biomarker and creatinine concentrations in maternal urine was done by the National Center for Environmental Health laboratory at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA (Silva et al. 2007; Ye et al. 2005). We measured the urinary concentrations of eleven phthalate metabolites in samples from all mothers (n = 287, 72 cases and 215 controls because the vial of 1 control broke during the transport to the CDC laboratory). Nine phenols were measured in urine samples collected from mothers in the Eden cohort only (n = 191, 48 cases and 143 controls) (Phenols could not be measured in the Pélagie cohort because a preservative added to the samples interferes with the assay used).

Molar concentrations of 4 metabolites of di(2-ethylhexyl) phthalate (DEHP) (mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)) were summed as total DEHP; concentrations of phthalate metabolites of MW > 250 g/mol and of MW < 250 g/mol were summed as total of high MW phthalates (∑HMW) and of low MW phthalates (∑LMW), respectively. Total paraben concentration (∑PB) was calculated by summing methyl paraben (MP), ethyl paraben (EP), propyl paraben (PB), and butyl paraben (BP) molar concentrations.

Statistical analyses

We replaced concentrations below the limit of detection (LOD) by LOD/√2. We corrected the over-representation of congenital abnormalities, induced by the case-control design, using a reweighting approach; we used center-specific weights corresponding to the inverse of the inclusion probability of controls, so as to give cases and controls the same relative weight as

in the original cohorts (Richardson et al. 2007). Sensitivity analyses restricted to controls were also conducted.

To limit the impact of between-subject variations in urine sampling conditions, we standardized biomarker concentrations using a 2-step standardization method based on regression residuals. First, we estimated associations between ln-transformed biomarker concentrations and sampling conditions [hour of sampling (for EDEN only), gestational age at collection, duration of storage at room temperature before freezing, season and day of sampling] using separate linear regression models for each biomarker adjusted for maternal age, body mass index before pregnancy, parity, year of sampling, education, current occupation, active smoking and center. Next, we used these data to estimate biomarker concentrations that would have been observed if all samples had been collected under the same conditions (e.g., 7:30 A.M for hour of sampling). Unless otherwise specified, all concentrations are the standardized values; we also report associations with biomarker concentrations not standardized for sampling conditions.

Associations between each standardized maternal urinary biomarker concentration and either birthweight, birthlength or head circumference were estimated using separate weighted linear regressions. Biomarker concentrations (μg/L) were ln-transformed or coded in tertiles. We performed tests of heterogeneity in outcome value across exposure tertiles; p-values of trend tests were estimated using categorical variables whose values corresponded to the tertile-specific median biomarker levels. Situations in which biomarkers exhibited heterogeneity in outcome across tertiles (low p-value, heterogeneity test) but with little support for a trend (high p-value, trend test) were considered as suggestive of a non-monotonic association (A monotonic trend does not reverse direction but may have flat segment (Rothman et al. 2008)). We also estimated adjusted relationships between standardized biomarker concentrations and birthweight using restricted cubic splines (Harrell 2001). Adjustment factors were all

variables possibly related to birth outcomes (based on *a priori* knowledge) including maternal pre-pregnancy weight (broken stick model with a knot at 60 kg) (Slama and Werwatz 2005), maternal height (continuous), maternal smoking (never, 1-5, 6 cigarettes per day and more), parity (0, 1, ≥ 2), education level (high school or less, up to 2 years after high school, 3 years and more after high school), gestational duration (linear and quadratic terms) and recruitment center. In addition, we adjusted for urinary creatinine concentration (continuous, non-transformed), as a marker of urine dilution. Gestational duration was estimated using the date of last menstrual period (LMP) (Slama et al. 2008) or gestational duration assessed by the obstetrician if it differed from the LMP-based estimate by more than two weeks. Adjustment for the obstetrician-estimated gestational age instead of the LMP-based gestational age did not modify results (not shown). Models for head circumference at birth were also adjusted for the mode of delivery (since passage through the birth canal may influence head circumference at birth).

We performed sensitivity analyses excluding women with pregnancy-induced hypertension (n=17) or gestational diabetes (n=15).

All analyses were performed using STATA/SE (College station, TX 77845), version 11.

To draw our conclusion we gave more weight to results in agreement with our a priori hypotheses, namely an effect of BP3 and 2,5-DCP on male birthweight (Wolff et al. 2008). Other associations (highlighted on the basis of their p-values, without relying on threshold p-value to define statistical significance) were considered as hypothesis-generating.

Results

Study population

The 287 women were on average 29 years old; 17 % of them smoked during the first trimester of pregnancy (Table 1). Average gestational age at delivery was 39.8 weeks, average birthweight was 3393 g (5^{th}-95^{th} centiles, 2640-4130) and 7 newborns (2 %) weighed less than 2500 g. Average birth length was 50 cm (5^{th}-95^{th} centiles, 47-54) and average head circumference at birth was 35 cm (5^{th}-95^{th} centiles, 32-37) (Table 1).

We detected 8 of the 11 phthalate metabolites and 5 of the 9 phenols in at least 95 % of the samples (Table 2).

Phenols and birth outcomes

Birthweight decreased by 49 g (95% Confidence Interval (CI), -86; -13) in association with a 1-unit increase in ln-transformed 2,5-DCP concentration; after categorizing exposures in tertiles, boys in the highest exposure tertile were 152 g lighter on average, compared with boys in the lowest tertile (95% CI, -299; -5) (Table 3). We observed a similar association between 2,4-DCP and birthweight (Table 3 and Supplemental Material, Figure 1), consistent with the high correlation between 2,4-DCP and 2,5-DCP (r=0.95). 2,5-DCP ln-transformed concentration was also inversely associated with head circumference at birth (-0.1 cm, 95% CI, -0.2; 0.0).

Each 1-unit increase in ln-transformed BP3 concentration was associated with an increase of 26 g in birthweight (95% CI, -2; 54) and of 0.1 cm in head circumference at birth (95% CI, 0.0; 0.2) (Table 3).

For BPA, estimates were suggestive of an inverse U-shape association: birthweight increased by 169 g (95% CI, 14, 324) in the second BPA concentration tertile and by 85 g (95% CI, -62,

233) in the third concentration tertile, compared to the first (Table 3 and Supplemental Material, Figure 2 for associations based on a restricted cubic spline model). BPA concentrations were positively associated with head circumference, which increased by 0.8 cm in the highest BPA concentration tertile, compared to the lowest tertile (95% CI 0.2; 1.3, Table 3).

For all other phenols, there was no evidence of associations with offspring measures at birth [all p for heterogeneity were above 0.24 (Table 3) and curves obtained using restricted cubic splines did not clearly support an association, see Supplemental Material, Figure 2].

Phthalates and birth outcomes

For phthalate metabolite concentrations and birthweight, all p for trend were above 0.14 (Table 4). There was some evidence of heterogeneity in mean birthweight across concentration tertiles for some phthalate metabolites: the lowest p-values for heterogeneity were observed for MCPP and MECPP for which, given the high values of p for trend, results were suggestive of non-monotonic associations (Table 4). For MECPP, but less so for MCPP, this non-monotonic association was also to some extent supported by the restricted cubic spline analysis (see Supplemental Material, Figure 3).

Regarding other birth outcomes, the lowest p-values for heterogeneity were observed with MCPP, MCOP, MCNP, MEHP and the sum of the high MW phthalates for birthlength and with the sum of the low MW phthalates for head circumference at birth (Table 4).

Sensitivity analyses

For phenols, associations with birth outcomes remained similar after exclusion of 48 cases of male malformations of the genitalia (See Supplemental Material, Table 1). Using biomarker concentrations not standardized for sampling conditions instead of concentrations

standardized for sampling conditions did not markedly change associations between either 2,4-DCP, 2,5-DCP, BP3 or BPA and birthweight. Similarly, associations between either BP3 or BPA and head circumference at birth remained similar (See Supplemental Material, Table 1).

In analyses restricted to controls only or using concentrations not standardized for sampling conditions, findings concerning phthalates were consistent with those obtained in the main analysis, except for MECPP: The birthweight change observed in the second MECPP concentration tertile was -141g (95%CI, -277; -5) in the whole study population, -79 g (95% CI, -220; 61) after exclusion of cases and -51g (95%CI, -187; 84) using non-standardized biomarker concentrations (See Supplemental Material, Table 2). These sensitivity analyses are difficult to interpret because the restriction to controls decreased population size, and because standardization sometimes induced strong variations in the distribution of biomarker concentrations and hence in the cut-off values of tertiles.

Excluding women with pregnancy-induced hypertension or gestational diabetes did not modify our main results (data not shown).

Discussion

Within our study population of male newborns, maternal urinary concentrations of 2,4-DCP and 2,5-DCP were associated with a birthweight decrease, while urinary concentrations of BP3 were positively associated with weight and head circumference at birth. BPA urinary concentrations were positively associated with head circumference; there was no evidence of monotonic associations between phthalate metabolite concentrations and birthweight.

Phenols and birth outcomes

In our study population, birthweight decreased by 152 g in the highest 2,5-DCP concentration tertile compared to the lowest tertile (95% CI, -299; -5); the only other human study addressing this issue reported a decrease by 210 g in the third 2,5-DCP concentration tertile compared to the first (95% CI, -348, -71) (Wolff et al. 2008). Concentrations of 2,5-DCP (and hence tertiles) were much higher in the study by Wolff et al. (median: 53 µg/L) than in ours (median standardized concentration: 6.4 µg/L). Wolff et al. also reported that boys were 0.3 cm shorter at birth per increase by one in ln(2,5-DCP) (95% CI, -0.6; -0.4); our results did not clearly support such an association (0.0 cm per increase by one in ln(2,5-DCP), 95% CI; -0.2; 0.2), but birthlength is not very accurately assessed, implying potentially strong measurement error. 2,5-DCP is a metabolite of 1,4-dichlorobenzene, which is used as chemical intermediate in the production of dyes and organic chemicals and which is found in mothballs and toilet-deodorizer blocks (Agency for Toxic Substances and Disease 2006; Yoshida et al. 2002). Dichlorophenols may also be released from water treatments (Abrahamsson and Xie 1983).

2,4-DCP was also associated with a birthweight decrease. It is a metabolite of 1,3-dicholorobenzene, a minor contaminant of 1,4-dichlorobenzene (Agency for Toxic Substances and Disease 2006; Yoshida et al. 2002), which may explain the high correlation reported between concentrations of both DCPs. 2,4-DCP is also an environmental transformation intermediate of the antiseptic agent triclosan and of some herbicides such as 2,4-dichlorophenoxyacetic acid and 2-(2,4-dichlorophenoxy) propionic acid (Yang et al. 2010; Zona et al. 2002). Our results concerning 2,4-DCP are difficult to compare with those of Wolff et al (2008), who studied male and female newborns altogether for this compound.

Taken together, these studies suggest an effect of dichlorophenols, or one of their precursors, on birthweight.

BP3 urinary concentrations were positively associated with weight and head circumference at birth. Boys were 105 g heavier (95% CI, -40; 250) in the highest BP3 concentration tertile compared with the lowest. Similarly, Wolff et al (2008) noted a birthweight increase in male infants in the highest BP3 concentration tertile compared to the lowest (betas not reported); they did not report effect estimates for BP3 and head circumference in males. Exposure to BP3 likely results from use of consumer products as sunscreens or cosmetics (Calafat et al. 2008).

BPA urinary concentrations were positively associated with head circumference at birth. After categorizing exposures in tertiles, we observed an inverse U-shape association between BPA concentrations and birthweight. Such non-monotonic dose-response curves between perinatal exposures to BPA and weight in early life have been reported in rodents (Rubin et al. 2001; Rubin and Soto 2009). However, urinary BPA concentrations were relatively low in our study population, enhancing the analytical uncertainties and hence the potential for exposure misclassification, which may limit our ability to distinguish monotonic from non-monotonic associations.

Phthalates and birth outcomes

There was no strong evidence of monotonic association between phthalate metabolite concentrations and birth outcomes, excepted for the possible positive association between MCNP and birthlength. Our analyses suggested non-monotonic associations with birthweight and birthlength for some phthalate metabolites. Such associations between phthalate metabolites and birthweigh have, to our knowledge, never been reported previously in rodents or in humans and therefore should be considered cautiously.

Study population

To correct the over-representation of cases induced by our case-control design, we weighted the observations in regression models (Richardson et al. 2007). We also performed non-weighted analyses, restricted to controls, and our main results regarding birthweight remained similar to those based on the whole weighted study population.

Exposure assessment

Sampling conditions, such as hour of urine sampling or storage duration before freezing, may influence the concentrations of several biomarkers (Mahalingaiah et al. 2008; Samandar et al. 2009). We used a 2-step standardization method based on regression residuals to reduce undesirable variability in biomarker urinary concentrations due to sampling conditions. To our knowledge it is the first time that such an approach has been applied to study associations between phthalate or phenol prenatal exposures and birth outcomes. We repeated our analyses using concentrations not standardized for sampling conditions and associations between DCPs or BP3 and birthweight or between BP3 and BPA and head circumference were similar.

Limitations

The assayed phenols and phthalates and their metabolites have relatively short half-lives in humans (typically, 1 day or less), but accurate information on half-lives in pregnant women, in whom metabolism may differ compared to non-pregnant women, is not available. We assessed exposures from the urinary concentrations at a single point during pregnancy; increasing the number of urine samples collected would have provided a more accurate estimate of the average exposure during the whole gestation. Adibi et al. reported that for phthalates, the probability of correctly classifying a woman into a low exposure group based on a single urine sample, if she truly had low exposure based on multiple measurements, was between 0.43 for monoethyl phthalate (MEP) and 0.95 for mono-isobutyl phthalate (MiBP)

(Adibi et al. 2008). Concerning phenols, bisphenol A concentrations also vary during pregnancy (Braun et al. 2011). Therefore, there clearly is exposure misclassification, whose amplitude differs according to the biologically relevant exposure window (if any) and to the compound considered.

We adjusted for many potential confounders, but residual confounding cannot be discarded. For example, specific metabolic disorders associated with both fetal growth and xenobiotic metabolism would constitute potential confounders; in our study, excluding women with pregnancy-induced hypertension or gestational diabetes did not alter associations with BPA and BP3 (not shown). Multiple comparisons are generally an issue in studies relying on several biomarkers; although we did not formally correct for multiple comparisons, our choice to focus our conclusions on previously reported associations limits the risk of chance being a likely explanation for our main findings.

Conclusions

In our study, there was no strong evidence of monotonic association between phthalate metabolite concentrations and birth outcomes. Urinary concentrations of 2,4-DCP and 2,5-DCP were negatively associated with birthweight while BP3 concentrations were associated with a birthweight increase. Results concerning 2,5-DCP and BP3 are in agreement with another publication concerning male newborns from New-York (Wolff et al. 2008).

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Table 1: Characteristics of French pregnant women and of their offspring after correction for the case-control sampling (Eden and Pélagie cohorts, 2002-2006).

Characteristic	Overall (n=287)				
	N or mean [a]	(%)	Percentiles		
			5th	50th	95th
Maternal age (years) (mean)	29.3		22	29	38
Duration of gestation[b] (mean)	39.8		37	40	42
Birthweight (g) (mean)	3393		2640	3390	4130
Birthlength (cm) (mean)	50		47	50	54
Head circumference at birth (cm) (mean)	34.7		32	35	37
Gestational age at sampling[b] (weeks) (mean)	22		9	26	28
Creatinine concentration (g/L) (mean)	1.2		0.4	1.1	2.2
Parity					
0	115	(40)			
1 previous child	114	(40)			
≥ 2 previous children	58	(20)			
Maternal Education					
≤ high school	133	(47)			
high school + 2 years	62	(22)			
≥ high school + 3 years	86	(31)			
missing value	6				
Active smoking					
0	238	(83)			
1-5 cigarettes/day	30	(11)			
≥ 6 cigarettes/day	17	(6)			
missing value	2				
Pre-pregnancy BMI (kg/m^2)					
< 18.5	29	(10)			
18.5 to 25.0	181	(64)			
> 25.0	73	(26)			
missing value	4				
Hour of urinary sampling					
before 8 AM	108	(65)			
8 to 10 AM	40	(24)			
after 10 AM	18	(11)			
missing value	121				

[a] Sample size, unless otherwise specified
[b] Weeks of amenorrhea assessed by the date of the last menstrual period
BMI: Body Mass Index

Table 2: Urinary phenol (n=191) and phthalate (n=287) biomarker concentrations after correction for case-control sampling (Eden and Pélagie cohorts, 2002-2006).

Analyte	LOD (µg/L)	%>LOD	Standardized concentrations[a] Percentiles (µg/L)			Measured concentrations Percentiles (µg/L)		
			5th	50th	95th	5th	50th	95th
Phenols								
2,4-DCP	0.2	95.9	0.2	0.8	8.6	0.2	0.9	10.2
2,5-DCP	0.2	99.5	1.4	6.4	316.0	1.8	10.2	442.0
BPA	0.4	98.5	0.8	3.1	10.1	0.6	2.7	9.8
BP3	0.4	80.5	0.2	1.3	74.5	0.3	1.7	143.0
TCS	2.3	84.1	1.0	17.5	464.6	1.6	24.1	634.0
MP	1.0	100.0	9.0	104.3	2689.7	9.1	97.8	3520
EP	1.0	67.7	0.2	1.5	38.2	0.7	4.1	62.3
PP	0.2	96.9	0.3	10.4	267.7	0.5	12.5	402.0
BP	0.2	79.5	0.1	2.2	63.6	0.1	1.7	53.8
Phthalates								
MEP	0.8	100.0	42.6	159.6	1101.5	37.8	167.0	1490.0
MBP	0.6	100.0	10.2	58.1	487.5	7.6	48.1	398.0
MiBP	0.3	100.0	15.6	64.7	365.3	10.9	45.9	219.0
MBzP	0.3	100.0	3.8	30.2	290.6	2.8	24.6	162.0
MCPP	0.2	98.3	0.6	3.2	13.8	0.4	2.2	10.0
MEHP	1.2	91.8	1.8	10.5	62.3	0.8	7.1	40.7
MEHHP	0.7	100	8.0	48.3	246.2	4.6	32.3	147.0
MEOHP	0.7	99.7	6.3	36.0	169.6	3.6	25.0	112.0
MECPP	0.6	100.0	18.9	67.2	303.0	11.6	43.8	183.0
MCOP	0.7	92.1	0.9	3.9	25.8	0.5	2.7	17.2
MCNP	0.6	91.8	0.9	3.1	22.8	0.6	1.7	11.7

Abbreviations: BP: butyl paraben, BPA: bisphenol A, BP3: benzophenone 3, EP: ethyl paraben, LOD: limit of detection, MBP: mono-n-butyl phthalate, MBzP: monobenzyl phthalate, MCNP: monocarboxy-isononyl phthalate, MCOP: monocarboxy-isooctyl phthalate, MCPP: mono(3-carboxypropyl) phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MEHP: mono(2-ethylhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEP: monoethyl phthalate, MiBP: mono-isobutyl phthalate, MP: methyl paraben, PP: propyl paraben, TCS: Triclosan, 2,4-DCP: 2,4-dichlorophenol, 2,5-DCP: 2,5-dichlorophenol

[a] Concentrations were standardized for conditions of sampling such as hour of sampling (Eden only), time elapsed between sample collections and freezing, season and day of sampling and gestational age at collection.

Table 3: Adjusted associations between maternal urinary concentrations of phenol biomarkers standardized for sampling conditions[a] and birth outcomes (Eden cohort, 2003-2006).

Analytes (µg/L)[a]	Change[b] in birthweight n=191				Change[b] in birthlength n=190				Change[b] in head circumference n=189			
	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (cm)	95% CI	p_{het}[c]	p_{trend}[d]	ß (cm)	95% CI	p_{het}[c]	p_{trend}[d]
2,4-DCP												
< 0.6	0	0	<0.01	<0.01	0	0	0.09	0.77	0	0	<0.01	0.01
0.6 - 1.3	24	[-129; 177]			0.7	[0.1; 1.3]			0.8	[0.2; 1.4]		
≥ 1.3	-181	[-323; -40]			0.2	[-0.5; 0.9]			-0.3	[-0.8; 0.3]		
Ln(2,4-DCP)	-77	[-129; -25]			-0.1	[-0.4; 0.2]			-0.1	[-0.3; 0.1]		
2,5- DCP												
< 3.9	0	0	0.10	0.03	0	0	0.53	0.70	0	0	0.14	0.10
3.9 – 13.9	-49	[-206; 108]			0.4	[-0.3; 1.0]			-0.3	[-0.8; 0.3]		
≥ 13.9	-152	[-299; -5]			0.3	[-0.4; 1.0]			-0.5	[-1.1; 0.0]		
Ln (2,5-DCP)	-49	[-86; -13]			0.0	[-0.2; 0.2]			-0.1	[-0.2; 0.0]		
BPA												
< 2.2	0	0	0.10	0.70	0	0	0.98	0.83	0	0	0.04	0.01
2.2 - 4.7	169	[14; 324]			0.0	[-0.7; 0.8]			0.3	[-0.3;0.9]		
≥ 4.7	85	[-62; 233]			0.1	[-0.7; 0.9]			0.8	[0.2; 1.3]		
Ln(BPA)	-9	[-98; 80]			0.0	[-0.4; 0.4]			0.3	[0.0; 0.7]		
BP3												
< 0.7	0	0	0.20	0.09	0	0	0.17	0.14	0	0	0.12	0.04
0.7 - 2.7	-15	[-155; 124]			-0.3	[-0.1; 0.3]			0.2	[-0.5; 0.8]		
≥ 2.7	105	[-40; 250]			0.4	[-0.3; 1.0]			0.5	[-0.0; 1.0]		
Ln(BP3)	26	[-2; 54]			0.1	[-0.1; 0.2]			0.1	[0.0; 0.2]		
TCS												
< 4.5	0	0	0.68	0.79	0	0	0.68	0.59	0	0	0.31	0.18
4.5 - 51.3	-58	[-194; 78]			-0.2	[-0.9; 0.4]			0.2	[-0.3; 0.7]		
≥ 51.3	-40	[-171; 90]			0.1	[-0.6; 0.7]			-0.2	[-0.7; 0.3]		
Ln(TCS)	-6	[-31; 19]			0.0	[-0.1; 0.1]			-0.1	[-0.2; 0.0]		
MPB												
< 62.8	0	0	0.75	0.58	0	0	0.47	0.23	0	0	0.79	0.58
62.8 – 213.0	-32	[-168; 105]			0.2	[-0.5; 0.8]			0.2	[-0.4; 0.7]		
≥ 213.0	24	[-121; 168]			0.4	[-0.3; 1.2]			0.2	[-0.4; 0.8]		
Ln(MPB)	-2	[-37; 34]			0.1	[-0.1; 0.3]			0.0	[-0.1, 0.2]		

Table 3 (continued)

Analytes (µg/L)[a]	Change[b] in birthweight n=191				Change[b] in birthlength n=190				Change[b] in head circumference n=189			
	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]
EPB												
< 0.6	0	0	0.98	0.86	0	0	0.24	0.97	0	0	0.47	0.94
0.6 - 3.7	10	[-129; 148]			0.6	[-0.1; 1.3]			0.4	[-0.2; 1.0]		
≥ 3.7	17	[-145; 178]			0.3	[-0.4; 0.9]			0.2	[-0.4; 0.8]		
Ln(EPB)	-1	[-43; 41]			0.1	[-0.1; 0.3]			0.1	[-0.1; 0.3]		
PPB												
< 4.7	0	0	1.00	0.95	0	0	0.98	0.93	0	0	0.52	0.62
4.7 – 24.8	-2	[-137; 132]			-0.1	[-0.7; 0.6]			-0.3	[-0.8; 0.2]		
≥ 24.8	-5	[-151; 140]			0.2	[-0.8; 0.7]			-0.2	[-0.8; 0.3]		
Ln(PPB)	-10	[-40; 19]			0.0	[-0.2; 0.2]			-0.1	[-0.2; 0.1]		
BPB												
< 0.6	0	0	0.97	0.95	0	0	0.58	0.49	0	0	0.61	0.45
0.6 – 6.8	-15	[-156; 126]			0.2	[-0.5; 1.0]			0.2	[-0.3; 0.7]		
≥ 6.8	-2	[-155; 150]			0.1	[-0.9; 0.7]			0.3	[-0.3; 0.8]		
Ln(BPB)	-1	[-32; 29]			0.0	[-0.2, 0.2]			0.1	[-0.1; 0.2]		
∑**PB** (µmol/L)												
< 0.5	0	0	0.95	0.86	0	0	0.61	0.38	0	0	0.80	0.66
0.5 – 1.6	-16	[-150; 118]			0.2	[-0.4; 0.9]			0.2	[-0.4; 0.7]		
≥ 1.6	6	[-143; 156]			0.4	[-0.4; 0.1]			0.2	[-0.4; 0.7]		
Ln(∑PB)	-3	[-39; 33]			0.1	[-0.1; 0.3]			0.0	[-0.2; 0.1]		

Abbreviations: BP: butyl paraben BPA: bisphenol A, BP3: benzophenone 3, MP: methyl paraben, EP: ethyl paraben, PP: propyl paraben,, TCS: Triclosan, 2,4-DCP: 2,4-dichlorophenol, 2,5-DCP: 2,5-dichlorophenol ∑PB: molecular sum of parabens.

Regression models were corrected for the over-representation of cases of malformations of the genitalia by a weighting approach.

[a] Concentrations were standardized for conditions of sampling such as hour of sampling, time elapsed between sample collections and freezing, season and day of sampling and gestational age at collection.

[b] Adjusted for gestational duration, maternal pre-pregnancy weight and height, maternal smoking, maternal education level, parity, recruitment center and creatinine level. Models for head circumference at birth were also adjusted for mode of delivery (cesarean section yes/no).

[c] p-values of heterogeneity test.

[d] p-values of monotonic trend test.

Table 4: Adjusted associations between maternal urinary concentrations of phthalate biomarkers standardized for sampling conditions[a] and birth outcomes (Eden and Pélagie cohort, 2002-2006).

Analytes (µg/L)[a]	Change[b] in birthweight n=287				Change[b] in birthlength n=286				Change[b] in head circumference n=285			
	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (cm)	95% CI	p_{het}[c]	p_{trend}[d]	ß (cm)	95% CI	p_{het}[c]	p_{trend}[d]
MEP												
< 113.8	0	0	0.61	0.60	0	0	0.22	0.58	0	0	0.32	0.14
113.8 – 275.7	46	[-102; 194]			0.5	[-0.2; 0.1]			0.2	[-0.3; 0.7]		
≥ 275.7	-14	[-162; 133]			0.0	[-0.6; 0.7]			0.4	[-0.1; 1.0]		
Ln(MEP)	3	[-51; 57]			0.0	[-0.3; 0.2]			0.1	[-0.2; 0.3]		
MBP												
< 45.6	0	0	0.44	0.42	0	0	0.69	0.91	0	0	0.89	0.63
45.6 – 85.5	52	[-101; 206]			0.3	[-0.4; 0.9]			0.1	[-0.5; 0.6]		
≥ 85.5	-30	[-174; 114]			0.1	[-0.6; 0.7]			0.1	[-0.4; 0.7]		
Ln(MBP)	-13	[-61; 35]			0.1	[-0.2; 0.3]			0.0	[-0.2; 0.2]		
MiBP												
< 48.2	0	0	0.41	0.48	0	0	0.46	0.54	0	0	0.50	0.40
48.2 – 97.9	61	[-77; 200]			0.4	[-0.3; 1.1]			-0.1	[-0.6; 0.4]		
≥ 97.9	-31	[-190; 129]			0.3	[-0.4; 1]			0.2	[-0.5; 0.9]		
Ln(MiBP)	-44	[-110; 23]			0.0	[-0.3; 0.3]			-0.1	[-0.4; 0.1]		
MCPP												
< 2.1	0	0	0.03	0.73	0	0	0.03	0.55	0	0	0.20	0.77
2.1 – 4.4	-198	[-343; -52]			-0.7	[-1.4; -0.1]			-0.5	[-0.1; 0.1]		
≥ 4.4	-95	[-243; 52]			-0.1	[-0.8; 0.7]			-0.3	[-0.9; 0.4]		
Ln(MCPP)	-34	[-91; 22]			0.1	[-0.2; 0.4]			-0.2	[-0.4; 0.1]		
MBzP												
< 17.6	0	0	0.67	0.43	0	0	0.99	0.88	0	0	0.55	0.32
17.6 – 57.2	14	[-141; 170]			0.0	[-0.7; 0.7]			-0.2	[-0.8; 0.4]		
≥ 57.2	-50	[-223; 123]			0.1	[-0.9; 0.7]			-0.3	[-0.9; 0.3]		
Ln(MBzP)	-23	[-71; 24]			0.1	[-0.3; 0.2]			0.0	[-0.2; 0.2]		
MEHP												
< 6.8	0	0	0.20	0.93	0	0	0.12	0.69	0	0	0.55	0.56
6.8 – 17.1	-122	[-261; 17]			-0.6	[-1.2; 0.0]			0.2	[-0.7; 0.3]		
≥ 17.1	-37	[-184; 110]			-0.3	[-0.9; 0.3]			0.1	[-0.5; 0.6]		
Ln(MEHP)	1	[-60; 62]			0.0	[-0.3; 0.2]			0.0	[-0.2; 0.2]		

Table 4 (continued)

Analytes (µg/L)[a]	Change[b] in birthweight n=287				Change[b] in birthlength n=286				Change[b] in head circumference n=285			
	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]
MEOHP												
< 25.2	0	0	0.42	0.28	0	0	0.33	0.27	0	0	0.94	0.75
25.2 – 56.8	-37	[-179; 105]			-0.2	[-0.8; 0.4]			0.0	[-0.5; 0.6]		
≥ 56.8	60	[-89; 209]			0.3	[-0.4; 1.0]			-0.1	[-0.6; 0.5]		
Ln(MEOHP)	5	[-56; 66]			0.1	[-0.2; 0.3]			0.0	[-0.3; 0.2]		
MEHHP												
< 32.2	0	0	0.58	0.65	0	0	0.61	0.80	0	0	0.88	0.76
32.2 – 77.9	-60	[-202; 81]			-0.3	[-0.9; 0.4]			-1.0	[-0.6; 0.4]		
≥ 77.9	7	[-139; 154]			0.0	[-0.7; 0.7]			-0.1	[-0.7; 0.4]		
Ln(MEHHP)	4	[-54; 62]			0.1	[-0.2; 0.3]			0.0	[-0.2; 0.2]		
MECPP												
< 45.8	0	0	0.08	0.59	0	0	0.40	0.43	0	0	0.90	0.65
45.8 – 105.4	-141	[-277; -5]			-0.3	[-1.0; 0.4]			0.0	[-0.5; 0.6]		
≥ 105.4	-20	[-162; 121]			0.2	[-0.6; 0.9]			0.1	[-0.4; 0.6]		
Ln(MECPP)	5	[-64; 73]			0.1	[-0.2; 0.4]			0.0	[-0.2; 0.3]		
MCOP												
< 2.4	0	0	0.87	0.87	0	0	0.11	0.19	0	0	0.77	0.79
2.4 – 5.9	-40	[-192; 110]			-0.2	[-0.9; 0.4]			-0.1	[-0.7; 0.4]		
≥ 5.9	-27	[-200; 147]			0.4	[-0.5; 1.2]			0.0	[-0.6; 0.6]		
Ln(MCOP)	-8	[-72; 55]			0.1	[-0.2; 0.4]			0.0	[-0.2; 0.3]		
MCNP												
< 2.3	0	0	0.85	0.99	0	0	0.11	0.08	0	0	0.89	0.72
2.3 – 4.6	-40	[-186; 107]			0.5	[-0.1; 1.2]			-0.1	[-0.7; 0.4]		
≥ 4.6	-15	[-189; 158]			0.9	[0.0; 1.7]			-0.1	[-0.8; 0.5]		
Ln(MCNP)	-3	[-67; 61]			0.3	[-0.1; 0.6]			-0.1	[-0.3; 0.1]		
DEHP (µmol/L)												
< 0.4	0	0	0.43	0.29	0	0	0.18	0.39	0	0	0.80	0.68
0.4 – 0.9	-54	[-197; 88]			-0.4	[-1.0; 0.2]			0.1	[-0.3; 0.6]		
≥ 0.9	36	[-112; 186]			0.1	[-0.6; 0.9]			0.2	[-0.4; 0.7]		
Ln(DEHP)	5	[-60; 70]			0.1	[-0.2; 0.4]			0.0	[-0.2; 0.2]		

Table 4 (continued)

Analytes (µg/L)[a]	Change[b] in birthweight n=287				Change[b] in birthlength n=286				Change[b] in head circumference n=285			
	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]	ß (g)	95% CI	p_{het}[c]	p_{trend}[d]
∑LMW (µmol/L)												
< 1.2	0	0	0.32	0.14	0	0	0.29	0.53	0	0	0.12	0.52
1.2 – 2.7	-3	[-141; 135]			0.4	[-0.2; 1.1]			0.5	[0.0; 0.9]		
≥ 2.7	-100	[-248; 47]			0.0	[-0.7; 0.7]			0.4	[-0.3; 1.0]		
Ln(∑LMW)	-38	[-109; 34]			-0.1	[-0.4; 0.2]			-0.1	[-0.4; 0.2]		
∑HMW (µmol/L)												
< 0.5	0	0	0.17	0.37	0	0	0.06	0.26	0	0	0.82	0.54
0.5 – 1.3	-99	[-243; 44]			-0.5	[-1.2; 0.1]			0.0	[-0.5; 0.5]		
≥ 1.3	19	[-161; 198]			0.2	[-0.6; 1.0]			0.2	[-0.5; 0.8]		
Ln(∑HMW)	-2	[-70; 65]			0.1	[-0.2; 0.4]			0.0	[-0.2; 0.2]		

Abbreviations: MBP: mono-n-butyl phthalate**,** MBzP: monobenzyl phthalate, MCNP: monocarboxyisononyl phthalate**,** MCOP: monocarboxy-isooctyl phthalate**,** MCPP: mono(3-carboxypropyl) phthalate, MECPP: mono(2-ethyl-5-carboxypentyl) phthalate**,** MEHP: mono(2-ethylhexyl) phthalate, MEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate, MEOHP: mono(2-ethyl-5-oxohexyl) phthalate, MEP: monoethyl phthalate, MiBP: mono-isobutyl phthalate. DEHP: molecular sum of 4 metabolites of di(2-ethylhexyl) phthalate (MEHP, MEHHP, MEOHP,MECPP), ∑LMW: molecular sum of low molecular weight phthalates (MEP, MBP, and MiBP), ∑HMW: molecular sum of high molecular weight phthalates (MBzP, MCPP, MEHP, MECPP, MEHHP, MEOHP, MCOP and MCNP).

Regression models were corrected for the over-representation of cases of malformations of the genitalia by a weighting approach.

[a] Concentrations were standardized for conditions of sampling such as hour of sampling (Eden only), time elapsed between sample collections and freezing, season and day of sampling and gestational age at collection.

[b] Adjusted for gestational duration, maternal pre-pregnancy weight and height, maternal smoking, maternal education level, parity, recruitment center and urine dilution (creatinine level). Models for head circumference at birth were also adjusted for mode of delivery (cesarean section yes/no).

[c] p-values of heterogeneity test.

[d] p-values of monotonic trend test.