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Prenatal Exposure to Phenols and Growth in Boys

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Abstract

Background—Phenols interact with nuclear receptors implicated in growth and adipogenesis regulation. Only a few studies have explored their effects on growth in humans.

Objectives—We studied the associations of maternal exposure to phenols during pregnancy with prenatal and postnatal growth of male newborns.

Methods—Within a cohort of women recruited during pregnancy, we selected 520 mother–son pairs and quantified 9 phenols in spot urine samples collected during pregnancy. We used ultrasonography during pregnancy, together with birth measurements, to assess fetal growth. We modeled individual postnatal growth trajectories from repeated measures of weight and height in the first 3 years of life.

Results—Triclosan concentration was negatively associated with growth parameters measured at the third ultrasound examination but not earlier in pregnancy. At birth, this phenol tended to be negatively associated with head circumference (−1.2 mm for an interquartile range [IQR] increase in ln-transformed triclosan concentration [95% confidence interval = −2.6 to 0.3]) but not with weight or height. Parabens were positively associated with weight at birth. This positive association remained for 3 years for methylparaben (β = 193 g [−4 to 389]) for an IQR increase in ln-transformed concentrations.

Conclusion—We relied on only 1 spot urine sample to assess exposure; because of the high variability in phenol urinary concentrations reported during pregnancy, using only 1 sample may

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result in exposure misclassification, in particular for bisphenol A. Our study suggested associations between prenatal exposure to parabens and triclosan and prenatal or early postnatal growth.

Phenolic compounds are used in common products such as solar filters (benzophenone-3), cosmetics (parabens), antibacterial soaps (triclosan), and polycarbonate plastics or epoxy resins used in can linings (bisphenol A). Precursors of dichlorophenols are used in indoor deodorizers and mothballs. Some of these chemicals are known to be endocrine disruptors and to interact with nuclear receptors involved in the control of adipogenesis and weight gain, such as glucocorticoid, estrogen, and thyroid receptors.[1]

In vitro studies have reported adipogenic effects for bisphenol A[2,3] and parabens.[4,5] In rodents, perinatal exposure to bisphenol A (doses of 0.25–100 μg/kg of body weight/day) has been associated with increased weight at birth and during early life.[6–8] There are reports of reduced body weight at birth, but at high exposure levels (300 and 1000 mg/kg).[9]

The human literature is mixed. Some epidemiologic studies are in line with the toxicological results, with positive associations between prenatal exposure to bisphenol A and birth weight,[10] waist circumference, body mass index (BMI), and the risk of being overweight at 4 years.[11] However, there are also negative associations.[12,13] Prenatal exposure to bisphenol A was negatively associated with fetal weight and head circumference, determined from ultrasound measurements.[12] The associations were observed only in the offspring of 80 women for whom 3 measurements of bisphenol A urinary concentrations during pregnancy were used to assess exposure; no association was observed when only 1 (n = 219) or 2 (n = 120) samples were used. This, together with studies showing high within-subject variability in phenol urinary concentrations,[14] highlights the potential impact of measurement error in studies of bisphenol A effects relying on only 1 urine sample, although selection effects cannot be ruled out as an explanation of the variations in effect estimates.[12] Decreased BMI at the age of 9 years in girls, but not boys, has been observed in association with prenatal exposure to bisphenol A.[13]

Data are sparse regarding effects of the other phenols on prenatal and postnatal weight. In a preliminary study, among a subsample of 191 male newborns from the French Eden mother–child cohort, we observed a negative association between 2,4- and 2,5-dichlorophenol and birth weight and a positive association between benzophenone-3 and birth weight.[15] These results were in agreement with another publication concerning male newborns from New York City.[10] No study has explored the effects of these phenols on postnatal growth, nor simultaneously considered the growth continuum from conception until childhood.

The objective of this study was to explore the associations between phenol exposures during pregnancy and offspring growth from mid-pregnancy until 3 years of age in boys.

METHODS

Population

The study population is a subgroup of the French EDEN mother–child cohort, which consisted of 2002 pregnant women recruited before the end of the 28th gestational week from the maternity wards of Poitiers and Nancy University hospitals (France) between April 2003 and March 2006. Exclusion criteria were personal history of diabetes, multiple fetuses, intention to deliver outside the university hospital or to move out of the study region within the next 3 years, and inability to speak French. Among the 2002 recruited women, 1899 gave birth to a singleton live birth, for whom we collected birth weight (eFigure 1, http://links.lww.com/EDE/A801). We restricted the present analysis to boys (n = 998), with at least 1 maternal urine sample available for phenol measurements (n = 983) and complete data on prenatal (3 ultrasound measurements and biometry at birth, n = 779) and postnatal growth (≥4 measurements of weight and height within the first 3 years of life and present at the 3 years clinical exam), for a final sample size of 520 mother–child pairs. Our choice to focus on 1 sex was motivated by the fact that, in the context where sex-specific effects of exposures are expected,[10,13] a study restricted to 1 sex likely has a higher statistical power than a study including both sexes in which 2 sex-specific analyses, with half of the initial sample size, are conducted.

The EDEN cohort received approval from the ethics committee of Kremlin-Bicêtre University hospital. The involvement of the Centers for Disease Control and Prevention (CDC) did not constitute engagement in human subject research. The participants gave informed written consent for themselves and for their child to be part of the cohort.

Growth Assessments

We assessed biparietal diameter by ultrasound during pregnancy at on average 12.6 gestational weeks (12 weeks, 4.2 days) (5th–95th centiles = 11.1–14.0), 22.5 gestational weeks (20.7–24.4), and 32.6 gestational weeks (30.6–34.2). The other measures of fetal size (head circumference, abdominal circumference, and femur length) were assessed only during the 2 last ultrasound examinations.[16] We estimated fetal weight using the formula from Hadlock et al[17]: log (fetal weight) = 1.3596 - (0.00386 × abdominal circumference × femur length) + (0.0064 × head circumference) + (0.00061 × biparietal diameter × abdominal circumference) + (0.0424 × abdominal circumference) + (0.174 × femur length). Weight and length at birth were extracted from hospital maternity records. Infants were weighed and measured at 1 and 3 years during standardized study-specific examinations. Additionally, at 4, 8, 12, 24, and 36 months, mothers mailed questionnaires with the boys' weight and height measures, as recorded in the child health booklet by health care practitioners.

We used the Jenss nonlinear model to individually model child growth and predict weight and height at 6, 12, 24, and 36 months.[18] This model provided very good fit to the observations in the EDEN cohort (eFigure 2, http://links.lww.com/EDE/A801) and was meant to provide a height and weight estimate at exactly the same age for all subjects.[19] Head circumference was assessed in duplicate within 4 days after birth and at 3 years; we

used the average of the 2 measures at each age. Because head circumference could be distorted by the labor of giving birth, we preferred to use the measures of head circumference performed a few days after birth rather than at birth. At 3 years, children's abdominal circumference was measured in duplicate and averaged. We computed average growth rates between 2 successive measurements as growth rate = (measurement at t_2 − measurement at t_1)/($t_2 - t_1$).

Biological Sampling and Exposure Assessments

Urine samples were collected between 22 and 29 gestational weeks. Women were asked to collect the first morning urine at home before the hospital study visit. If forgotten, the urine sample was collected at the hospital during the prenatal study visit. Urine samples were aliquoted and stored at −80°C. Measurements of 2,4- and 2,5-dichlorophenol, bisphenol A, benzophenone-3, triclosan, methyl-, ethyl-, propyl-, and butylparabens,[20] and creatinine were performed at the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. Depending on the phenol biomarkers, the coefficients of variation of about 60 replicates in a period of 9 months were between 3% and 10% at concentrations ranging from around 2 to 70 ng/ml. Total paraben concentration (∑PB) was calculated by summing molar concentrations of the 4 parabens.

Sample shipments to CDC and phenol measurements were performed during 2 periods. Among the 191 male newborns in our previous study that assessed the associations of phenols with male genital anomalies and birth outcomes (weight, height, head circumference),[15,21] 110 matched the inclusion criteria of the present study and were considered here. Their urine samples were analyzed for phenols in 2008. In 2011, we extended phenol measurements to the remaining 410 women matching the inclusion criteria (eFigure 1, http://links.lww.com/EDE/A801). Year of analysis was taken into account in statistical analyses (see below). The laboratory used the same analytic methodology to analyze all samples.

Statistical Methods

For phenol biomarker concentrations below the limit of detection, we used instrumental reading values. To allow ln-transformation, instrumental reading values equal to 0 (ie, indicative of no signal) were replaced by the lowest instrumental reading value divided by the square root of 2. Concentrations were standardized for collection conditions: we first studied associations between each ln-transformed phenol concentration, sampling conditions (hour of sampling, gestational age at collection, duration of storage at room temperature before freezing, day of sampling, and creatinine concentrations), and analysis year (2008 or 2011) using phenol-specific adjusted linear regression models. We used the measured urinary bio-marker concentrations and the estimated effects of collection conditions on the measured urine concentrations (for conditions associated with urine concentrations with $P < 0.2$) to predict standardized concentrations, that is, concentrations that would have been observed if all samples had been collected under the same conditions.[22] This approach was used with the aim of reducing variability in biomarker urinary concentrations due to heterogeneity in sampling conditions. Unless otherwise specified, all reported concentrations are the standardized values.

We performed cross-sectional analyses to study the associations between phenol concentrations, growth parameters measured at birth, and growth rates. We used linear regression models with a random effect variable corresponding to the mother–son pair,[23] to study the associations between phenol concentrations and growth parameters measured by ultrasound examinations during pregnancy and predicted during childhood. To allow for effect-measure modifications throughout pregnancy, we included interaction terms between phenol concentration and gestational age at outcome measurement (third-order polynomial) estimated using the date of last menstrual period (LMP), or gestational duration assessed by the obstetrician if it differed from the LMP-based estimate by more than 2 weeks.[15]

Models for prenatal and postnatal growth were adjusted for maternal and paternal height (continuous) and pre-pregnancy weight (continuous), maternal active (continuous) and passive (yes/no) smoking during pregnancy, maternal education level (high school or less, up to 2 years after high school, ≥3 years after high school), recruitment center, and parity. The model for head circumference was additionally adjusted for the number of days between birth and the assessment of head circumference. Analyses of postnatal growth were additionally adjusted for breastfeeding duration (never, ≤3 months, >3 months). Crude analyses are reported in eTable 1 (http://links.lww.com/EDE/A801).

The effect estimates are reported for an increase by 1 interquartile range (IQR) of ln-transformed phenol standardized concentrations. Analyses in tertiles were conducted but are not reported.

Sensitivity Analyses

In sensitivity analyses, models for postnatal weight were additionally adjusted for the following: (1) birth weight, which is a potential intermediate factor in the pathway between prenatal exposures and postnatal growth and was therefore not controlled for in main analyses; (2) height predicted at the same age, to study the association with body mass; and (3) child caloric intake at 4 or 8 months for models of weight at 6 or 12 months and more, respectively. Caloric intake was computed based on 3-day dietary records at 4 and 8 months. We ran models of head circumference based on the measurement performed at birth instead of a few days after birth. For all outcomes, we performed sensitivity analyses excluding women with pregnancy-induced hypertension (n = 25) or gestational diabetes (n = 28), using biomarker concentrations not standardized for sampling conditions rather than the standardized values, and using the actual postnatal growth measurements rather than the values predicted by the Jenss model.

RESULTS

Population

Average maternal age was 29.7 years; most women (87%) did not smoke during pregnancy, 26% were overweight or obese (BMI > 25 kg/m^2). Twenty-three of the boys (4%) were born before 37 gestational weeks and 11 (2%) had a birth weight below 2500 g (Table 1). Women in the present study were similar to all Eden women who delivered a boy, except for active and passive smoking, which were less frequent in the present study (Table 1). The

proportion of newborns with congenital abnormalities among the subsample of 520 boys of the study population (5.2%) was similar to those observed among boys of the whole EDEN cohort (4.8%).

Exposure

Among the 397 women reporting the hour of urine collection, 268 (68%) collected their urine before 8 am, 96 (24%) between 8 and 10 am, 30 (8%) between 10 am and 12 pm, and 3 (1%) after 12 pm. We detected 6 of the 9 target phenols in at least 93% of the samples (Table 2). Relative changes in the median concentration of urinary biomarkers between the samples analyzed in 2008 and 2011 varied between −14% (triclosan) and +22% (methylparaben).

Association Between Phenols and Growth Parameters

We observed negative associations between (ln-transformed) triclosan concentrations and all of the anthropometric and growth parameters measured at the third ultrasound examination, but not earlier in pregnancy (Table 3). At birth, triclosan concentration tended to be negatively associated with head circumference (−1.2 mm for an IQR increase in ln-transformed triclosan concentration [95% confidence interval (CI) = −2.6 to 0.3]) but not with weight (4.6 g [−49 to 58]) or height (−0.2 mm [−2.6 to 2.3]). Regarding prenatal growth rate, triclosan concentration was negatively associated with biparietal diameter growth between the first and second ultrasound examinations (−0.03 mm/week [−0.07 to 0.00]) and with weight growth between the second and third ultrasound examinations (−3.3 g/week [−6.1 to −0.4]) and positively with weight growth between the third ultrasound examination and birth (7.0 g/week [0.3 to 14], Table 4). Triclosan concentration was not clearly associated with size parameters measured after birth (Table 3).

Concentrations of all parabens, as well as their sum, tended to be positively associated with weight growth between the third ultrasound examination and birth (Table 4) and with weight at birth, but not with estimated fetal weight at the second and third ultrasound examinations (Table 3). Methylparaben were also positively associated with weight and abdominal circumference at 36 months (Table 3, Figure). Regarding postnatal growth rate, parabens tended to be positively associated with average weight growth between 12 and 24 months and between 24 and 36 months, but not before 12 months (Table 4). The positive associations between methylparaben and postnatal weight remained after adjustment for child caloric intake and weakened after adjustment for birth weight (eTable 2, http://links.lww.com/EDE/A801) or height (eTable 3, http://links.lww.com/EDE/A801).

We did not observe clear associations between bisphenol A and any of the prenatal and postnatal measurements (Table 3). After adjustment for height, bisphenol A was not associated with weight either at birth or at 6 months but tended to be positively associated with weight at 12, 24, and 36 months (eTable 3, http://links.lww.com/EDE/A801). The effect estimates were 47 g (95% CI = −45 to 138), 76 g (−37 to 190), and 72 g (−67 to 211) at 12, 24, and 36 months, respectively, compared with 23 g (−92 to 139), 38 g (−108 to 184), and 35 g (−145 to 214) in the analysis not adjusted for child height. Additional adjustment for child caloric intake did not change these effect estimates (data not shown).

2,4-dichlorophenol was negatively associated with abdominal circumference at the third ultrasound examination (−1.2 mm [−2.5 to 0.1]) and positively with this outcome recorded at 36 months (2.3 mm [−0.2 to 4.9], Table 3). This phenol was positively associated with weight growth between 24 and 36 months (0.9 g/weeks [0.1 to 1.8]) but not with weight measured at 36 months (38 g [−107 to 183]). We also observed a positive association between 2,5-dichlorophenol and head circumference at the third ultrasound examination (1.2 mm [0.0 to 2.3]).

We did not observe clear associations between benzophenone-3 and the studied growth parameters (Table 3). When we used head circumference at birth rather than a few days after birth, a positive association with benzophenone-3 was observed (1.0 mm [−0.2 to 2.3]), which was not suggested with the measure shortly after birth (0.3 mm [−0.6 to 1.3]).

Our conclusions were not changed by excluding women with pregnancy-induced hypertension or gestational diabetes or by using the nonstandardized phenol concentrations (eTable 4, http://links.lww.com/EDE/A801) or the actual postnatal growth measures rather than the values predicted by the Jenss growth model.

DISCUSSION

Within our population of male newborns, maternal urinary triclosan concentration was associated with reduced fetal growth measurements late in pregnancy and with reduced head circumference at birth. Parabens were associated with increased weight at birth but not with estimated fetal weight during pregnancy. The positive association of methylparaben with weight remained until 36 months.

Our study is the first to explore the effects of early-life exposure to phenols on growth from early pregnancy until childhood. Strengths of our study are the prospective design (with exposure assessment during the biologically relevant fetal period) and the use of repeated measurements of growth during fetal and early postnatal life. The sample size is larger than in previous studies.[10,12,15] In our study population, about two-thirds of women collected their urine sample before 8 am, which is likely to correspond to the first morning void. Pooled urine samples are expected to provide a better estimate of exposure than spot urine samples, but if spot urine samples are to be used, then there is no reason to consider that the first morning void is better than other spot samples. Given their short half-life and the temporal variations in exposure, hour of urine sampling is likely to influence phenol biomarker urinary concentrations,[24] and between-subject variations in urine sampling hour constitutes an undesirable source of variability in biomarker concentrations.

In order to reduce this variability, we used a 2-step standardization method based on regression residuals.[22] This approach corrects each biomarker's concentration so as to obtain an estimate closer to what would be expected if all women had collected their urine at the same hour. Because this approach is not common, we repeated our analyses using concentrations not standardized for sampling conditions and this did not change our conclusion.

Because we used only 1 urine sample to assess phenol concentrations, our results might be affected by exposure misclassification, which is a clear limitation, in particular for bisphenol A (for which a high within-subject variability in urine concentrations has been reported during pregnancy).[14,25] Higher reproducibility in urine concentrations has been observed for the other phenols (intraclass correlation coefficients ranging between 0.5 and 0.6)[14]; however, even with a correlation of this magnitude, a bias in the dose response is expected. Assuming classical type error, the bias in the estimates from linear regression models relying on a single urine sample is expected to correspond to an attenuation by a multiplicative factor equal to the intraclass correlation coefficient (eg, a 40% decrease in the estimated parameter for compounds with an intraclass correlation coefficient of 0.6).[26] Finally, we performed many comparisons and cannot exclude chance findings.

The negative association between triclosan and head circumference at birth is consistent with the results obtained in the subsample of 191 male newborns from the EDEN cohort, of whom 110 were included in the present analysis.[15] Head circumference is a predictor of brain volume.[27] In animals, triclosan disturbed the homeostasis of thyroid hormones, which are required for fetal normal growth and brain development.[28,29] In humans, to our knowledge, no study has investigated the effects of triclosan exposure on thyroid hormone levels during pregnancy.

Maternal urinary concentrations of parabens were associated with higher weight at birth and during early childhood. This was explained by an effect on weight growth between the third trimester of pregnancy and birth and between 1 and 3 years. In vitro, parabens have estrogenic activities[30,31]; they also promote adipocyte differentiation in murine cells by an activation of the glucocorticoid receptor or the peroxisome proliferator-activated receptor gamma.[4,5] An effect on these nuclear receptors may increase susceptibility to gain weight and might play a role in the positive associations observed with abdominal circumference at 36 months and with postnatal weight. To our knowledge, except for our previous study,[15] which did not find an association between parabens and birth weight (−3 g [95% CI = −39 to 33]), no other epidemiologic study has explored the associations between these chemicals and growth.

A few studies have explored the effect of bisphenol A on fetal growth in humans; both positive[10,15] and negative[12] associations have been reported. We did not observe any association between this phenol and fetal growth measurements. However, because we used only 1 urine sample to categorize exposure to this chemical, for which urinary concentrations show high intra-individual variability, our findings could be affected by classical type measurement error, which is expected to strongly bias dose–response relationships toward the null.[32] Regarding postnatal growth, 1 study has reported a positive association between bisphenol A and waist circumference, BMI and the risk of being overweight at 4 years, although not earlier in childhood.[11] Another study of older children did not observe any association with boys' BMI or waist circumference at the age of 9 years.[13] In our population, after height adjustment, bisphenol A tended to be positively associated with weight at 12, 24, and 36 months. The main source of bisphenol A is diet.[33] We cannot exclude the possibility that bisphenol A urinary concentration is a surrogate for factors predictive of child overweight, such as maternal and child eating behaviors, which

therefore constitute potential confounders. We were limited in our ability to control for confounding by eating behaviors because we had only an estimation of the mother and child caloric intake, rather than data on the type of food (canned, processed, or fresh) usually eaten. In addition, data on food intake were collected by questionnaires, so that our estimation is likely to suffer from lack of precision. Adjustment for the child caloric intake did not affect the associations of maternal pregnancy bisphenol A concentration with child weight, adjusted for height.

The negative associations between dichlorophenols and birth weight observed in our previous study[15] were not replicated in this study with a larger sample size (520 vs. 191, eFigure 3, http://links.lww.com/EDE/A801). Exposure levels did not strongly differ between the populations; however, women in the present study were more educated and less likely to smoke compared with the 191 women of the previous study; the distribution of unmeasured factors confounding the associations between phenols and birth outcomes also could have differed across subpopulations. Differences in findings between our 2 studies might also be explained by random variations or exposure measurement errors resulting from the use of 1 urine sample to assess exposure to chemicals with a short half-life.

In conclusion, our study lends support to potential effects of some phenols on prenatal and early postnatal growth. However, because of the short half-life of the studied phenols and the likely episodic nature of the exposures (in particular bisphenol A), our findings based on concentrations of the target biomarkers in a single urine sample may be affected by exposure misclassification. Replications are needed in other populations with large sample size and improved assessment of exposure to phenols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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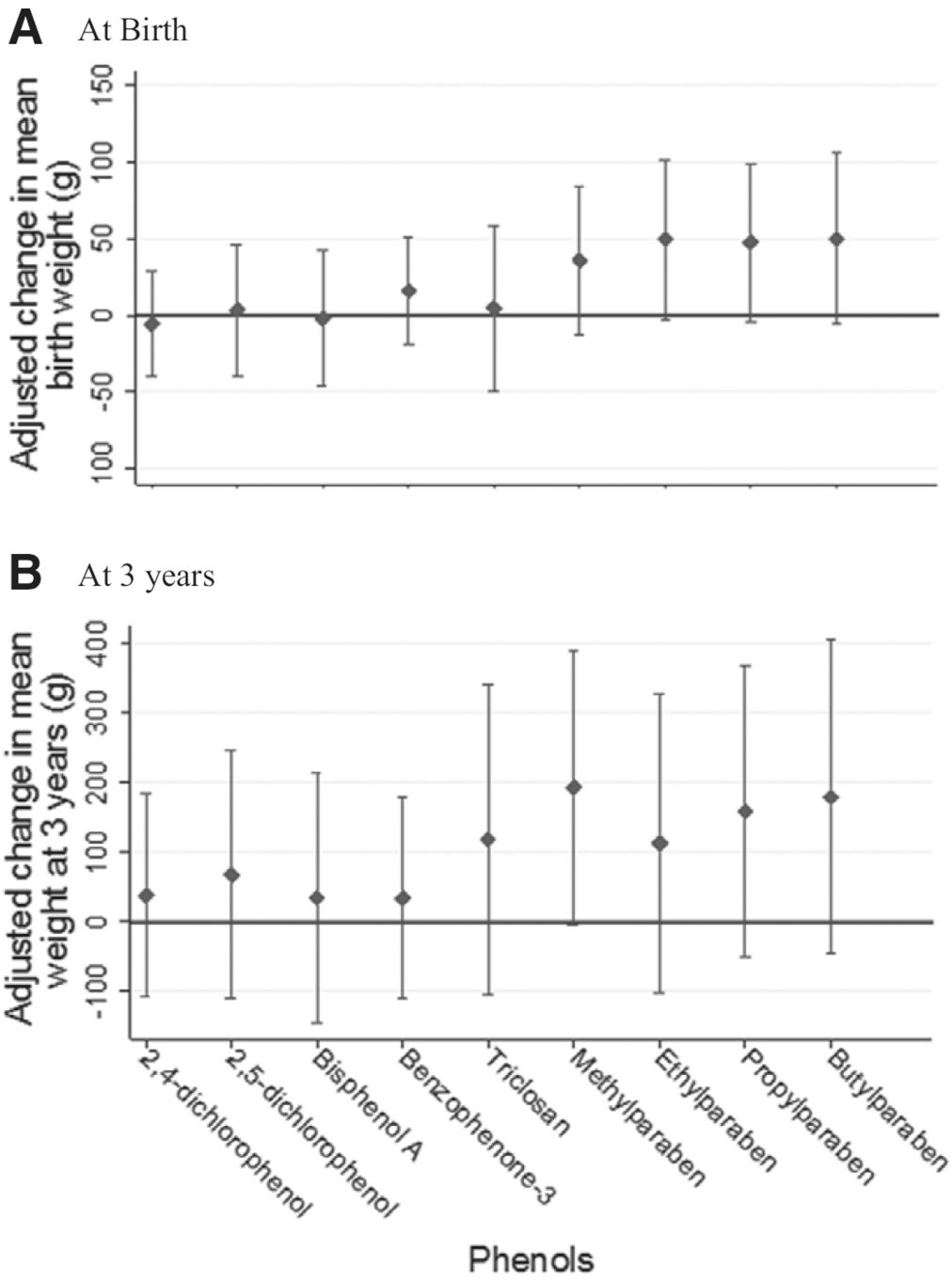

Figure.

Adjusted associations between maternal urinary concentrations of phenols and weight (A) at birth and (B) at the age of 3 years (Eden cohort, 2003–2006, 520 male newborns). Effect estimates are given for an increase by 1 IQR of ln-transformed phenol standardized concentrations. Adjustment factors for the birth weight analysis: gestational age, maternal and paternal height, pre-pregnancy weight, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, and parity. Adjustment factors for the analysis of weight at 3 years: maternal and paternal height, pre-pregnancy weight,

maternal active and passive smoking during pregnancy, maternal education level, recruitment center, parity, and breastfeeding duration.

Table 1

Characteristics of the Study Population (PEnDevE) and Comparisons with the Whole EDEN Cohort Delivering Boys

	All Male Newborns, EDEN Cohort (n = 998)[a]	Women of EDEN Cohort Included in PEnDevE Study (n = 520)[b]	Women of EDEN Cohort Include Gona_PE Study (n = 191)[c]
Characteristic	**No. (%)**	**No. (%)**	**No. (%)**
Maternal age (years)			
<25	200 (20)	85 (16)	35 (18)
25–29	378 (38)	200 (38)	71 (37)
30–34	285 (29)	159 (31)	57 (30)
≥35	135 (14)	76 (15)	28 (15)
Parity			
0	436 (44)	248 (48)	72 (38)
1	374 (37)	192 (37)	75 (39)
≥2	187 (19)	79 (15)	44 (23)
Missing	1 (0)	1 (0)	
BMI (kg/m^2)			
<18.5	92 (9)	45 (9)	19 (10)
18.5 to 24.9	634 (64)	331 (64)	115 (60)
≥25	251 (25)	137 (26)	54 (28)
Missing	21 (2)	7 (1)	3 (2)
Maternal education			
<2 years after high school	459 (46)	211 (41)	95 (50)
High school + 2 years	219 (22)	124 (24)	39 (20)
≥High school + 3 years	297 (30)	178 (34)	51 (27)
Missing	23 (2)	7 (1)	6 (3)
Active smoking (cig/day)[d]			
0	827 (83)	453 (87)	159 (83)
1 to 5	82 (8)	39 (8)	15 (8)
>5	86 (9)	27 (5)	17 (9)
Missing	3 (0)	1 (0)	
Passive smoking			
No	711 (71)	411 (79)	131 (69)
Yes	278 (28)	108 (21)	59 (31)
Missing	9 (1)	1 (0)	1 (1)
Center			
Poitiers	533 (53)	312 (60)	91 (48)
Nancy	465 (47)	208 (40)	100 (52)
Gestational duration			
<37 gestational week	63 (6)	23 (4)	5 (3)
≥37 gestational week	935 (94)	497 (96)	186 (97)
Birth weight			

Characteristic	All Male Newborns, EDEN Cohort (n = 998)[a] No. (%)	Women of EDEN Cohort Included in PEnDevE Study (n = 520)[b] No. (%)	Women of EDEN Cohort Include Gona_PE Study (n = 191)[c] No. (%)
<2500 g	47 (5)	11 (2)	4 (2)
≥2500 g	951 (95)	509 (98)	187 (98)
Year of birth			
2003–2004	560 (56)	286 (55)	89 (47)
2005–2006	438 (44)	234 (45)	102 (53)
Breastfeeding			
Never	270 (27)	135 (26)	51 (27)
≤3 months	422 (42)	209 (40)	84 (44)
>3 months	298 (30)	176 (34)	56 (29)
Missing	8 (1)	0 (0)	0 (0)

Gona_PE indicates study aiming at studying the associations between phenols, male genital anomalies, and birth outcomes among 191 male newborns from the Eden cohort.

[a] Singleton live births.

[b] Study population of this paper

[c] Study population of the birth outcome analysis published in 2012.[8]

[d] Second trimester of pregnancy.

Table 2

Concentrations of Phenol Biomarkers in Maternal Urine (Eden Cohort, 2003–2006; n = 520)

Phenols	LOD (μg/L)	% > LOD	Measured Concentrations Percentiles (μg/L) 5th	50th	95th	Standardized Concentrations Percentiles (μg/L) 5th	50th	95th	Spearman Correlation Between Standardized and Measured Concentrations
2,4-Dichlorophenol	0.2	98	0.3	1.0	10.1	0.3	1.0	9.8	0.91
2,5-Dichlorophenol	0.2	100	1.6	9.8	291	1.8	9.1	305	0.96
Bisphenol A	0.4	99	0.7	2.5	11	0.8	2.4	8.8	0.85
Benzophenone-3	0.4	93	<LOD	2.2	85	<LOD	2.3	71	0.94
Triclosan	2.3	81	<LOD	30	755	<LOD	29	732	0.99
Methylparaben	1	100	8.1	122	2020	8.3	107	1155	0.94
Ethylparaben	1	73	<LOD	4.7	72	<LOD	3.6	66	0.93
Propylparaben	0.2	99	0.6	17	317	0.5	14	249	0.97
Butylparaben	0.2	84	<LOD	2.0	59	<LOD	2.1	61	0.96

LOD indicates limit of detection.

Table 3

Adjusted Associations[a] Between Phenol Maternal Urinary Concentrations and Prenatal and Postnatal Size (520 Male Newborns, Eden Cohort, 2003–2006)

	Phenolic Compounds								
	2,4-Dichlorophenol	2,5-Dichlorophenolv	Bisphenol A	Benzophenone-3	Triclosan	Methylparaben	Ethylparaben	Propylparaben	Butylparaben
Growth Parameter	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
Biparietal diameter (mm)									
1st ultrasound	−0.09 (−0.30 to 0.13)	−0.11 (−0.37 to 0.15)	−0.01 (−0.28 to 0.25)	0.02 (−0.19 to 0.23)	0.16 (−0.17 to 0.48)	0.09 (−0.20 to 0.38)	−0.01 (−0.33 to 0.30)	0.03 (−0.28 to 0.34)	−0.03 (−0.36 to 0.31)
2nd ultrasound	−0.07 (−0.32 to 0.17)	−0.03 (−0.33 to 0.27)	−0.04 (−0.35 to 0.27)	−0.12 (−0.37 to 0.13)	−0.15 (−0.53 to 0.23)	0.06 (−0.28 to 0.40)	0.10 (−0.27 to 0.47)	0.02 (−0.34 to 0.38)	0.31 (−0.08 to 0.70)
3rd ultrasound	−0.03 (−0.33 to 0.27)	0.26 (−0.11 to 0.63)	−0.22 (−0.60 to 0.16)	0.11 (−0.19 to 0.42)	−0.42 (−0.89 to 0.04)	−0.10 (−.51 to 0.31)	0.05 (−0.40 to 0.50)	−0.12 (−0.56 to 0.32)	0.37 (−0.10 to 0.84)
Head circumference (mm)									
2nd ultrasound	−0.32 (−1.14 to 0.51)	0.11 (−0.90 to 1.12)	0.45 (−0.60 to 1.50)	−0.27 (−1.11 to 0.57)	0.06 (−1.23 to 1.35)	0.26 (−0.89 to 1.41)	0.92 (−0.34 to 2.18)	−0.11 (−1.33 to 1.11)	0.95 (−0.41 to 2.30)
3rd ultrasound	0.10 (−0.88 to 1.07)	1.19 (0.00 to 2.37)	−0.65 (−1.86 to 0.56)	0.29 (−0.68 to 1.27)	−1.21 (−2.69 to 0.28)	−0.02 (−1.35 to 1.31)	0.73 (−0.73 to 2.18)	0.30 (−1.12 to 1.71)	1.15 (−0.37 to 2.68)
At birth	−0.25 (−1.21 to 0.71)	0.02 (−1.16 to 1.2)	0.16 (−1.05 to 1.37)	0.34 (−0.63 to 1.3)	−1.20 (−2.63 to 0.33)	0.13 (−1.21 to 1.48)	0.10 (−1.32 to 1.58)	0.64 (−0.79 to 2.1)	0.00 (−1.6 to 1.53)
At 36 months	−0.19 (−1.35 to 0.97)	0.07 (−1.35 to 1.49)	0.03 (−1.43 to 1.50)	−0.35 (−1.51 to 0.81)	−1.02 (−2.80 to 0.76)	0.28 (−1.32 to 1.88)	−0.71 (−2.45 to 1.03)	0.20 (−1.49 to 1.89)	−0.55 (−2.41 to 1.31)
Femoral length (mm)									
2nd ultrasound	−0.04 (−0.22 to 0.15)	0.06 (−0.17 to 0.29)	0.14 (−0.09 to 0.38)	−0.02 (−0.21 to 0.17)	−0.01 (−0.30 to 0.28)	0.05 (−0.21 to 0.31)	0.07 (−0.22 to 0.35)	0.02 (−0.25 to 0.29)	0.10 (−0.20 to 0.41)
3rd ultrasound	−0.13 (−0.35 to 0.08)	0.00 (−0.27 to 0.26)	−0.19 (−0.46 to 0.08)	0.05 (−0.16 to 0.27)	−0.32 (−0.65 to 0.01)	−0.06 (−0.36 to 0.24)	0.14 (−0.18 to 0.47)	−0.20 (−.52 to 0.11)	0.09 (−0.25 to 0.43)
Length(mm)									
At birth	−0.79 (−2.36 to 0.78)	−0.75 (−2.67 to 1.17)	0.79 (−1.19 to 2.78)	0.48 (−1.11 to 2.07)	−0.16 (−2.60 to 2.27)	1.86 (−0.34 to 4.05)	0.49 (−1.89 to 2.86)	1.42 (−0.93 to 3.76)	1.57 (−0.97 to 4.10)

	Phenolic Compounds								
	2,4-Dichlorophenol	2,5-Dichlorophenolv	Bisphenol A	Benzophenone-3	Triclosan	Methylparaben	Ethylparaben	Propylparaben	Butylparaben
Growth Parameter	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
At 6 months[b]	−0.01 (−1.79 to 1.77)	0.37 (−1.81 to 2.55)	−0.14 (−2.37 to 2.10)	0.74 (−1.04 to 2.52)	0.00 (−2.71 to 2.72)	2.32 (−0.12 to 4.76)	0.33 (−2.33 to 2.99)	1.36 (−1.22 to 3.94)	1.05 (−1.79 to 3.88)
At 12 months[b]	−0.55 (−2.63 to 1.53)	v0.26 (−2.81 to 2.29)	−1.05 (−3.65 to 1.56)	0.82 (−1.26 to 2.90)	−0.22 (−3.40 to 2.96)	1.97 (−0.88 to 4.82)	−0.11 (−.21 to 2.99)	0.73 (−2.28 to 3.75)	1.18 (−2.10 to 4.47)
At 24 months[b]	−0.67 (−3.18 to 1.84)	−0.26 (−3.33 to 2.82)	−1.72 (−4.84 to 1.40)	1.18 (−1.32 to 3.69)	−0.17 (−4.01 to 3.66)	2.54 (−0.88 to 5.96)	0.39 (−3.34 to 4.11)	0.80 (−2.82 to 4.43)	2.42 (−1.50 to 6.35)
At 36 months[b]	−0.14 (−3.15 to 2.87)	0.22 (−3.47 to 3.90)	−1.68 (−5.41 to 2.04)	1.35 (−1.65 to 4.35)	0.19 (−4.40 to 4.79)	3.58 (−0.51 to 7.67)	1.04 (−3.42 to 5.50)	1.26 (−3.08 to 5.59)	3.23 (−1.45 to 7.91)
Abdominal circumference (mm)									
2nd ultrasound	−0.14 (−1.16 to 0.88)	0.14 (−1.12 to 1.40)	0.45 (−0.86 to 1.76)	0.17 (−0.87 to 1.22)	0.17 (−1.42 to 1.77)	−0.10 (−1.53 to 1.33)	−0.05 (−1.61 to 1.52)	−0.16 (−1.68 to 1.35)	0.47 (−1.22 to 2.17)
3rd ultrasound	−1.21 (−2.47 to 0.05)	−0.05 (−1.58 to 1.49)	1.22 (−0.36 to 2.79)	0.40 (−0.87 to 1.67)	−2.39 (−4.31 to −0.47)	0.09 (−1.64 to 1.81)	0.86 (−1.02 to 2.74)	−0.08 (−1.91 to 1.76)	1.31 (−0.67 to 3.29)
At 36 months	2.34 (−0.19 to 4.86)	2.18 (−0.91 to 5.27)	0.62 (−2.57 to 3.81)	1.18 (−1.36 to 3.71)	2.66 (−1.21 to 6.53)	4.18 (0.70 to 7.65)	1.89 (−1.91 to 5.69)	3.37 (−0.30 to 7.04)	3.61 (−0.43 to 7.66)
Weight (g)									
2nd ultrasound[c]	−2.37 (−16.5 to 11.8)	0.24 (−17.2 to 17.7)	6.34 (−11.8 to 24.5)	−0.73 (−15.2 to 13.7)	−1.91 (−24.0 to 20.2)	−2.43 (−22.2 to 17.3)	−2.10 (−23.7 to 19.6)	−2.10 (−23.1 to 18.9)	1.70 (−21.7 to 25.1)
3rd ultrasound	−16.3 (−33.7 to 1.08)	3.06 (−18.2 to 24.4)	1.54 (−20.3 to 23.8)	6.89 (−10.7 to 24.4)	−35.2 (−61.8 to −8.58)	−4.61 (−28.5 to 19.3)	13.00 (−13.1 to 39.1)	−6.80 (−32.3 to 18.6)	23.5 (−3.96 to 50.9)
At birth	−5.40 (−40.0 to 29.2)	3.46 (−38.9 to 45.8)	−1.80 (−45.6 to 42.0)	16.0 (−18.9 to 51.0)	4.60 (−49.0 to 58.3)	36.0 (−12.5 to 84.4)	49.9 (−2.21 to 102)	48.0 (−3.64 to 99.6)	50.1 (−5.69 to 106)
At 6 months[b]	−9.80 (−83.9 to 64.2)	−5.09 (−95.7 to 85.6)	−7.70 (−101 to 85.3)	33.7 (−40.5 to 107)	17.5 (−95.7 to 131)	85.3 (−16.5 to 187)	17.8 (−92.9 to 129)	80.1 (−27.4 to 188)	55.8 (−62.0 to 174)
At 12 months[b]	−34.0 (−127 to 58.7)	−22.5 (−136 to 91.0)	23.2 (−92.4 to 139)	54.9 (−37.7 to 148)	21.9 (−120 to 164)	81.2 (−45.4 to 208)	2.60 (−135 to 140)	79.1 (−54.9 to 213)	54.5 (−91.1 to 200)
At 24 months[b]	−14.4 (−132 to 103)	7.65 (−136 to 151)	38.0 (−108 to 184)	54.9 (−62.3 to 172)	65.6 (−114 to 245)	128 (−31.9 to 287)	45.3 (−128 to 219)	116 (−53.3 to 285)	111 (−71.2 to 294)
At 36 months[b]	38.4 (−107 to 183)	68.4 (−109 to 246)	34.5 (−145 to 214)	34.9 (−110 to 180)	119 (−103 to 340)	193 (−3.88 to 389)	113 (−101 to 327)	159 (−49.4 to 368)	179 (−45.3 to 404)

[a] The effect estimates are reported for an increase by 1 IQR of the ln-transformed phenol standardized concentrations. Models for prenatal growth were adjusted for maternal and paternal height, pre-pregnancy weight, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, gestational age at measurement, and parity. The model for head circumference at birth was additionally adjusted for the number of days between birth and the assessment of head circumference. Models for postnatal growth were adjusted for maternal and paternal height, pre-pregnancy weight, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, breastfeeding duration, and parity.

[b] Parameter individually predicted by Jenss growth curve model from repeated measures.

[c] Estimated fetal weight.

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Table 4

Adjusted Associations Between Phenol Maternal Urinary Concentrations and Growth Rate (520 Male Newborns, Eden Cohort, 2003–2006)

	2,4-Dichlorophenol	2,5-Dichlorophenol	Bisphenol A	Benzophenone-3	Triclosan	Methylparaben	Ethylparaben	Propylparaben	Butylparaben
Growth Rate	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
Biparietal diameter[a]									
1st to 2nd ultrasound	0.00 (−0.02 to 0.02)	0.01 (−0.02 to 0.04)	0.00 (−0.03 to 0.03)	−0.01 (−0.03 to 0.01)	−0.03 (−0.07 to 0.00)	v.01 (−0.04 to 0.02)	0.01 (−0.03 to 0.04)	−0.01 (−0.04 to 0.02)	0.03 (−0.01 to 0.06)
2nd to 3rd ultrasound	0.01 (−.02 to 0.04)	0.02 (−.01 to 0.06)	−0.02 (−0.06 to 0.02)	0.01 (−0.02 to 0.04)	−.03 (−.07 to 0.02)	0.00 (−.04 to 0.04)	0.01 (−.03 to 0.06)	0.00 (−0.04 to 0.04)	0.01 (−04 to 0.06)
Head circumference[a]									
2nd to 3rd ultrasound	0.06 (−0.04 to 0.16)	0.07 (−0.06 to 0.20)	−.05 (−0.19 to 0.08)	0.03 (−0.07 to 0.14)	−0.07 (−.23 to 0.09)	0.01 (−.14 to 0.15)	0.05 (−.11 to 0.21)	0.10 (−.05 to 0.26)	0.06 (−0.11 to 0.23)
3rd ultrasound to birth	−.12 (−.35 to 0.12)	−0.23 (−0.52 to 0.06)	0.16 (−0.14 to 0.47)	0.05 (−0.19 to 0.29)	−0.07 (−0.44 to 0.30)	−.05 (−0.39 to 0.28)	−0.25 (−0.61 to 0.11)	−0.20 (−.55 to 0.15)	−.31 (−0.69 to 0.08)
Femoral length[a]									
2nd to 3rd ultrasound	0.00 (−.03 to 0.02)	−0.02 (−.04 to 0.01)	−0.02 (−0.05 to 0.00)	0.00 (−.02 to 0.03)	−0.01 (−0.05 to 0.02)	0.00 (−0.03 to 0.03)	0.02 (−0.01 to 0.05)	0.00 (−.04 to 0.03)	0.01 (−0.02 to 0.05)
Size[a]									
0 to 6 months	0.03 (−0.04 to 0.10)	0.03 (−0.05 to 0.11)	−.06 (−0.14 to 0.03)	0.02 (−0.04 to 0.09)	−0.05 (−0.15 to 0.06)	−0.02 (−0.11 to 0.08)	0.00 (−0.11 to 0.10)	−0.08 (−0.18 to 0.02)	−0.02 (−0.13 to 0.09)
6 to 12 months	−0.02 (−.06 to 0.01)	−0.03 (−.07 to 0.01)	−.03 (−0.07 to 0.01)	0.00 (−.03 to 0.03)	−.01 (v.07 to 0.04)	−.01 (−0.06 to 0.03)	−0.02 (−0.07 to 0.03)	−0.02 (−0.07 to 0.03)	0.00 (−0.06 to 0.05)
12 to 24 months	−0.01 (−0.02 to 0.01)	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.01)	0.00 (−0.02 to 0.02)	−0.01 (−.03 to 0.02)	0.01 (−0.02 to 0.03)	0.00 (−0.02 to 0.03)	0.00 (−0.02 to 0.03)	0.01 (−0.01 to 0.04)
24 to 36 months	0.01 (0.00 to 0.02)	0.01 (−0.01 to 0.02)	0.00 (−0.02 to 0.02)	0.00 (−0.01 to 0.01)	0.00 (−0.02 to 0.03)	0.02 (0.00 to 0.04)	0.01 (−.01 to 0.03)	0.01 (−0.01 to 0.03)	0.01 (−.01 to 0.03)
Abdominal circumference[a]									
2nd to 3rd ultrasound	−.11 (−0.23 to 0.02)	−0.08 (−0.24 to 0.08)	0.11 (−0.05 to 0.28)	−0.02 (−0.15 to 0.11)	−.21 (−0.40 to −0.01)	0.04 (−0.14 to 0.22)	0.13 (−.07 to 0.32)	0.07 (−0.12 to 0.26)	0.12 (−0.09 to 0.33)
Weight[b]									

Growth Rate	2,4-Dichlorophenol β (95% CI)	2,5-Dichlorophenol β (95% CI)	Bisphenol A β (95% CI)	Benzophenone-3 β (95% CI)	Triclosan β (95% CI)	Methylparaben β (95% CI)	Ethylparaben β (95% CI)	Propylparaben β (95% CI)	Butylparaben β (95% CI)
2nd to 3rd ultrasound	−1.41 (−3.28 to 0.45)	−.29 (−2.57 to 2.00)	0.75 (−.61 to 3.12)	0.20 (−1.69 to 2.09)	−3.26 (−6.12 to −0.41)	−0.23 (−2.82 to 2.37)	1.35 (.46 to 4.17)	−0.07 (−2.82 to 2.67)	1.80 (−1.22 to 4.81)
3rd ultrasound to birth	2.18 (−.21 to 6.56)	0.21 (−5.16 to 5.58)	−1.84 (−7.41 to 3.72)	1.90 (−2.50 to 6.31)	7.03 (0.33 to 13.7)	5.76 (−.30 to 11.2)	5.81 (−0.76 to 12.4)	7.24 (0.83 to 13.7)	5.09 (−.95 to 12.1)
0 to 6 months	−0.13 (−2.38 to 2.11)	−0.77 (−3.51 to 1.98)	−0.36 (−3.19 to 2.47)	0.78 (−.47 to 3.03)	−.85 (−4.28 to 2.58)	1.34 (−.76 to 4.43)	−1.21 (−.57 to 2.15)	−0.03 (−3.30 to 3.23)	0.25 (−.35 to 3.84)
6 to 12 months	−.85 (−2.14 to 0.45)	−0.69 (−2.28 to 0.90)	1.33 (−0.30 to 2.96)	0.70 (−0.60 to 2.00)	0.05 (−1.93 to 2.04)	0.00 (−1.79 to 1.79)	−0.56 (−2.50 to 1.39)	0.13 (−1.76 to 2.02)	−.26 (−2.33 to 1.82)
12 to 24 months	0.31 (−0.48 to 1.09)	0.36 (−.60 to 1.32)	0.52 (−0.46 to 1.51)	−0.17 (−0.96 to 0.61)	0.53 (−.67 to 1.72)	0.97 (−0.11 to 2.04)	0.73 (−.45 to 1.90)	0.87 (−0.27 to 2.00)	0.97 (−0.28 to 2.22)
24 to 36 months	0.94 (0.12 to 1.75)	0.93 (−.07 to 1.93)	0.15 (−.89 to 1.18)	−0.55 (−1.37 to 0.27)	0.71 (−.54 to 1.97)	1.38 (0.25 to 2.50)	1.27 (0.05 to 2.49)	1.03 (−0.16 to 2.22)	1.29 (−.02 to 2.60)

Models for prenatal growth were adjusted for maternal and paternal height, pre-pregnancy weight, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, gestational age at measurement, and parity. The model for head circumference at birth was additionally adjusted for the number of days between birth and the assessment of head circumference. Models for postnatal growth were adjusted for maternal and paternal height, pre-pregnancy weight, maternal active and passive smoking during pregnancy, maternal education level, recruitment center, breastfeeding duration, and parity.

[a] β corresponds to changes in growth rate (mm/week) estimated for each increase by 1 IQR of ln-transformed phenol standardized concentrations.

[b] β corresponds to changes in growth rate (g/week) estimated for each increase by 1 IQR of ln-transformed phenol standardized concentrations.