Environmental Research 122 (2013) 38–44

Contents lists available at SciVerse ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Urinary concentrations of bisphenol A in an urban minority birth cohort in New York City, prenatal through age 7 years

Lori A. Hoepner [a,b,*], Robin M. Whyatt [a,b], Allan C. Just [a,1], Antonia M. Calafat [c], Frederica P. Perera [a,b], Andrew G. Rundle [a,d]

[a] Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, 722W. 168th St, New York, NY 10032, USA
[b] Columbia Center for Children's Environmental Health, Mailman School of Public Health, Columbia University, 722W. 168th St, New York, NY 10032, USA
[c] National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Hwy, MS F53 Atlanta, GA 30341, USA
[d] Department of Epidemiology, Mailman School of Public Health, Columbia University, 722W. 168th St, New York, NY 10032, USA

ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form
5 December 2012
Accepted 7 December 2012
Available online 8 January 2013

Keywords:
Bisphenol A
Urine
Child
Prenatal
Minority

ABSTRACT

Background: Despite growing concern over potential health effects associated with exposures to the endocrine disruptor, bisphenol A (BPA), insufficient information is available on determinants of BPA concentrations among minority populations in the US.
Objectives: To describe concentrations and predictors of BPA in an inner-city longitudinal birth cohort.
Methods: We analyzed spot urines for total BPA collected during pregnancy and child ages 3, 5, and 7 years from African Americans and Dominicans ($n=568$) enrolled in the Columbia Center for Children's Environmental Health birth cohort and residing in Northern Manhattan and the South Bronx. Adjusting for specific gravity, generalized estimating equations were used to compare BPA concentrations across paired samples and linear regression analyses were used to determine relationships between BPA, season of sample collection, socio-demographic variables and urinary concentrations of phthalate metabolites.
Results: BPA was detected in $\geq 94\%$ of samples. Prenatal concentrations were significantly lower than postnatal concentrations. Geometric means were higher among African Americans compared to Dominicans in prenatal ($p=0.008$), 5 year ($p<0.001$) and 7 year ($p=0.017$) samples. Geometric means at 5 and 7 years were higher ($p=0.021$, $p=0.041$ respectively) for children of mothers never married compared to mothers ever married at enrollment. BPA concentrations were correlated with phthalate metabolite concentrations at prenatal, 3, 5 and 7 years (p-values <0.05). Postnatal BPA concentrations were higher in samples collected during the summer.
Conclusions: This study shows widespread BPA exposure in an inner-city minority population. BPA concentration variations were associated with socio-demographic characteristics and other xenobiotics.

1. Introduction

Bisphenol A (BPA), a xenoestrogenic monomer, was originally investigated for efficacy as a synthetic hormone treatment during the 1930s–1940s. Today BPA is used commercially as a key component in manufacturing polycarbonate plastics and epoxy resins. BPA has applications in everyday consumer products such as baby bottles, toys, dental sealants, eyeglass lenses, reusable water bottles, plastic stretch films, consumer electronics, digital media (CDs, DVDs), automobiles, medical equipment, food and beverage can linings and glass jar tops (Vandenberg et al., 2007, 2010). Approximately 4 million tons of BPA are produced annually (Vandenberg et al., 2010). Global market prices and demand for polycarbonate are on the rise and expected to grow at an average annual rate of 5.8% to 4.9 million tons by 2015 (CMAI, 2010).

This widespread use has resulted in significant exposures (Calafat et al., 2008). Known routes of exposure include dermal and inhalation, but dietary intake is of primary concern (Wilson et al., 2003; Zalko et al., 2011). BPA has been found in fresh and pre-packaged foods, including infant formula in Europe, Asia and the United States (US) (Kuo and Ding, 2004; Noonan et al., 2011; Rudel et al., 2011; Schecter et al., 2010; Vandenberg et al., 2007; Wilson et al., 2007). Results from a recent study of US preschool children ages 23–64 months, suggest that diet contributes 95% of childhood exposure to BPA and that solid food is a significant contributor (Morgan et al., 2011). Human maternal exposure has been quantified in breast milk, serum, plasma, urine, ovarian follicular fluid, amniotic fluid and placental tissue (Ikezuki et al., 2002; Schönfelder et al.,

* Corresponding author at: Department of Environmental Health Sciences, Joseph L. Mailman School of Public Health, Columbia University, 1051 Riverside Drive, Unit 47, New York, NY 10032, USA. Fax: +1 212 543 5684.
E-mail address: lah45@columbia.edu (L.A. Hoepner).
[1] Permanent address: Environmental and Occupational Medicine and Epidemiology Program, Harvard School of Public Health, 401 Park Drive, 3rd Floor East, Boston, MA 02215, USA.

0013-9351/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.envres.2012.12.003

2002; Vandenberg et al., 2007, 2010; Vandentorren et al., 2011). Using data from the 2003–2004 NHANES which includes Mexican American and non-Hispanic Black women, Woodruff et al. (2011) found detectable concentrations of BPA in 96% of pregnant women. The discovery of BPA in human pregnancy fluids and tissues led researchers to determine that conjugated BPA can cross the placenta (Ikezuki et al., 2002; Schönfelder et al., 2002). However, there is also evidence that the use of catheters during delivery may introduce BPA into the mother's body (Vandentorren et al., 2011). The biologic half-life of BPA has long been accepted to be approximately 4 h. To date, there is no conclusive evidence regarding clearance rate of BPA from the developing human fetus or child.

Experimental and preliminary epidemiological studies suggest associations between BPA exposure and numerous adverse health effects, including cardiovascular disease, breast cancer, metabolic disorders, male sexual function, polycystic ovary syndrome, recurrent miscarriages, female adult obesity, endometrial hyperplasia and thyroid effects (Alonso-Magdalena et al., 2010; Crofton, 2008; Hiroi et al., 2004; Lang et al., 2008; Li et al., 2010; Melzer et al., 2010; Matsumoto et al., 2005; Sugiura-Ogasawara et al., 2005; Takeuchi et al., 2004; Vandenberg et al., 2007). A positive association has been shown between BPA exposure and higher estrogenic gene expression in male adults (Melzer et al., 2011).

There is little prior information on prenatal and early childhood exposure to BPA among minority populations in the US. Much of the current prenatal data comes from Asia and Europe (Casas et al., 2011; Ikezuki et al., 2002; Padmanabhan et al., 2008; Schönfelder et al., 2002; Yamada et al., 2002; Ye et al., 2008, 2009). Both the US National Health and Nutritional Examination Survey (NHANES) and the Canadian Health Measures Survey report on BPA concentrations among different ethnic groups but are limited to analyses of BPA in adults and in children ages 6 years and older (Calafat et al., 2008; Health Canada, 2010). Another study limited to girls aged 6 years and older of multiple ethnicities in the US by Wolff and Teitelbaum had detectable concentrations of BPA in 95% of subjects (Teitelbaum et al., 2008; Wolff et al., 2010). In the US, the Children's Total (aggregate) Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study of preschool children in North Carolina and Ohio has published on BPA exposure, but did not analyze data based on race, ethnicity or gender (Wilson, personal communication, 2011).

Additionally, little is known about inter-correlations between BPA concentrations and other chemical exposures that might affect childhood development. While Woodruff et al. performed analyses on groups of chemicals in the same chemical classes from NHANES samples, they did not examine the relationships between phenols and phthalates (Woodruff et al., 2011). There is growing concern regarding effects from mixtures of chemical exposures in the literature (Casals-Casas and Desvergne, 2011; Kavlock et al., 1996; Landrigan et al., 2003).

In this paper we report on BPA concentrations in a minority, low income birth cohort of African American and Dominican mothers and children living in New York City. We also identify associations between BPA concentrations and season of sample collection, socio-demographic characteristics and phthalate metabolites, a family of chemicals shown to be weakly associated with BPA in prior studies (Braun et al., 2011a) and which should be considered for confounding effects when analyzing BPA in health outcomes research.

2. Material and methods

2.1. Study design and population

Participants ($n=568$) were selected from the mothers and newborns longitudinal cohort study of the Columbia Center for Children's Environmental Health (CCCEH) based in Northern Manhattan and the South Bronx, New York (Perera et al., 2003; Whyatt et al., 2003). The mother was selected for our analysis if she had a spot urine sample analyzed for BPA prenatally and her child was selected if he or she had at least one sample analyzed at age 3, 5 or 7 years. For the first 5 years of the CCCEH study, enrolled participants were contacted every 3 months after delivery for questionnaire follow-up and every 6 months thereafter, with biological samples collected from the children at age 3, 5, and 7 years. Biological samples were collected from the children regardless of any prior missed collection intervals. At the time of our analysis, the 7 year old follow-up was not yet complete.

Study protocols for the CCCEH cohort are described elsewhere (Perera et al., 2003; Whyatt et al., 2003). Briefly, the study enrolled pregnant women 18–35 years old who self-identified as either African American or Dominican and had resided in Northern Manhattan or the South Bronx for at least 1 year before pregnancy. Women were excluded at enrollment if they reported that they smoked cigarettes or used other tobacco products during pregnancy, used illicit drugs, had diabetes, hypertension or known HIV, or had their first prenatal visit after the 20th week of gestation. A 45 min baseline questionnaire was administered to the mother by a trained bilingual interviewer during the third trimester of pregnancy and at each follow-up interval (child age 3, 5 and 7 years). Medical records of the mother and infant at delivery were abstracted by the research staff to ascertain birth outcomes.

2.2. Urinary biomarker collection

In the mothers, urine was collected during the third trimester of pregnancy between 1999 and 2006 (mean gestational age: 34.7 weeks; SD: 3.4). In the children, urine was collected concurrent with the follow-up questionnaires between 2001 and 2010. The samples were all spot urine samples collected at varying times of day. The date, but not the exact time of collection, was consistently available. The total (free plus conjugated) BPA urinary concentrations (ng/ml) were measured at the National Center for Environmental Health, Centers for Disease Control and Prevention (CDC). Urine samples were analyzed using online solid-phase extraction coupled to high-performance liquid chromatography, and detected with isotope-dilution tandem mass spectrometry with peak focusing as previously described (Calafat et al., 2008). The assay limit of detection (LOD) was 0.4 ng/ml. For results below LOD, the value of LOD/2 was substituted where applicable, consistent with prior analyses (Whyatt et al., 2003, 2009). Specific gravity, as a measure of urinary dilution, was quantified at room temperature at Columbia University with a handheld refractometer (PAL 10-S, Atago, Bellevue, WA).

The following phthalate metabolites were also measured in the spot urine samples at CDC as previously described (Kato et al., 2005; Silva et al., 2007): mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-benzyl phthalate (MBzP), mono-3-carboxypropyl phthalate (MCPP), mono-*n*-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP) and mono-ethyl phthalate (MEP). The LODs ranged from 0.2 to 1.2 ng/ml for all phthalate metabolites. The value of LOD/2 was assigned to the few phthalate metabolite concentrations below LOD. We multiplied the reported MEP and MBzP concentrations by 0.66 and 0.72, respectively, to correct for the inadequate purity of the analytic standards used (Calafat, personal communication, 2012). Due to a higher rate of non-detectable results, MEHP was dropped from analysis in favor of the other three metabolites of di-2-ethylhexyl-phthalate (DEHP): MECPP, MEHHP and MEOHP.

Study procedures, questionnaires and collection of biological samples were explained to each subject at enrollment and a signed consent, approved by the IRB of Columbia University Medical Center and the CDC, was obtained.

2.3. Statistical analysis

BPA concentrations were natural log-transformed and *z*-scored urinary specific gravity measures were included in regression models as a covariate. Specific gravity values have a very narrow range and cluster tightly around 1.0, which can cause instability in estimating model constants. Specific gravity values were *z*-score transformed, which does not alter the beta coefficients for the other variables in the model, but does stabilize the estimate of the model constant. Means of the log-transformed BPA data were calculated and exponentiated to calculate geometric mean BPA concentrations. Natural log-transformed BPA concentrations at each age interval of collection were compared by generalized estimating equations to account for repeated measures within individuals at different ages. The BPA concentration in a child aged 3 years was used as the referent group due to the consistently higher geometric mean we observed at this age.

To determine Pearson correlations between BPA samples at each collection (i.e. prenatal vs. each child sample; child vs. each later child sample) we used the formula: $BPA_{\text{Specific gravity adjusted/log-transformed}} = LN(BPA_{raw} \times [(\text{mean for age specific gravity} - 1)/(\text{individual specific gravity} - 1)])$ (Hauser et al., 2004). For example, the prenatal BPA was first corrected with prenatal specific gravity in the algorithm and then natural-log transformed.

Socio-demographic predictors of BPA concentrations at each time point were assessed using two separate regression analyses. The first was a series of linear regression models including one socio-demographic predictor variables as well as standardized specific gravity as the correction covariate. The second was a series of linear regression GLM models including season of collection as a categorical model with summer as the reference group. Socio-demographic variables we included were: race/ethnicity classified as African American or Dominican, child's sex, income classified as above or below $20,000 per year, marriage status classified as never or ever married at enrollment, maternal education classified as no high school diploma or high school diploma or higher education level, and breastfeeding status classified as ever or never within 3 months of the child's birth. Season of urine collection was coded using June to August (summer) as the reference group with 3 month units composing Fall (September–November), Winter (December–February) and Spring (March–May) (Wolff et al., 2010). Partial correlation coefficients from linear regression models for the association between log-transformed BPA and log-transformed phthalate metabolites, adjusted for specific gravity (as a covariate), are reported.

We considered results with $p<0.05$ to be statistically significant. All of our analyses were performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population characteristics

Of the 568 participants, we measured BPA concentration in $n=375$ prenatal samples, $n=408$ age 3 year samples, $n=401$ age 5 year samples, and $n=318$ age 7 year samples. Demographic characteristics during the prenatal period are presented in Table 1. There were no significant differences in demographic characteristics for those children with all 3 childhood urine samples analyzed compared to those with fewer than 3 childhood samples.

BPA was detected in 94% of prenatal samples, 98% of 3 year and 5 year samples, and 96% of 7 year samples. BPA concentrations (ng/ml) are presented in Table 2. The geometric mean BPA remained stable in prenatal samples collected between 1999 and 2006 and a temporal trend was not observed (Fig. 1, Supplemental Table S1). Similarly, for each of the follow-up samples collected from 2001 to 2009 (age 3), 2003 to 2010 (age 5) and 2005 to 2010 (age 7) there were no temporal trends in geometric mean BPA concentrations (Supplemental Table S2).

Maternal prenatal BPA concentrations were not correlated with any of the child concentrations (all p-values ≥ 0.40). Among children, only the age 3 and 7 year concentrations were weakly correlated ($r=0.164$, p-value$=0.012$) while the 3 and 5 year concentrations and 5 and 7 year concentrations did not correlate ($p=0.823$, $p=0.079$ respectively). Maternal prenatal BPA concentrations were significantly lower than those of their children at all ages (see Table 2). Child BPA concentrations at age 3 years were significantly higher than repeat samples at ages 5 and 7 years. However, BPA concentrations did not significantly differ at ages 5 and 7 years. When complementary analyses were done in subjects with BPA concentrations at all three postnatal ages ($n=227$) to account for the differing sample sizes at ages 3, 5 and 7 years the correlation and GEE results were similar.

3.2. Socio-demographic predictors of BPA

Table 3 shows BPA concentration by demographic characteristics and season. Adjusting for specific gravity, BPA geometric means concentrations were higher among African American as compared to Dominicans in prenatal ($p=0.008$), 5 year ($p<0.001$) and 7 year ($p=0.017$) samples but not in 3 year samples ($p=0.89$) (Table 3). Geometric means at 5 and 7 years were higher ($p=0.021$, $p=0.041$ respectively) for children of mothers never married at cohort enrollment compared to mothers ever married at cohort enrollment. Comparisons of BPA concentrations by child's sex, maternal education at enrollment, and household income at enrollment did not reveal significant differences at any assessment interval.

3.3. Season of collection predictors of BPA

After adjusting for specific gravity, calendar season of urine collection predicted log-transformed BPA concentration. Geometric means for urine collections during the summer at ages 3,

Table 2
Unadjusted BPA concentrations (ng/ml) in spot urine samples collected from the mother during the 3rd trimester of pregnancy and from the child at ages 3–7 years.

	# > LOD (%)	GM (95%CI)	25%	50%	75%	95%	p-Value[a]
Prenatal	351/375 (94%)	1.8 (1.7, 2.0)	1.0	1.8	3.5	9.0	<0.001
Child age 3	398/408 (98%)	3.7 (3.3, 4.2)	1.8	3.8	7.4	29.7	–
Child age 5	392/401 (98%)	3.2 (2.9, 3.6)	1.7	3.1	6.4	18.3	0.048
Child age 7	306/318 (96%)	2.9 (2.6, 3.3)	1.4	2.7	6.0	19.1	0.001

[a] p-Values for difference in the geometric mean between age groups calculated by GEE analysis of log-transformed BPA using age 3 as the referent group.

Table 1
Subject demographics.

Characteristic [*Categorical: n (%)*]	All subjects ($n=568$)	Prenatal ($n=375$)	3 Year ($n=408$)	5 Year ($n=401$)	7 Year ($n=318$)
Race/Ethnicity					
Dominican	351 (61.8)	244 (65.1)	246 (60.3)	246 (61.3)	176 (55.3)
African American	217 (38.2)	131 (34.9)	162 (39.7)	155 (38.7)	142 (44.7)
Gender of child					
Female	305 (53.7)	202 (53.9)	219 (53.7)	217 (54.1)	168 (52.8)
Male	263 (46.3)	173 (46.1)	189 (46.3)	184 (45.9)	150 (47.2)
Maternal education[a]					
< HS	197 (34.7)	134 (35.7)	147 (36.0)	135 (33.7)	107 (33.6)
Marital status[a]					
Never married	374 (65.8)	252 (67.2)	271 (66.4)	265 (66.1)	214 (67.3)
Household income[a]					
< $20K	385 (67.8)	240 (64.0)	280 (68.6)	276 (68.8)	223 (70.1)
Breastfed[a]					
Ever by 3 months	360 (63.4)	–	251 (61.5)	243 (60.6)	185 (58.2)
[*Continuous: median (IQR)*]					
Median age at urine collection (years)	–	24.7 (8)	3.0 (0.2)	5.0 (0.1)	7.0 (0.1)
Median gestational age at urine collection[a] **(weeks)**	–	39 (1)	–	–	–

[a] Missing from all subjects: maternal education $n=9$, marital status $n=2$, household income $n=39$, breastfed $n=100$, gestational age $n=4$.

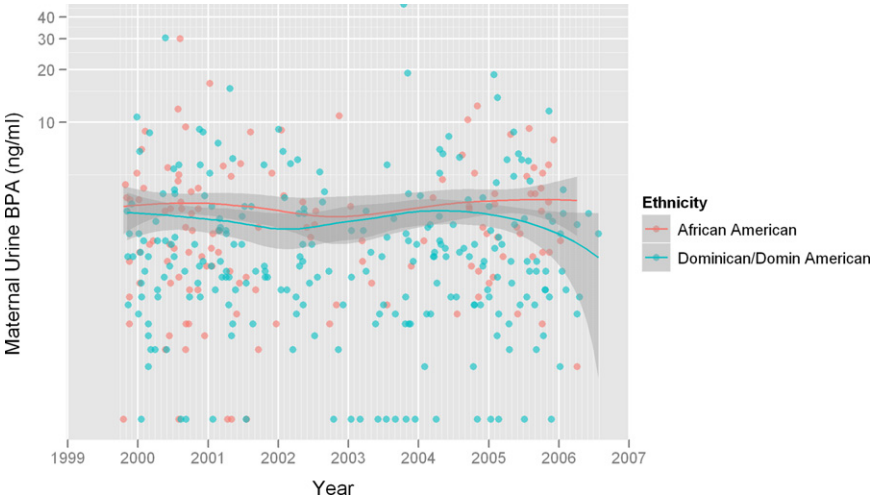

Fig. 1. Temporality of prenatal BPA urinary concentration.

Table 3
Geometric mean urinary BPA concentrations by demographic characteristics and season, within age group.

Prenatal characteristic [GM[95% CI]]	**Prenatal**	**3 Year**	**5 Year**	**7 Year**
Race/Ethnicity				
Dominican[a]	1.6 (1.4, 1.9)	3.4 (2.9, 4.0)	2.8 (2.4, 3.1)	2.3 (2.0, 2.8)
African American	2.3 (1.9, 2.7)*	4.1 (3.4, 4.8)	3.9 (3.4, 4.6)**	3.6 (3.0, 4.4)*
Gender of child				
Female[a]	1.8 (1.5, 2.1)	3.5 (3.0, 4.2)	3.2 (2.8, 3.7)	2.7 (2.3, 3.3)
Male	1.9 (1.6, 2.2)	3.8 (3.2, 4.5)	3.1 (2.7, 3.6)	3.0 (2.5, 3.6)
Maternal education				
< HS[a]	1.9 (1.6, 2.2)	3.5 (3.0, 4.2)	3.3 (2.8, 3.9)	2.9 (2.3, 3.6)
HS+	1.8 (1.6, 2.1)	3.7 (3.2, 4.3)	3.1 (2.7, 3.5)	2.8 (2.4, 3.3)
Marital status				
Ever married[a]	1.7 (1.4, 1.9)	4.1 (3.3, 5.0)	2.5 (2.1, 3.0)	2.3 (1.8, 2.8)
Never married	1.9 (1.7, 2.2)	3.4 (3.0, 4.0)	3.5 (3.2, 4.0)*	3.2 (2.7, 3.7)*
Household income				
< $20K[a]	1.8 (1.5, 2.0)	3.6 (3.2, 4.2)	3.3 (2.9, 3.7)	2.9 (2.5, 3.3)
> $20K	2.1 (1.7, 2.5)	3.9 (3.2, 4.9)	3.0 (2.4, 3.7)	2.8 (2.2, 3.7)
Season of collection				
Summer[a]	2.1 (1.7, 2.5)	5.1 (4.3, 6.0)	4.0 (3.4, 4.6)	4.1 (3.4, 4.9)
Fall	1.7 (1.4, 2.0)	3.4 (2.9, 4.0)**	2.9 (2.5, 3.3)*	3.0 (2.5, 3.6)*
Winter	1.8 (1.5, 2.1)	3.1 (2.6, 3.7)**	2.9 (2.5, 3.4)*	2.3 (1.9, 2.8)**
Spring	1.8 (1.6, 2.2)	3.2 (2.8, 3.7)**	3.0 (2.7, 3.4)*	2.2 (1.9, 2.7)**

p-Values for differences in geometric mean calculated using GLM analysis of ln-transformed BPA and controlling for specific gravity.

[a] Reference group.

* $p < 0.05$.

** $p \leq 0.001$.

5 and 7 years were consistently higher than those collected in all other seasons (*p*-values range: < 0.001–0.034) (Table 3). When the non-summer seasons were collapsed into a single category, regression analyses showed that BPA concentrations in samples collected in summer months remained significantly higher than concentrations in samples collected in non-summer months: 3 years: β: 0.4 ng/ml, CI: (0.65, 0.25), $p < 0.001$; 5 years: β: 0.30 ng/ml, CI: (0.50, 0.11), $p = 0.002$; 7 years: β: 0.50 ng/ml, CI: (0.72, 0.29), $p < 0.001$.

3.4. Phthalate correlations

Table 4 presents partial correlation coefficients for natural log-transformed BPA compared to natural log-transformed urinary metabolites of phthalates after adjustment for specific gravity. Prenatal BPA concentrations were weakly but significantly correlated with phthalate metabolite concentrations after adjusting for specific gravity. Similar to the prenatal findings, childhood BPA concentrations were weakly but significantly correlated with all urinary phthalate metabolite concentrations after adjusting for specific gravity at ages 3, 5 and 7 years. The highest correlations were with the DEHP metabolites at age 3 years.

4. Discussion

Results show BPA to be a pervasive contaminant with 94% or higher detection rates in this study population of inner-city mothers and children. We found that geometric means for maternal prenatal BPA concentrations were significantly lower than paired children's postnatal concentrations. BPA in pregnant women may be temporarily diverted from the excretory process due to transfer across the placenta. Human placenta does not act as a barrier to BPA (Schönfelder et al., 2002). Studies of radiolabeled-BPA in pregnant CD1 mice determined that after 24 h, only 6% of BPA was excreted in urine while a disaccharide conjugate of BPA accounted for 60%, 20% and 10% of radioactivity in placenta, amniotic fluid and fetuses, respectively (Zalko et al., 2003).

Table 4
Correlations of Ln-transformed urinary BPA and phthalate metabolites adjusted for specific gravity.

Biomarkers [*r* (*p*-value)]	Prenatal ($n=362$)	3 Year ($n=346$)	5 Year ($n=337$)	7 Year ($n=314$)
DEHP metabolites				
MEHHP	0.208 (<0.001)	0.304 (<0.001)	0.287 (<0.001)	0.182 (0.001)
MECPP	0.188 (<0.001)	0.344 (<0.001)	0.294 (<0.001)	0.157 (0.005)
MEOHP	0.239 (<0.001)	0.308 (<0.001)	0.295 (<0.001)	0.189 (0.001)
Non-DEHP metabolites				
MBZP	0.191 (<0.001)	0.135 (0.012)	0.154 (0.005)	0.131 (0.020)
MCPP	0.224 (<0.001)	0.288 (<0.001)	0.255 (<0.001)	0.153 (0.007)
MnBP	0.267 (<0.001)	0.267 (<0.001)	0.300 (<0.001)	0.261 (<0.001)
MIBP	0.220 (<0.001)	0.234 (<0.001)	0.269 (<0.001)	0.272 (<0.001)
MEP	0.169 (0.001)	0.159 (0.003)	0.144 (0.008)	0.262 (<0.001)

In humans, placenta has only a synctiotrophoblast monolayer separating the maternal and fetal blood vessels as opposed to the mouse placenta which has three layers. Early in pregnancy, amniotic fluid is comparable to maternal or fetal plasma and may be composed of secretions from the umbilical cord, placental membrane and developing epithelium (Beall et al., 2007). Towards the end of pregnancy, an estimated 10 ml/day of amniotic fluid cross into the maternal circulation via the transmembranous pathway (Beall et al., 2007; Underwood et al., 2005). While the literature has yet to describe it in humans, there remains the possibility that pregnant women may have less BPA in their urine due to transfer across the placenta. Alternatively, lower total BPA urinary concentration in the mothers than in their children may be related to the fact that diet is the main pathway of exposure to BPA (Morgan et al., 2011) and children eat more relative to body weight than adults (US EPA, 2011). Such a trend has been observed for other non-persistent chemicals to which diet is the main source of exposure (CDC, 2012). In contrast, some animal pharmacokinetic evidence suggests that total daily human exposure to BPA cannot be from diet alone and is much higher than previously understood (Taylor et al., 2011).

Our unadjusted geometric means are similar to data from two other studies comparing prenatal and childhood BPA concentrations. A European Spanish cohort of mothers and their 4 year old children, reported lower urinary concentrations of BPA in spot urine samples collected prenatally from the mothers as compared to their children (2.2 ng/ml, $n=120$ vs. 4.2 ng/ml, $n=30$, $p<0.05$, respective medians) (Casas et al., 2011). In a Cincinnati, Ohio study of 240 mother–child dyad spot urine samples, the mean prenatal BPA concentration was 2.0 μg/L and the childhood mean of ages 1, 2, and 3 years was 4.1 μg/L, while the median age 3 year BPA concentration was 2.6 μg/L (Braun et al., 2011b).

Our overall prenatal BPA geometric mean of 1.8 ng/ml is in accordance with findings from other investigators. In a US study looking at repeated measures of BPA in 249 women both prenatally and postnatally, Braun et al. (2011b) found median BPA concentrations of 1.8 μg/L (16 weeks), 1.7 μg/L (26 weeks) and 1.2 μg/L (at birth). Using NHANES data, Woodruff et al. (2011) reported a lower geometric mean in pregnant women compared to non-pregnant women (2.53 μg/L, $n=86$ vs. 2.89 μg/L, $n=489$, respectively). After adjusting for creatinine and socio-demographics (age, race/ethnicity, education, smoking, parity, BMI, albumin, duration of fasting prior to sample collection) the BPA concentration disparity increased between pregnant women (1.63 μg/L, $n=72$) and non-pregnant women (2.83 μg/L, $n=371$) (Woodruff et al., 2011).

Due to the metabolic characteristics of pregnant women and young children, we controlled for urinary specific gravity as opposed to creatinine in our regression and correlation analyses and this could result in some differences across studies. Renal clearance of creatinine is directly proportional to and dependent on glomerular filtration, such that changes in renal clearance that commonly occur during pregnancy could also cause changes in creatinine concentrations (Jatlow et al., 2003; Mahalingaiah et al., 2008). Creatinine, a product of muscle metabolism, relies on the liver and the kidney which are still maturing in children. Childhood levels of creatinine tend to be lower with more variability over time compared to levels in non-elderly adults. Creatinine comparisons in the NHANES III (1988–1994) study describe a mean of 102.1 mg/dL in children ages 6–11 years, whereas adult means were consistently higher by decade of age from 20 to 49 years (Barr et al., 2005). Little is known about BPA renal clearance during human pregnancy. Specific gravity is a unit-less ratio of the density of urine to the density of water, dependent on fluid intake, renal perfusion and renal function and thus should be less influenced by muscle mass and muscle retention.

At age 3 years, the children in our study had significantly higher BPA concentrations than they did at follow-up ages 5 and 7 years, a difference that may be related to changes in behavior as children age. While young children tend to have greater oral contact with their world than older children and adults, diet should still be considered the primary route of BPA exposure in young children (Reed et al., 1999). It is known that children between the ages of 3 and 6 years eat more relative to body weight than adults (US EPA, 2011). Additionally, children under the age of 6 years tend to have less varied diets (Goldman, 1995). Diet in preschool children may be more dependent on the feeding behaviors of their mothers whereas school-aged children are able to make food choices outside the presence of their mothers. Adult pregnant female eating behaviors are also likely to be different than those of children.

In our study population, African Americans had consistently significantly higher BPA concentrations than Dominican Americans, except among 3 year olds where BPA was elevated for African Americans but not significantly. Additionally we saw higher concentrations among older children of never married mothers compared to older children of ever married mothers. This suggests that BPA concentrations may vary by socioeconomic status. However, we did not see any differences based on household income nor maternal education. In contrast, other studies have found BPA concentration to be negatively associated with income and maternal education (Calafat et al., 2008; Braun et al., 2011b). Little is known about how dietary differences across race/ethnicity and maternal characteristics may affect BPA exposures in pregnancy or childhood. Our results have implications for guiding socio-demographic considerations in future health effects studies of BPA exposures.

We found postnatal BPA concentrations to be higher during the summer months than during the rest of the year. This could be due to different dietary patterns among children during the summer relative to other seasons. It could also be related to diurnal variation in renal clearance of BPA by season. This finding is consistent with previously reported BPA urinary geometric

means in a population of prepubertal girls from three sites in the US, including New York City.

Urinary concentrations of BPA and phthalate metabolites were correlated. These findings are similar to Braun et al. (2011a) in the US but are in contrast to those of Casas et al. (2011) in Spain. Given the ubiquitous presence of both BPA and phthalates in the environment, it is not surprising that they would both be widely detectable in our study population. However, the observation of correlations between BPA concentrations and these phthalate metabolites highlights the complex issue of analyzing the health effects of chemical mixtures in people.

We saw a consistent pattern of BPA exposure for race/ethnicity, marital status and season of collection despite no correlation between BPA concentrations in repeat samples. High variability and poor interclass correlations for BPA concentrations in spot urine samples have been reported by others, however spot urine samples may adequately reflect BPA exposure at the group level (Braun et al., 2011a; Teitelbaum et al., 2008; Ye et al., 2011). If, as expected, the errors in measures of BPA concentrations are non-differential, when BPA concentrations are analyzed as a dependent variable in the regression models, the standard errors for the regression coefficients are expected to be increased, resulting in lower statistical power (Cook and Campbell, 1979). Our significant findings indicate it is likely the differences are greater than we can detect due to the poor reliability of the biomarker. Regardless, our use of single spot urines for BPA analysis provides clear evidence that the children in our study population are exposed to BPA between ages 3 and 7 years. Cumulative exposure effects on health and development beginning prenatally and over a lifetime are a concern which should be investigated further.

Limitations of this study include the use of single spot urines and the lack of recording time of day for urine collection. The data on time of urine collection are not available for the prenatal samples or the age 3 samples, and are only available for a minority of the samples collected at ages 5 and 7. Diurnal variations in urinary BPA concentrations have been reported and it is possible collection time may confound our results. We also did not previously collect any dietary data but we have begun administering food frequency assessments among cohort children at older ages and these may give insight on dietary behaviors in future analyses.

5. Conclusion

We present evidence that BPA exposure is widespread among this cohort of inner-city mothers and children. Variations in BPA concentrations were associated with socio-demographic characteristics and exposures to other xenobiotics. The data presented here suggest specific areas for analytical attention due to confounding and covariate measurement issues. These analyses also demonstrate the critical need for studies to consider the effects of exposures to chemical mixtures and potentially complex interactions among exposures and socio-demographic characteristics. New statistical methods to analyze the effects of chemical mixtures are urgently needed. Further analyses will be undertaken in the cohort to determine the effects of early life exposure to BPA on health outcomes.

Disclosure statement

The authors have no actual or potential financial or nonfinancial conflicts of interest to disclose.

Role of the funding source

Study sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgments

Funding for the study is provided by the National Institute of Environmental Health Sciences (Grant 1RC2ES018784), the US Environmental Protection Agency (Grant RD-83214101), the National Institute of Health (Grant P01ES09600), and the John and Wendy Neu Family Foundation. The authors gratefully acknowledge the technical assistance of Manori Silva, Ella Samandar, Jim Preau, Xiaoyun Ye, Ryan Hennings, Xiaoliu Zhou and Lily Jia for measuring the urinary concentrations of phthalate metabolites and bisphenol A. We are grateful to the participating families who have so generously contributed their time and effort to the study. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2012.12.003.

References

Alonso-Magdalena, P., Vieira, E., Soriano, S., Menes, L., Burks, D., Quesada, I., Nadal, A., 2010. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ. Health Perspect. 118 (9), 1243–1250.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalaz, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the US population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113 (2), 192–200.

Beall, M.H., van den Wijngaard, J.P.H.M., van Gemert, M.J.C., Ross, M.G., 2007. Amniotic fluid water dynamics. Placenta 28, 816–823.

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Bernert, J.T., Ye, X., Silva, M.J., et al., 2011a. Variability and predictors of urinary bisphenol A concentrations during pregnancy. Environ. Health Perspect. 119 (1), 131–137.

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Yolton, K., Ye, X., Dietrich, K.N., et al., 2011b. Impact of early-life bisphenol A exposure on behavior and executive function in children. Pediatrics 128 (5), 873–882.

Calafat, A.M., Ye, X., Wong, L., Reidy, J.A., Needham, L.L., 2008. Exposure of the US population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. Environ. Health Perspect. 116 (1), 39–44.

Casals-Casas, C., Desvergne, B., 2011. Endocrine disruptors: from endocrine to metabolic disruption. Annu. Rev. Physiol. 73, 135–162.

Casas, L., Fernandez, M.F., Llop, S., Guxens, M., Ballester, F., Olea, N., et al., 2011. Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. Environ. Int. 37, 858–866.

C.D.C. (Centers for Disease Control and Prevention),. 2012. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, February 2012. Available at: 〈http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Feb2012.pdf〉 (accessed 26.03.12).

Chemical Market Associates, Inc.,. 2010. CMAI Completes 2011 World Polycarbonate & ABS Analysis. Available at: 〈http://www.cmaiglobal.com/Marketing/News/WPCABSA2011.pdf〉 (accessed 31.12.10).

Cook, T.D., Campbell, D.T., 1979. Quasi-Experimentation: Design and Analysis Issues for Field Settings. Houghton Mifflin Company, Boston, pp. 42–43.

Crofton, K.M., 2008. Thyroid disrupting chemicals: mechanisms and mixtures. Int. J. Androl. 31, 209–223.

Goldman, L.R., 1995. Children—unique and vulnerable. Environmental risks facing children and recommendations for response. Environ. Health Perspect. 103 (Suppl. 6), 13–18.

Hauser, R., Meeker, J.D., Park, S., Silva, M.J., Calafat, A., 2004. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. Environ. Health Perspect. 112 (17), 1734–1740.

Health Canada,. 2010. Report on Human Biomonitoring of Environmental Chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 1 (2007–2009). Available at: 〈http://www.hc-sc.gc.ca/ewh-semt/alt_formats/

hecs-sesc/pdf/pubs/contaminants/chms-ecms/report-rapport-eng.pdf〉 (accessed 17.06.11).
Hiroi, H., Tsutsumi, O., Takeuchi, T., Momoeda, M., Ikezuki, Y., Okamura, A., et al., 2004. Differences in serum bisphenol A concentrations in premenopausal normal women and women with endometrial hyperplasia. Endocr. J. 51 (6), 595–600.
Ikezuki, Y., Tsutsumi, O., Takai, Y., Kamei, Y., Taketani, Y., 2002. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum. Reprod. 17 (11), 2839–2841.
Jatlow, P., McKee, S., O'Malley, S.S., 2003. Correction of urine cotinine concentrations for creatinine excretions: is it useful? Clin. Chem. 49 (11), 1932–1934.
Kavlock, R.J., Daston, G.P., DeRosa, C., Fenner-Crisp, P., Gray, L.E., Kaattari, S., et al., 1996. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the US EPA-sponsored workshop. Environ. Health Perspect. 104 (Suppl. 4), 715–740.
Kato, K., Silva, M.J., Needham, L.L., Calafat, A.M., 2005. Determination of 16 phthalate metabolites in urine using automated sample preparation and on-line preconcentration/high-performance liquid chromatography/tandem mass spectrometry. Anal. Chem 77 (9), 2985–2991.
Kuo, H., Ding, W., 2004. Trace determination of bisphenol A and phytoestrogens in infant formula powders by gas chromatography-mass spectrometry. J. Chromatogr. A 1027, 67–74.
Landrigan, P., Garg, A., Droller, D.B.J., 2003. Assessing the effects of endocrine disruptors in the National Children's Study. Environ. Health Perspect. 111 (13), 1678–1682.
Lang, I.A., Galloway, T.S., Scarlett, A., Henley, W.E., Depledge, M., Wallace, R.B., Melzer, D., 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. J. Amer. Med. Assoc. 300 (11), 1303–1310.
Li, D., Zhou, Z., Qing, D., He, Y., Wu, T., Miao, M., et al., 2010. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. Hum. Reprod. 25 (2), 519–527.
Mahalingaiah, S., Meeker, J.D., Pearson, K.R., Calafat, A.M., Ye, X., Petrozza, J., et al., 2008. Temporal variability and predictors of urinary bisphenol A concentrations in men and women. Environ. Health Perspect. 116 (2), 173–178.
Matsumoto, H., Adachi, S., Suzuki, Y., 2005. Bisphenol A in ambient air particulates responsible for the proliferation of MCF-7 human breast cancer cells and its concentration changes over 6 months. Arch. Environ. Contam. Toxicol. 48, 459–466.
Melzer, D., Harries, L., Cipelli, R., Henley, W., Money, C., McCormack, P., et al., 2011. Bisphenol A exposure is associated with in vivo estrogenic gene expression in adults. Environ. Health Perspect. 119 (12), 1788–1793.
Melzer, D., Rice, N.E., Lewis, C., Henley, W.E., Galloway, T.S., 2010. Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. PLoS One 5 (1), e8673.
Morgan, M.K., Jones, P.A., Calafat, A.M., Ye, X., Croghan, C.W., Chang, J.C., et al., 2011. Assessing the quantitative relationships between preschool children's exposures to bisphenol A by route and urinary biomonitoring. Environ. Sci. Technol. 45 (12), 5309–5316.
Noonan, G.O., Ackerman, L.K., Begley, T.H., 2011. Concentration of bisphenol A in highly consumed canned foods on the US market. J. Agric. Food Chem. 59 (13), 7178–7185.
Padmanabhan, V., Siefert, K., Ransom, S., Johnson, T., Pinkerton, J., Anderson, L., et al., 2008. Maternalbisphenol-A levels at delivery: a looming problem? J. Perinatol. 28, 258–263.
Perera, F.P., Rauh, V., Tsai, W., Kinney, P., Camann, D., Barr, D., et al., 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ. Health Perspect. 111 (2), 201–205.
Reed, K.J., Jimenez, M., Freeman, N.C.G., Lioy, P.J., 1999. Quantification of children's hand and mouthing activities through a videotaping methodology. JEAEE 9, 513–520.
Rudel, A.R., Gray, J.M., Engel, C.L., Rawsthorne, T.W., Dodson, R.E., Ackerman, J.M., et al., 2011. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalateexposure: findings from a dietary intervention. Environ. Health Perspect. 119 (7), 914–920.
Schecter, A., Malik, N., Haffner, D., Smith, S., Harris, T.R., Paepke, O., 2010. Bisphenol A (BPA) in US food. Environ. Sci. Technol. 44 (24), 9425–9430.
Schönfelder, G., Wittfoht, W., Hopp, H., Talsness, C.E., Paul, M., Chahoud, I., 2002. Parent bisphenol A accumulation in the human maternal–fetal–placental unit. Environ. Health Perspect. 110 (11), A703–A707.
Silva, M.J., Samandar, E., Preau, J.L., Reidy, J.A., Needham, L.L., Calafat, A.M., 2007. Quantification of 22 phthalate metabolites in human urine. J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci. 860, 106–112.
Sugiura-Ogasawara, M., Ozaki, Y., Sonta, S., Makino, T., Suzumori, K., 2005. Exposure to bisphenol A is associated with recurrent miscarriage. Hum. Reprod. 20 (8), 2325–2329.
Takeuchi, T., Tsutsumi, O., Ikezuki, Y., Takai, Y., Taketani, Y., 2004. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal woman and women with ovarian dysfunction. Endocr. J. 51 (2), 165–169.
Taylor, J.A., vom Saal, F.S., Welshons, W.V., Drury, B., Rottinghaus, G., Hunt, P.A., et al., 2011. Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. Environ. Health Perspect. 119 (4), 422–430.
Teitelbaum, S.L., Britton, J.A., Calafat, A.M., Ye, X., Silva, M.J., Reidy, J.A., et al., 2008. Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. Environ. Res. 106, 57–269.
Underwood, M.A., Gilbert, W.M., Sherman, M.P., 2005. Amniotic fluid: not just fetal urine anymore. J. Perinatol. 25, 341–348.
U.S. EPA (U.S. Environmental Protection Agency), 2011. Exposure Factors Handbook 2011 edition (final). EPA/600/R-09/052F. Available at: 〈http://www.epa.gov/ncea/efh/pdfs/efh- complete.pdf〉 (accessed 04.01.12).
Vandenberg, L.N., Chahoud, I., Heindel, J.J., Padmanabhan, V., Paumgartten, F.J.R., Schoenfelder, G., 2010. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environ. Health Perspect. 118 (8), 1055–1070.
Vandenberg, L.N., Hauser, R., Marcus, M., Olea, N., Welshons, W.V., 2007. Human exposure to bisphenol A (BPA). Reprod. Toxicol. 24, 139–177.
Vandentorren, S., Zenan, F., Morin, L., Sarter, H., Bidondo, M., Oleko, A., et al., 2011. Bisphenol-A and phthalates contamination of urine samples by catheters in the Elfe pilot study: implications for large-scale biomonitoring studies. Environ. Res. 111 (6), 761–764.
Wilson, N.K., Chuang, J.C., Lyu, C., Menton, R., Morgan, M.K., 2003. Aggregate exposures of nine preschool children to persistent organic pollutants at day care and at home. JEAEE 13 (3), 187–202.
Wilson, N.K., Chuang, J.C., Morgan, M.K., Lordo, R.A., Sheldon, L.S., 2007. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. Environ. Res. 103, 9–20.
Wolff, M.S., Teitelbaum, S.L., Pinney, S.M., Windham, G., Liao, L., Biro, F., et al., 2010. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates and phenols and pubertal stages in girls. Environ. Health Perspect. 118 (7), 1039–1046.
Woodruff, T.J., Zota, A.R., Schwartz, J.M., 2011. Environmental chemicals in pregnant women in the US: NHANES 2003–2004. Environ. Health Perspect. 119 (6), 878–885.
Whyatt, R.W., Barr, D.B., Camann, D.E., Kinney, P.L., Barr, J.R., Andrews, H.F., et al., 2003. Contemporary-use pesticides in personal air samples during pregnancy and blood samples at delivery among urban minority mothers and newborns. Environ. Health Perspect. 111 (5), 749–756.
Whyatt, R.W., Adibi, J.J., Calafat, A.M., Camann, D.E., Rauh, V., Bhat, H.K., et al., 2009. Prenatal di(2-ethylhexyl)phthalate exposure and length of gestation among an inner-city cohort. Pediatrics 124, e1213–e1220.
Yamada, H., Furuta, I., Kato, E.H., Kataoka, S., Usuki, Y., Kobashi, G., et al., 2002. Maternal serum and amniotic fluid bisphenol A concentrations in the early second trimester. Reprod. Toxicol. 16, 735–739.
Ye, X., Wong, L., Bishop, A.M., Calafat, A.M., 2011. Variability of urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour concentrations. Environ. Health Perspect. 119 (7), 983–988.
Ye, X., Pierik, F.H., Angerer, J., Meltzer, H.M., Jaddoe, V.W.V., Tiemerier, H., et al., 2009. Levels of metabolites of oganophosphate pesticides, phthalates, and bisphenol A in pooled urine specimens from pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa). Int. J. Hyg. Environ. Health 212, 481–491.
Ye, X., Pierik, F.H., Hauser, R., Duty, S., Angerer, J., Park, M.M., et al., 2008. Urinary metabolite concentrations of organophosphorus pesticides bisphenol A, and phthalates among pregnant women in Rotterdam, the Netherlands: the Generation R study. Environ. Res. 108, 260–267.
Zalko, D., Jacques, C., Duplan, H., Bruel, S., Perdu, E., 2011. Viable skin efficiently absorbs and metabolizes bisphenol A. Chemosphere 82 (3), 424–430.
Zalko, D., Soto, A.M., Dolo, L., Dorio, C., Rathahao, E., Debrauwer, L., et al., 2003. Biotransformations of bisphenol A in a mammalian model: answers and new questions raised by low-dose metabolic fate studies in pregnant CD1 mice. Environ. Health Perspect 111 (3), 309–319.