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Bisphenol A concentrations in maternal breast milk and infant urine

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Abstract

Purpose—The present report describes the distribution of breast milk and urinary free and total bisphenol A (BPA) concentrations, from 27 post-partum women and their 31 infants, and explores the influence of age, sex, and nutritional source on infant BPA urinary concentration.

Methods—Both free (unconjugated) and total (free plus conjugated) BPA concentrations from women's breast milk samples and infants' urine samples were measured by online solid-phase extraction coupled to high-performance liquid chromatography–isotope dilution tandem mass spectrometry. Descriptive statistics and non-parametric tests of group comparisons were conducted.

Results—Total BPA was detected in 93% of urine samples in this healthy infant population aged 3–15 months who were without known environmental exposure to BPA (interquartile range [IQR]=1.2 – 4.4 µg/L). Similarly, 75% of the mothers' breast milk samples had detectable concentrations of total BPA (IQR=0.4 – 1.4 µg/L). The magnitude and frequency of detection of free BPA in the children's urine and the mothers' breast milk were much lower than the total concentrations.

Conclusions—Total BPA was detected in 93% of this healthy infant population aged 3–15 months who are without known environmental exposure to BPA. Neither free nor total BPA urinary concentrations differed significantly by infant's sex or by nutritional source (breast milk and/or formula) while age group was of borderline significance. There were no significant

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correlations between free or total BPA concentrations in mothers' breast milk and their infants' urine.

Keywords

Bisphenol A; breast milk; urine; infant; exposure

Introduction

Bisphenol A (BPA) has been used in the manufacturing of polycarbonate plastics and epoxy resins since the 1950s (National Toxicology Program [NTP] 2008). Polycarbonate plastics are found in products such as refillable drinking containers, plastic utensils, and safety equipment; epoxy resins can be found in dental sealants and in the linings of metal cans (NTP 2008). Welshons et al. (2006) review several studies exploring pathways through which BPA can initiate cellular responses in certain tissues at very low doses. Low level exposures during vulnerable periods such as fetal and neonatal development may be of particular concern (Welshons et al. 2006). Key findings from a recent review of prenatal exposures to BPA on developmental toxicity include effects on: (i) offspring viability in the higher range of doses tested; (ii) sex-differentiation of exploratory and affective behavior at lower doses; (iii) immune hyperresponsiveness at lower doses; and (iv) gender-differentiated morphology (Golub et al. 2010). Epidemiologic studies on the effects of prenatal exposure to BPA are limited, with reported effects on behavior and executive function in children (Braun et al. 2011a) and shortened anogenital distance in male offspring (Chevrier et al. 2012; Miao et al. 2011), and two studies finding no effects on length of gestation or birth weight (Padmanabhan et al. 2008; Wolff et al. 2008) and one reporting an inverted U-shape with birth weight and positive association with head circumference (Philippat et al. 2012).

BPA is rapidly metabolized in the liver and excreted in the urine mainly as a glucuronide conjugate with a half-life of less than six hours (Völkel et al. 2002). Total BPA (free plus conjugated) has been detected in 93% and 91% of urine samples from nationally representative populations in both the United States (geometric mean (95% CI) = 2.6 (2.4–2.9) and Canada (geometric mean (95% CI) = 1.2 (1.1–1.2), respectively (Calafat et al. 2008; Bushnik et al. 2010). U.S. children 6–11 years of age had higher urinary concentrations of total BPA than adolescents and adults while females had higher concentrations than males (Calafat et al. 2008). However Canadian teens had higher total BPA concentrations than children 6–11 years of age and males had higher concentrations than females (Bushnik et al. 2010; Lakind et al. 2012). To date, only two studies have reported infant urinary concentrations of BPA (Calafat et al. 2009; Völkel et al. 2011).

Dietary ingestion of free BPA likely accounts for the major route of exposure for the general population, with infants and children shown to have the highest estimated daily intake of BPA per body weight (NTP 2008; Environment Canada and Health Canada 2008; World Health Organization [WHO] 2010). A WHO Expert Meeting has concluded the following: breast fed infants between 0–6 months of age consume on average 0.3 µg/kg body weight BPA daily; infants receiving canned liquid formula from bottles made with polycarbonate plastics consume on average 2.4 µg/kg body weight, whereas infants receiving canned liquid

formula from polycarbonate-free bottles consume a mean of 0.5 µg/kg body weight; and adults consume on average 1.4 µg/kg body weight under the highest exposure scenario (WHO 2010). Several studies have measured BPA in the breast milk of healthy women (Otaka et al. 2003; Sun et al. 2004; Ye et al. 2006; Kuruto-Niwa et al. 2007; Ye et al. 2008; Yi et al. 2010). One study found that free BPA concentrations in breast milk obtained from lactating women ranged from less than the limit of detection [LOD] (0.3 µg/L) to 6.3 µg/L with a median of 0.4 µg/L and total BPA ranging from <LOD to 7.3 µg/L with a median of 1.1 µg/L (Ye et al. 2006).

The present report describes breast milk and urinary free and total BPA concentrations from 27 post-partum women and their 31 infants, respectively, who participated in a larger study on environmental exposures and reproductive health. The objective was to determine if ingestion of breast milk was correlated with BPA exposure in infants by comparing BPA concentrations in mothers' breast milk with those in their infants' urine.

Methods

Data were collected as part of the ongoing Environment and Reproductive Health (EARtH) Study conducted at the Massachusetts General Hospital (MGH) and Harvard School of Public Health (HSPH). In the EARtH study, men and women were recruited from the Fertility Center at MGH and a convenience sample of participants who had healthy babies between 3 and 18 months old were contacted and asked to participate in this pilot study. All participants gave their informed consent prior to being included in the study. Twenty seven women and their infants (N = 31) were recruited between November 2006 and August 2008. The women filled out a questionnaire on demographic characteristics and medical history. IRB approval was obtained from MGH, HSPH, the Centers for Disease Control and Prevention (CDC), Health Canada, and Simmons College.

Infant urine and maternal breast milk were collected on the same day from mother-infant pairs. The breast milk was collected at home before the study visit or was obtained during the visit. The mother was instructed to clean her hands and nipple with purified water and gauze provided to her by the study personnel. A breast milk specimen was either hand expressed or obtained using a breast pump after the infant had been fed. Two tablespoons of milk were requested and dispensed into a storage container. The containers were taken from the Harmony Breast Pump kit (manual, single pump) by Madela Inc. (McHenry, IL) which is made of polypropylene and not known to contain BPA. The breast milk samples brought in from home remained on ice during transport until processing. Prior to the visit, mothers were provided with non-gel disposable diapers (Tushies) to use for urine collection. The diaper brand is made with non-chlorine bleached woodpulp blended with absorbent cotton. The time of urine collection was not recorded. Instead, the mother was asked to place the diaper on her infant during a regular diaper change before the study visit. The diaper was either removed by the mother and brought to the visit in a ziplock bag kept on ice packs or was removed during the visit. Urine was not stored at room temperature but kept on ice until processed. After urine collection, the wet part of the diaper was cut out and placed into a syringe to express the urine from the diaper. The syringe had a polypropylene barrel and polyethylene plunger. 100% recovery of free and conjugated urinary BPA from the diaper

was assumed. Breast milk and urine were aliquoted and promptly stored at -80°C . The samples analyzed for this pilot study were shipped frozen on dry ice to the CDC laboratory for analysis in September 2008.

Within the laboratory, rigorous quality control measures were used to ensure valid BPA concentrations in both urine and breast milk (Ye et al. 2005; 2006; 2008). The concentrations of free and total (free plus conjugated) BPA in urine and milk were determined using online solid-phase extraction (SPE) coupled to high-performance liquid chromatography (HPLC)–isotope dilution tandem mass spectrometry (MS/MS) (Ye et al. 2005; 2008). Briefly, to estimate the concentrations of total BPA, the conjugates in 100 μL of urine or milk were hydrolyzed by use of β -glucuronidase/sulfatase (H. pomatia; Sigma Chemical Co., St. Louis, MO); this step was omitted for the determination of the concentration of free species. After acidification of the samples, BPA was preconcentrated by online SPE, separated from other chemical components in the milk or urine by reversed-phase HPLC, and detected by MS/MS. The LODs were 0.4 $\mu\text{g/L}$ (urine) and 0.3 $\mu\text{g/L}$ (milk). Two low-concentration and two high-concentration quality control (QC) materials, prepared with pooled human urine or milk spiked with free BPA, were analyzed with the analytical standards, reagent blanks, and study samples. The concentrations of the QCs, averaged to obtain one measurement of high-concentration QC and one of low-concentration QC for each run, were evaluated using standard statistical probability rules (Caudill et al. 2008).

The data were analyzed using SPSS version 16. Descriptive statistics are provided for unadjusted BPA concentration. Breast milk and urinary BPA concentrations were not normally distributed and were right skewed. Log transformation did not improve the normality of distribution so non-parametric tests such as the Spearman correlation, Mann-Whitney U- test and the Kruskal-Wallis tests were performed to compare distributions among groups. Concentrations $<\text{LOD}$ were assigned a value equal to the LOD divided by the square root of two (Hornung and Reed 1990). Statistical significance was set at $P < 0.05$.

Results

There were 15 female and 16 male infants with a mean age of 6.5 months (range 2.3 to 15.1 months). There were 8 (26%) infants younger than 3 months, 14 (45%) were between 3 and 8 months old and 9 (29%) were over 8 months of age. There were four sets of twins. Mothers' mean age was 36 years. Mothers and infants were predominately white (94% and 87% respectively) with only one Asian and one Hispanic mother (Table 1). None of the mothers reported current smoking and only one of the infants was potentially exposed to secondhand smoke. Ten infants were fed exclusively breast milk, 9 were exclusively formula fed and 10 supplemented breast milk feedings with formula feedings. Infants aged 0–4 months were fed exclusively breast milk more often (67%) than those between 4 and 8 months of age (21%) and those older than 8 months (33%). After 8 months of age, switching to formula was more prevalent than before.

Two infants were missing urine samples and 7 mothers were formula feeding their infants at the time of urine collection and could not provide a breast milk sample. The distribution of BPA concentrations are shown in Table 2. Free BPA and total BPA urinary concentrations

were above the limits of detection in 28% and 93% of infants' respectively. Similarly, 20% of the mothers' breast milk samples were above the LOD for free BPA and 75% were above the LOD for total BPA concentrations. Of the 5 infants who consumed breast milk with free BPA concentrations greater than the LOD, only one infant had a detectable free BPA urinary concentration (1.2 µg/L); all 5 infants had measurable total BPA in their urine (ranging from 0.5 – 5.0 µg/L).

Neither free nor total BPA urinary concentration differed significantly by infant's sex, age group or by nutritional source (Table 3). Among the 21 paired mother's breast milk and infant's urine samples, we found no associations between free BPA concentration in the mother's breast milk and free BPA concentration in her infant's urine (Spearman Correlation -0.117, p-value= 0.44) or between total BPA concentrations in the mother's breast milk and total BPA concentration in the infants' urine (Spearman correlation -0.11, p-value = 0.63). Interestingly, the geometric means for free BPA, but not total BPA, in infant urine remained fairly constant and did not vary appreciably across categories (Table 3). There were no significant correlations between free BPA urinary concentration for twin 1 compared to twin 2 (Spearman correlation -0.33; p-value = 0.66) nor between total BPA urinary concentrations for twin 1 compared to twin 2 (Spearman correlation 0.63; p-value= 0.37).

Discussion

Data on urinary concentrations of BPA in infants are very limited. A study of approximately 40 low birth weight infants in neonatal intensive care units in Boston reported a geometric mean of 30.3 (maximum 946) and 1.8 (maximum 17.3) µg/L for total BPA and free BPA, respectively for urine collected with a cotton gauze inserted in the diaper (Calafat et al. 2009), with 8% of the urines having detectable concentrations of free BPA. In a study of 47 infants ages 1 to 5 months who were born term, and urine was collected using a urine bag, the median total BPA was less than 0.45 µg/L and the maximum concentration was 18 µg/L (Völkel et al. 2011). Free BPA was only quantified in 6% of those urine samples. One of those urine samples had a maximum concentration of 16 µg/L free BPA with a corresponding total BPA of 18 µg/L which the authors attributed to contamination (Völkel et al. 2011). In the current study of 29 infants between 2 and 15 months of age the geometric means were 2.3 (maximum 89) and 0.4 (maximum 1.5) µg/L for total and free BPA in urine, respectively. In all of these studies, more than 90% of total BPA was present in conjugated form, indicating that infants at an early age are able to metabolize BPA. Similar to Völkel et al. (2011) we found no statistically significant increase in total BPA urinary concentration by age group, although the geometric mean total BPA in our study was approximately 3 times higher in infants 4 months or older compared to younger infants (p = 0.07).

The geometric mean urinary total BPA concentration in the infants in our study (2.3 µg/L) was similar to a representative sample of children from the United States between the ages of 6 to 11 years (2.48 µg/L) (CDC 2012) and to another sample of 1 year old children (median 3.9 µg/L) in a prospective birth cohort study in the United States (Braun et al. 2011a), was somewhat higher than a national sample of Canadian children age 6–11 (1.3 µg/L) (Bushnik et al. 2010) and somewhat lower than a representative sample of German

children aged 3–5 years (3.5 µg/L) (Becker et al. 2009) and of a group of 81 US preschool children 23 to 64 months of age (median = 5.2 µg/L) for whom diet contributed 95% of the exposure to BPA (Morgan et al. 2011).

We found that 20% (N=5) of breast milk samples had BPA concentrations greater than both the LOD and the limit of quantification (3*LOD). Median total (0.8 µg/L) and free (<LOD) BPA breast milk concentrations were, comparable to those from other studies (Table 4) with the exception of a Korean study which reported a median total BPA concentration of 10.4 µg/L (Yi et al. 2010).

We found no pattern of higher free BPA ratio in breast milk associated with higher free or total BPA urinary concentrations among different infant age groups. The small sample size limited our ability to evaluate the metabolic capacity of these young infants. One woman had free (23.6 µg/L) and total (22.6 µg/L) concentrations of BPA in her breast milk that were more than 3 times higher than the maximum reported by Ye et al. (2006). However, her infant had fairly low (0.5 µg/L) total BPA urinary concentration (and undetectable free concentration). Of interest, another infant in our study had a free urinary BPA concentration of 0.5 µg/L and a total urinary BPA concentration of 89 µg/L which is higher than the 95th percentile concentration reported in NHANES 2007–2008 for children (13.4 µg/L) (CDC 2012). Interesting, the mother had rather low breast milk BPA concentrations (free: < LOD; total: 0.4 µg/L) suggesting that additional non-dietary sources of exposure are important. The only non-dietary exposures that differed in this infant compared to others was the reported use of a pacifier virtually ‘all day’ which is at least twice the amount of hours a day that the other infants’ used a pacifier. Although the soft teat/nipple part of the pacifier that typically enters the mouth does not contain BPA, the hard plastic shield that prevents the infant from swallowing the pacifier may contain BPA depending on the plastic used. It was unknown if the infant mouthed this part of the pacifier. This infant’s age (6.5 months) was at the median age of the rest of the infants. This infant is the only one who was reported to have been exposed to second hand smoke after birth. Secondhand or active smoking has been suggested as a potential source of BPA exposure (Braun et al. 2011b).

BPA urinary concentrations among twin infants were not correlated; however the sample size was quite small. There are currently limited data on urinary BPA concentrations among family members. One study showed that urinary BPA concentrations of male and female partners collected on the same day had a moderate correlation (Spearman correlation= 0.36; p-value= 0.02) (Mahalingaiah et al. 2008) while another found that 11% of the variability in BPA urinary concentrations was explained by family membership (Rudel et al. 2011). In a study of 104 mother-child pairs with children age 6–8 years, total urinary BPA concentration showed low but a significant correlation (Spearman correlation = 0.22; p-value 0.05) (Kasper- Sonnenberg et al. 2012),

There has been some discussion in the literature on toxicokinetics of BPA, especially as it applies to young infants. BPA undergoes first-pass metabolism to produce conjugated species, primarily BPA glucuronide (Völkel et al. 2002), with oxidative metabolism considered to be a minor pathway (Ye et al. 2011). Only two studies have attempted to determine the kinetics of BPA metabolism in humans (Völkel et al. 2002; 2005) and have

concluded that BPA is rapidly glucuronidated, and conjugated BPA is rapidly cleared from blood (Völkel et al. 2002). However, controversy exists about the relevance of these studies (Vandenberg et al. 2010). Other studies suggest that the toxicokinetics of BPA are likely different in fetuses and neonates compared to adults (Edginton and Ritter 2009; Mielke and Gundert-Remy 2009) and have raised the possibility that BPA glucuronide might be deconjugated in utero (Ginsberg and Rice 2009). Therefore, infants less than 3 months of age might not have their detoxifying enzymes such as UDP-glucuronosyl transferase fully developed (Edginton and Ritter 2009; Mielke and Gundert-Remy 2009); however, this has not been confirmed in either our study or that of Völkel et al. (2011).

The lack of variability in concentrations of free BPA in infant urine by infant age from our study may reflect no differences in metabolism of BPA by infant age or may be due to experimental limitations of our study as outlined below, including the fact that the free BPA concentrations were in most part very close to the LOD.

Limitations

In our pilot study, there are several important limitations. Studies have shown that collection and storage of biological specimens may affect biomonitoring results (Ye et al. 2010; Lee and Arbuckle 2009; Calafat and Needham 2009) and field blanks were not collected in our study. Concentrations of free BPA in infant urine must be interpreted with caution because the urine was extracted from a woodpulp and cotton diaper (Ye et al. 2010) and because we can't rule out that contamination of the urine may have occurred (Völkel et al. 2011). Caution should also be used interpreting the calculated averages of free BPA because there were a large percentage of samples with undetectable free BPA concentrations. Additional limitations include the convenience sample strategy and modest sample size.

In the present pilot study, we did not collect information on whether the breast milk specimens were collected at home or in the clinic and if they were hand expressed or collected using a breast pump. We did not verify that the mothers had followed the instructions correctly for hand expressing. Data on whether the breast milk samples were foremilk or hindmilk and on the fasting status or potential nutritional exposure sources to BPA of the mother were also not recorded. It is unknown whether BPA concentrations differ in hindmilk which generally has a higher fat content (Saarela et al. 2005). Also, the infants' age ranged from 3 to 15 months. For the younger infants aged 0–6 months, breast milk or formula would represent the main dietary source of BPA, while for the older infants aged 6–12 months, additional dietary sources of BPA may include ingestion of canned foods (NTP 2008) but we did not collect information on these other sources. In addition, we did not obtain information on the daily activities of these infants (e.g., at home vs. daycare) and these may also be associated with both dietary and non-dietary exposure to BPA. Infants spend more time on the floor and can be exposed through ingestion of non-food items such as dust or dirt or by placing plastic toys in their mouths while playing (NTP 2008).

Conclusion

Total BPA was detected in 93% of this healthy infant population aged 3–15 months who are without known environmental exposure to BPA. There were no significant correlations between free or total BPA concentrations in mothers' breast milk and their infants' urine. In addition, among a small set of twin infants there was no correlation of urinary free or total BPA concentrations among the dyads. Given the concerns with the binding affinity and extraction recovery of the target biomarkers to the material used to collect the infant urine (Ye et al. 2010), alternative collection approaches that do not require such an extraction (e.g., urine bags routinely used in hospitals) may be worth exploring (Lee and Arbuckle 2009). Although care was taken with the handling, transport and storage of the samples, it is still possible that contamination during collection or processing may have occurred or that some conjugated BPA may have reverted back to free BPA due to fluctuating temperatures (Ye et al. 2007).

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Abbreviations

BPA	Bisphenol A
CDC	US Centers for Disease Control and Prevention
GM	geometric mean
HPLC	High performance liquid chromatography
LOD	Limit of detection
MGH	Massachusetts General Hospital
HSPH	Harvard School of Public Health
MS/MS	Tandem mass spectrometry
NTP	National Toxicology Program
QC	quality control

WHO World Health Organization

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Table 1

Demographics of mothers (n=27) and infants (n= 31)

Characteristic	Mean (SD)	N (%)
Age of babies (months)	6.4 (2.9)	
Age of mothers (yrs)	36.5 (3.7)	
Sex of babies		
Female		15 (48)
Male		16 (52)
Race of babies ^a		
White		27 (90)
Other		3 (10)
Race of mothers		
White		25 (94)
Asian		1 (3)
Other		1 (3)
Hispanic		
No		26 (97)
Yes		1 (3)
Multiple Births		
Sets of Twins		4 (25)

Abbreviations: N= number of subjects, SD = standard deviation

^a Race missing on one baby

Table 2

Distribution of Free and Total Bisphenol A Concentrations ($\mu\text{g/L}$) in Infant Urine and Breast milk ^a.

		<u>Percentiles and Summary Statistics</u>					
Unadjusted BPA	N	Detection frequency	25 th	50 th	75 th	95 th	GM(95%CI)
<i>Infant Urine samples</i>							
BPA-total	29	93%	1.2	1.8	4.4	50.9	2.3 (1.5–3.6)
BPA-free	29	28%	<LOD	<LOD	0.5	1.5	<LOD
<i>Breast milk samples</i>							
BPA-total	23	75%	0.4	0.8	1.4	18.8	0.8 (0.5–1.3)
BPA-free	23	20%	<LOD	<LOD	<LOD	19.4	0.4 (<LOD-0.5)

Abbreviations: N= number; SD= standard deviation; Max= maximum; Mean= arithmetic mean; GM= geometric mean; 95%CI= 95% confidence interval; LOD=limit of detection: 0.3 $\mu\text{g/L}$ (breast milk), 0.4 $\mu\text{g/L}$ (urine).

^aBreast milk sample missing for 7 women who fed their infants formula; urine sample missing for 2 infants.

Table 3

Geometric mean (95% confidence interval) free and total urinary BPA ($\mu\text{g/L}$)^a concentration by sex, age group and nutrition source.

		Geometric mean (95% CI)	
	N ^a	Free BPA	Total BPA
Sex			
Female	13	<LOD (<LOD-0.57)	1.99 (0.78–5.1)
Male	16	<LOD (LOD-0.49)	2.57 (1.65–4.0)
P-Value for difference		0.78	0.53
Age			
< 4 months	7	<LOD (<LOD-0.65)	0.96 (0.5–2.0)
4–8 months	13	0.40 (<LOD-0.58)	3.01 (1.3–6.9)
> 8 months	9	<LOD (<LOD-0.52)	3.05 (1.5–6.1)
P-Value for difference		0.52	0.07
Nutrition source			
Breast milk only	10	0.41 (<LOD-0.65)	1.95 (0.52–7.3)
Mixture ^b	10	<LOD (<LOD-0.52)	2.74 (1.7–4.4)
Formula only	9	<LOD (<LOD-0.58)	2.26 (1.3–4.1)
P-Value for difference		0.77	0.31

^a2 infants missing urine samples. LOD (limit of detection) = 0.4 $\mu\text{g/L}$.

^bIncorporating formula feedings as breast milk feedings are weaning off

Table 4**Studies of Bisphenol A in Breast Milk**

Reference	Sample Size	Study Population	Total BPA	Free BPA
Otake et al. (2003)	3	Japanese women	Range: <LOD – 0.70 ng/g Median: 0.65 µg/L	
Sun et al. (2004)	23	Japanese women	Mean: 0.61 ± 0.042 µg/L Median: 0.61 µg/L	
Ye et al. (2006)	20	American women	Mean: 1.9 µg/L Median: 1.1 µg/L	Mean: 1.3 µg/L Median: 0.4 µg/L
Kunuto-Niwa et al. (2007)	101	Japanese women within 3 days of delivery	Mean: 3.41 ± 0.013 µg/L	
Ye et al. (2008)	4	American women	Mean: 1.02 µg/L Median 0.86 µg/L	Mean: 0.80 µg/L Median 0.62 µg/L
Yi et al. (2010)	100	Korean women	Median: 10.4 µg/L	Median: 6.6 µg/L
Mendonca et al. (2012)	23	American women	GM: 0.8 µg/L Median: 0.8 µg/L	GM: 0.4 µg/L Median: <LOD

Abbreviations: GM= geometric mean, LOD limit of detection.