Potential Sources of Bisphenol A in the Neonatal Intensive Care Unit

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KEY WORDS

bisphenol A, exposure, medical devices, nutrition, premature

ABBREVIATIONS

BPA—bisphenol A
BW—body weight
LOD—limit of detection
RfD—reference dose
SG—specific gravity

Dr Duty, Ms Mendonca, Drs Hauser and Ringer, Ms Cullinane, and Ms Faller were responsible for study design; Drs Duty and Hauser, Ms Mendonca, and Dr Meeker were responsible for the analysis and interpretation of data; Dr Duty, Ms Mendonca, Ms Faller, and Ms Cullinane were responsible for data collection; Drs Duty and Hauser were responsible for grant writing; Ms Mendonca and Drs Duty, Hauser, Ringer, Calafat, and Ackerman were responsible for manuscript preparation/editing; and Dr Calafat, Ms X. Ye, Drs Hauser and Duty, Ms Mendonca, and Ms Cullinane were responsible for the development of methods for biomarker collection, and handling, preparation, and methods for analysis of biological samples.

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WHAT'S KNOWN ON THIS SUBJECT: Bisphenol A (BPA) is an environmental endocrine disruptor that can leach from polycarbonate plastics and epoxy resins, leading to widespread exposure. Fetal and early postnatal periods are particularly vulnerable to exposure to BPA.

WHAT THIS STUDY ADDS: This study identified medical devices as a potential source of exposure to BPA among premature infants in the NICU, even when efforts to reduce polycarbonate plastics were taken.

abstract

OBJECTIVES: To determine whether nutritional intake and medical devices are bisphenol A (BPA) exposure sources among premature infants in the NICU.

METHODS: Mothers and their premature infants cared for in the NICU for the past 3 days were recruited for this exposure assessment study. Forty-three mothers contributed 1 nutrition sample (breast milk or formula) to characterize the infant's intake. Two urine samples (before and after feeding) were collected from each of 55 infants. Medical device use was categorized as "low" or "high" based on the number and invasiveness of devices used. BPA urinary concentrations used as a biomarker to estimate BPA exposure were measured by online solid-phase extraction, high performance liquid chromatography, isotope dilution, tandem mass spectrometry. Nonparametric equivalence tests, intraclass correlations, and hierarchical linear mixed-effects models were conducted.

RESULTS: Breast milk and formula samples did not differ in total BPA concentration nor did infants' median urinary concentration of total BPA before or after feedings. However, the median urinary total BPA concentration among infants who required the use of 4 or more medical devices in the past 3 days was significantly higher (36.6 $\mu\text{g/L}$) than among infants who required the use of 0 to 3 devices (13.9 $\mu\text{g/L}$). The calculated BPA exposures are lower than the US Environmental Protection Agency reference dose, but considerably higher (16- to 32-fold) than among infants or children from the general population.

CONCLUSIONS: The number of medical devices used in the past 3 days, but not nutritional intake, was positively associated with exposure to BPA. *Pediatrics* 2013;131:483–489

Bisphenol A (BPA) is a synthetic chemical used in the manufacture of polycarbonate plastics and epoxy resins.¹ Polycarbonate plastics are used in consumer products (eg, refillable drinking containers); epoxy resins are used to line beverage and food cans.¹ Diet is considered the major source of exposure to BPA for the general population. Infants and children have a higher estimated daily intake of BPA than adults.^{1,2} The World Health Organization estimated that the mean (95th percentile) BPA intake for breastfed infants between 0 and 6 months of age was 0.3 $\mu\text{g}/\text{kg}$ body weight (BW) per day (1.3 $\mu\text{g}/\text{kg}$ BW per day), whereas for infants receiving formula from polycarbonate bottles it was 2.4 $\mu\text{g}/\text{kg}$ BW per day (4.5 $\mu\text{g}/\text{kg}$ BW per day).² BPA is rapidly metabolized and excreted in the urine, mainly as a glucuronide conjugate with a half-life of <2 hours.³ The total (free plus conjugated) BPA urinary concentration is a valid biomarker of BPA exposure.⁴ The health effects of free BPA, a weak estrogen, have primarily been studied in animal models, but limited human studies during crucial periods of child development report effects on behavior and executive function in children⁵ and shortened anogenital distance in male offspring.^{6,7} Human breast milk is the preferred source of nutrients for low birth weight premature infants,⁸ because its use significantly reduces the incidence of necrotizing enterocolitis and late-onset sepsis.^{9,10} However, almost 70% of women who deliver prematurely have difficulty supplying sufficient breast milk to meet their infant's needs; supplementation with formula and the use of human milk fortifier are common¹¹ and necessary even as pasteurized donor milk has become available.¹²

Medical devices made from polycarbonate plastic such as intravenous administration sets, stopcocks, syringes, intravascular catheters, urinary catheters,

gastrointestinal tubes, and cardiopulmonary bypass circuits are sources of exposure to BPA.^{13–15} Data on medical devices as sources of BPA exposure to premature infants in NICU settings are scarce.¹⁶ In 41 premature infants in 2 NICUs, total BPA was detected in 100% of urine samples ranging from 1.6 $\mu\text{g}/\text{L}$ to 946 $\mu\text{g}/\text{L}$ (median, 28.6 $\mu\text{g}/\text{L}$).¹⁶ On average, infants undergoing high-intensity medical treatment had urinary BPA concentrations 8.75 times higher than infants undergoing low-intensity treatment.

The current study was conducted to determine if nutritional intake and medical devices were sources of BPA exposure in the NICU. In addition, as far as we are aware, there are no studies of the correlation between BPA concentrations in mothers' breast milk and their infants' urine or of the potential correlation of BPA concentrations among multiple-birth siblings.

METHODS

Sample/Participants

Between November 2009 and March 2010, mother/infant pairs were identified by using a targeted sampling strategy to identify infants with low or high exposure to medical devices. Infants had to spend at least 3 consecutive days in the NICU, and mothers had to be >18 years and able to read and write English. Infants with hepatic or renal failure or genetic abnormalities were excluded. The low-intensity medical device use group included infants who received only nutritional support by bottle-feeding or intermittent gavage via a nasogastric tube or were using nasal oxygen within the preceding 3 days. The high-intensity group included infants with invasive treatments including any vascular catheter, ventilator, continuous positive airway pressure, chest tube, or parenteral nutrition or blood transfusion in addition to bottle-feeding or intermittent gavage. Infants' source of nutrition was identified as exclusively

breastfed, formula fed, or a mixture of the 2 and any use of milk fortifiers. Harvard School of Public Health, Partner's Healthcare System, and Simmons College provided institutional review board approval. The involvement of the Centers for Disease Control and Prevention laboratory was determined not to constitute engagement in human subject research. Informed consent was obtained from each mother.

Exposure Source Evaluation

Questionnaires and medical records were used to collect information on maternal demographics, lifestyle, pregnancy history, perinatal medical care and interventions, medications, and medical history. Infant data included gestational age and weight, head circumference, length, Apgar scores, serum bilirubin levels, and kidney, liver, and thyroid functions if available. The type (breast milk or formula) and method of nutrition (gavage, bottle, or breast) was recorded, along with the use and amount of milk fortifiers or parenteral nutrition, as was oxygen usage and method of delivery, and the use of other medical devices and equipment.

Sample collection devices were pre-screened for BPA. Maternal milk was expressed by mechanical pumping and frozen in BPA-free storage containers provided by the hospital. BPA-free breast pump disposable devices (Medela Inc, McHenry, IL) were routinely made available to mothers by the hospital, although some mothers could have used different systems. Before use, milk was thawed in a "warm to touch" tap water bath. One milliliter of maternal breast milk or formula from the milk storage container was obtained immediately before the feeding by using a plastic pipette. Samples were stored in 10-mL polypropylene Cryovials at 4°C for up to 8 hours and then stored at –80°C.

Infant urine samples were collected by positioning 2 or 3 100% cotton balls within the diaper, immediately before

a feeding and after the feeding at the time of the next scheduled cluster of care (up to 3–4 hours). Wet cotton balls were placed in a plastic specimen cup and, in general, were stored for <2 hours at 4°C until the urine could be extracted by manual squeezing by using nitrile gloves. The urine was then pipetted into a polypropylene Cryovial and stored at –80°C. Urine specific gravity (SG) was measured by using the Atago digital handheld “pocket” SG refractometer (PAL-10S model, Bellevue, WA), which was calibrated before use. One field blank from cotton balls soaked in deionized water was collected and analyzed for each day's biological samples.

Analytical Methods for the Quantification of BPA in Urine and Nutrition Samples

Total urinary concentrations of BPA and total and free concentrations of BPA in nutrition samples were determined as described before.^{17,18} In brief, the conjugated species of BPA in 100 μ L of urine or milk were hydrolyzed enzymatically. After hydrolysis (the hydrolysis step was omitted for the determination of the concentration of free species), samples were acidified; BPA was preconcentrated by online solid-phase extraction, separated from other components by high-performance liquid chromatography, and detected by atmospheric pressure chemical ionization (urine) or atmospheric pressure photoionization (nutrition samples), tandem mass spectrometry. The limits of detection (LODs) were 0.4 μ g/L (urine) and 0.3 μ g/L (milk). The method accuracy ranged from 98% to 113% (urine) and 90% to 108% (milk) at 4 concentrations.^{17,18} The coefficients of variation of repeated measures of low- and high-concentration quality-control materials, prepared with spiked pooled human urine ($\sim$ 3 μ g/L and $\sim$ 20 μ g/L) or milk ($\sim$ 9 μ g/L and $\sim$ 23 μ g/L), ranged from 6.3% to 8.3% (milk) and 6% to 17% (urine). Quality-control materials were

analyzed along with standards (range, 0.1–100 μ g/L), reagent blank, infants' samples, and field blanks. Urinary BPA concentrations were adjusted for dilution by using SG.¹⁹

Calculated Daily BPA Exposure

Premature infants in this study generally had normal renal function and hydration; therefore, the predicted urine output is 38 mL/kg per day.²⁰ Daily BPA exposure was calculated as described previously,^{21,22} and comparisons were made with other study populations.

Data Analysis

BPA concentrations below LOD were treated by imputing values of LOD/ $\sqrt{2}$. Daily nutritional BPA exposure estimates were modeled either qualitatively (breast milk versus formula), or quantitatively (μ g/kg BW per day intake estimates). Data were analyzed by using SPSS version 17 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). The influence of feeding was assessed by paired analysis of pre- and post-feeding differences in urinary total BPA concentration by using the Wilcoxon signed rank test. The Mann-Whitney *U* test was used to explore the type of feeding (breast milk or formula) on the cross-feed difference in urinary total BPA concentrations and for comparison of urinary total BPA concentrations between dichotomized medical treatment groups. Intraclass correlation coefficients assessed the ratio of between-infant to total (between- and within-infant) variability in urinary BPA concentrations by using linear mixed-effects models with ln-transformed urinary BPA concentrations as the dependent variable. Hierarchical linear mixed-effects models were used to identify determinants of ln-transformed urinary BPA concentrations and account for the clustering of infants within families and repeated urine samples within infant while adjusting for potential confounding factors. Regression coefficients

were back-transformed from the natural log scale and expressed as multiples of the concentrations of the reference group.

RESULTS

Subjects

Participants included 43 mothers and their infants (*n* = 55), who were predominately white (60% and 71%, respectively) (Table 1). There were 10 sets of multiple births with 70% of the deliveries by cesarean delivery, 58% of infants were very preterm (<32 weeks), whereas 49% were very low birth weight (<1500 g) (Table 1). The median age at birth was 30 weeks (range, 24–38 weeks), and the median postconception age of the infants at the time of urine collection was 34 weeks (range, 27–40 weeks).

Urinary BPA Concentrations

Of the anticipated 110 urine specimens, 104 were collected, including pre- and postfeeding samples from 49 infants, and a single sample from 6 infants. Total BPA was detected in all infants with median urinary concentrations before and after feeding of 17.2 and 18.3 μ g/L, respectively (Table 2).

Nutritional BPA Concentration

Thirty infants (55%) were exclusively fed breast milk, 24 (44%) were exclusively fed formula, and 1 received a mixture of breast milk and formula. All breast milk and 92% of formula samples had detectable concentrations of total BPA; free BPA was detected less frequently (29%, breast milk; 54%, formula) (Table 2). Two breast milk samples had concentrations of total (222 and 296 μ g/L) and free (189 and 252 μ g/L) BPA that were at least 1 order of magnitude higher than the concentrations in other nutritional samples. The next highest BPA concentration was 10.8 and 6.1 μ g/L for total and free BPA, respectively. These 2 statistical outlier samples were not included in further analyses.

TABLE 1 Subject Characteristics

Demographics	Maternal (<i>n</i> = 43)	Infant (<i>n</i> = 55)
Race, <i>n</i> (%)		
White	26 (61)	39 (71)
Black	10 (23)	11 (20)
Asian	4 (9)	—
Other	3 (7)	5 (9)
Hispanic, <i>n</i> (%)	4 (9)	5 (9)
Age at birth, wk, ^a <i>n</i> (%)		
Very preterm <32		32 (58)
Preterm 32–36		18 (33)
Term 37+		5 (9)
Birth weight, g, ^b <i>n</i> (%)		
Very low birth weight <1500		27 (49)
Low birth weight 1500–2499		19 (35)
Normal birth weight 2500+		9 (16)
Age at time of urine collection, wk, mean (SD)		34 (3)
Infant weight at time of urine collection, g, mean (SD)		1957 (785)
Infant length at time of urine collection, cm, mean (SD)		41 (7)
Infant head circumference at time of urine collection, cm, mean (SD)		29 (4)
Gender of infants, <i>n</i> (%)		
Female		25 (45)
Male		30 (55)

^a Gestational age and birth weight categories as defined by Matthews and MacDorman.²³

^b Missing birth weight and Hispanic status on 1 case.

The median concentrations of total or free BPA did not differ between breast milk and formula samples (Table 2). The median percentage of free to total BPA in breast milk was 30% compared with 44% for formula. Fortification of

formula or breast milk did not influence median urinary BPA concentrations.

Cross-feed Nutritional Influence

There was a 0.9 $\mu\text{g/L}$ difference in median urinary BPA concentration across feeding (17.2 $\mu\text{g/L}$ prefeed and 18.3 $\mu\text{g/L}$ postfeed; $P = .37$). The cross-feed change in median BPA was $-0.45 \mu\text{g/L}$ ($P = .47$) in infants breastfed and 2.4 $\mu\text{g/L}$ ($P = .13$) in formula-fed infants. In mixed-effects models, after adjustment for gestational age, birth weight, and time since feeding, there was no difference in urinary BPA across feedings based on source of nutrition ($P = .32$). Therefore, source of nutrition was ignored to explore the quantitative estimate of nutritional BPA intake ($\mu\text{g/kg}$ BW per day) with cross-feed urinary BPA concentrations. There were no cross-feed differences in urinary BPA ($P = .15$); therefore, the mean of the 2 urine samples per infant was used to test for differences between medical device use groups.

Medical Device Use

Using a priori medical device use groups (“high” and “low”), the high-group infants had median (25th, 75th percentile) urinary BPA concentrations (18.5 [13.3, 40.7] $\mu\text{g/L}$) greater than the low-group infants (13.2 [8.4, 38.2] $\mu\text{g/L}$; P value for difference = .13). On secondary analysis evaluating individual

medical devices, on average, infants requiring nasal oxygen, continuous positive airway pressure, or a nasogastric tube had significantly higher urinary BPA concentrations than infants not requiring these devices (see Table 3). In addition, the median (25th, 75th percentile) urinary BPA concentrations among 11 infants using 4 or more medical devices (36.6 [17.2, 47.3] $\mu\text{g/L}$) was significantly higher ($P = .01$) than among 44 infants using 0 to 3 devices (13.7 [9.2, 35.1] $\mu\text{g/L}$).

Calculated Daily BPA Exposure

Calculated exposures are presented in Table 4 for the median, 95th percentile, and maximum urinary total BPA concentrations. Comparisons with other populations are highlighted.

Variance Apportionment for Clustered Data

Urine concentrations collected after successive feedings had high temporal reliability; the intraclass correlation coefficient for unadjusted urinary BPA concentrations was 0.81 (95% confidence interval, 0.69–0.88), whereas for SG-adjusted BPA it was 0.65 (0.49–0.79). Between-mother variability was the highest (68% for uncorrected BPA, 58% for SG-corrected BPA), followed by within infant (19% for uncorrected BPA, 34% for SG-corrected BPA) and within mother/between infant (13% for uncorrected BPA, 8% for SG-corrected BPA) variability.

Prematurity and Birth Weight

Median urinary BPA concentrations differed significantly by gestational age group (4.3 $\mu\text{g/L}$ at >37 weeks, 12.4 $\mu\text{g/L}$ at 32–36 weeks, 34.2 $\mu\text{g/L}$ at <32 weeks; $P < .001$) and by birth weight (9.2 $\mu\text{g/L}$ among normal weight, 12.7 $\mu\text{g/L}$ for low birth weight, and 36.6 $\mu\text{g/L}$ for very low birth weight; $P < .001$). Birth weight and gestational age were highly correlated (Spearman correlation coefficient = 0.92;

TABLE 2 BPA Concentration ($\mu\text{g/L}$) in Breast Milk, Formula, and Urine, and Intake Estimates by Nutrition Type (Median [25th, 75th])

	Breast Milk (<i>n</i> = 30)	Formula (<i>n</i> = 24)
Concentration in nutritional samples ^a		
Total BPA, $\mu\text{g/L}$	1.3 (0.9, 2.5)	1.1 (0.7, 1.4)
Free BPA, $\mu\text{g/L}$	<LOD (<LOD, 0.6)	0.4 (<LOD, 1.4)
Percent free BPA, %	30 (20, 56)	44 (32, 71)
Nutritional intake estimate		
BPA ingested, $\mu\text{g/kg}$ BW per day ^b	0.16 (0.09, 0.36)	0.12 (0.06, 0.17)
Total BPA concentration ($\mu\text{g/L}$) in urine ^c		
Before feeding (<i>n</i> = 51)	21.8 (12.8, 35.1)	13.4 (6.8, 36.3)
After feeding (<i>n</i> = 51)	21.7 (11.7, 60.4)	15.4 (7.6, 33.6)
Average (<i>n</i> = 47)	23.3 (12.8, 40.7)	13.1 (9.2, 40.6)

^a One nutritional sample mixed breast milk and formula not included. Two outlier samples not included. LOD = 0.3 $\mu\text{g/L}$.

^b BPA ingested per day = [(total BPA $\times$ 24-h volume of feeding)/infant weight in kilograms]

^c Urine missing from 6 infants: 3 before feed samples, and 3 different infants' after feed samples; therefore, average of 2 samples may not fall between the average of each pre–post feed BPA concentration.

TABLE 3 Difference in Median (25th, 75th) Total BPA Urinary Concentrations ($\mu\text{g/L}$) and Calculated Daily Exposure Estimates by Type and Number of Medical Devices Used in the Past 3 Days^a

Medical Device	Used ^b			Not Used			<i>P</i> ^c
	Median	25th	75th	Median	25th	75th	
Nasal cannula							
Total urinary BPA concentration, $\mu\text{g/L}$	40	17	48	26	17	22	.024
Estimated exposure, $\mu\text{g/kg}$ per day	1.76	0.75	2.11	1.14	0.75	0.97	
CPAP							
Total urinary BPA concentration, $\mu\text{g/L}$	38	18	45	13	9	17	.034
Estimated exposure, $\mu\text{g/kg}$ per day	1.67	0.79	1.98	0.57	0.40	0.75	
Ventilator							
Total urinary BPA concentration, $\mu\text{g/L}$	17	15	32	31	13	49	.5
Estimated exposure, $\mu\text{g/kg}$ per day	0.75	0.66	1.41	1.36	0.57	2.16	
Peripheral IV							
Total urinary BPA concentration, $\mu\text{g/L}$	18	13	43	12	9	25	.55
Estimated exposure, $\mu\text{g/kg}$ per day	0.79	0.57	1.89	0.53	0.40	1.10	
Central IV							
Total urinary BPA concentration, $\mu\text{g/L}$	17	13	37	39	13	47	.54
Estimated exposure, $\mu\text{g/kg}$ per day	0.75	0.57	1.63	1.72	0.57	2.07	
Nasogastric tube							
Total urinary BPA concentration, $\mu\text{g/L}$	23	13	47	9	4	12	.003
Estimated exposure, $\mu\text{g/kg}$ per day	1.01	0.57	2.07	0.40	0.18	0.53	
Use of 4 or more medical devices ^d							
Total urinary BPA concentration, $\mu\text{g/L}$	36.6	17.2	47.3	13.9	9.2	35.1	.02
Estimated exposure, $\mu\text{g/kg}$ per day	1.61	0.76	2.08	0.61	0.40	1.54	

CPAP, continuous positive airway pressure; IV, intravenous.

^a Used average of 2 unadjusted urine samples to obtain values. Exposure calculation based on a urine daily volume of 38 mL/kg.²¹^b Used in past 3 days.^c Mann-Whitney *U* Test *P* value.^d Compared with 0 to 3 devices.

$P < .001$). Because gestational age was also significantly associated with medical device use group (91% of high-use group infants were <32 weeks versus 50% of lower-use group [$P = .03$]), there was colinearity when gestational age and birth weight were both included in regression models, so birth weight was removed. Infant gender was also significantly associated with prematurity and with urinary BPA concentrations; 73% of boys were <32 weeks versus 40% of

girls, $P = .01$; and median urinary BPA concentration in boys was $24.9 \mu\text{g/L}$ versus $13.7 \mu\text{g/L}$ in girls, $P = .03$. There was no association between gender and high medical device use.

Linear Hierarchical Mixed-Effects Regression Model

The final linear hierarchical mixed-effects regression model for SG-adjusted urinary BPA concentrations included as predictors nutritional

intake, medical device use, gender, and gestational age. Adding gestational age in the model attenuated the magnitude of the association between medical device use and urinary BPA concentration but not the significance. Prematurity remained a significant independent predictor of urinary BPA concentration in this final model, accounting for $\sim 30\%$ of the variability in urinary BPA concentration, and medical devices accounted for $\sim 10\%$. In this final model, infants using ≥ 4 medical devices had BPA concentrations 1.6 times higher (95% confidence interval, 1.01–2.58; $P = .045$) than those using 0 to 3 devices.

DISCUSSION

In the current study, all infants had detectable urinary concentrations of total BPA, ranging from 2.0 to $196 \mu\text{g/L}$. The median urinary BPA concentration in this group of premature infants was considerably higher ($17.2 \mu\text{g/L}$) than in healthy term infants aged 1 to 5 months ($<0.45 \mu\text{g/L}$) without known BPA exposure.²¹ Although immaturity of phase II metabolism may account for some of the association of urinary BPA concentrations with prematurity, premature infants have the ability to conjugate BPA.¹⁶ Interestingly, medical devices, but not nutritional intake, were positively associated with urinary BPA concentrations. On average, premature infants requiring ≥ 4 medical devices had urinary total BPA concentrations 1.6

TABLE 4 Calculated Exposure Based on Urinary Total BPA Concentrations

Population Age	Population Type	Urinary Concentration, $\mu\text{g/L}$			Calculated Exposure, $\mu\text{g/kg}$ per Day			Reference
		Median	95th Percentile	Max	Median	95th Percentile	Max	
24–38 wk gestational age	US premature infants	17.2	72.9	196	0.65 ^a	2.77 ^a	7.45 ^a	Current study
25–34 wk gestational age	US premature infants	28.6	NA	946	1.09 ^a	NA	35.95 ^a	Calafat et al 2009 ¹⁶
1–5 mo old	German healthy normal-term infants	<0.45	10.13	17.35	<0.02 ^b	0.45 ^b	0.76 ^b	Volkel et al 2011 ²¹
6–11 y old	US general population from NHANES 2007–2008 ²⁴	2.40	13.4	193	0.04 ^c	0.23 ^c	3.28 ^c	CDC, 2011

US Environmental Protection Agency RfD = $50 \mu\text{g/kg}$ per day.²⁵ CDC, US Centers for Disease Control and Prevention; NA, not available.^a Calculation based on a urine daily volume of 38 mL/kg.²¹^b Calculation based on a urine daily volume of 44 mL/kg.²¹^c Calculation based on a urine daily volume of 17 mL/kg.²²

times higher than those requiring fewer devices independent of their gestational age, gender, or nutritional intake. Respiratory devices were associated with higher urinary BPA concentrations than other devices. These findings suggest that medical devices were an important source of BPA exposure for these infants.

Median BPA concentrations among the infants in this study were 36% lower than those reported by Calafat et al.¹⁶ Calafat also reported a larger magnitude of association between high and low medical device use (8.75-fold versus 1.6-fold observed in our study), but adjustments were only made for infant gender and institution. Adjustment for urinary dilution, nutritional intake, infant gender, and gestational age as done in our analysis provides for a more precise estimate of association with medical device use. It is also likely that concerted efforts over the past years to eliminate or decrease the use of plastics containing BPA in devices and feeding equipment in this particular NICU have led to a decrease in overall BPA exposure. In the model presented, prematurity and medical device use accounted for ~30% and 10%, respectively, of the variability in urinary BPA. It seems reasonable to suspect that prematurity could have accounted for some of the association between medical devices and urinary BPA observed in the Calafat et al study.

In the general population, diet is considered the primary source of BPA exposure, but that was not true in this medically complex NICU population. Similar to findings by World Health Organization,² the calculated mean (95th percentile) exposure to BPA of exclusively breast milk fed infants was 0.23 $\mu\text{g/kg BW per day}$ (1.1 $\mu\text{g/kg BW per day}$), and the estimated mean (95th percentile) exposure of formula fed infants was 0.16 $\mu\text{g/kg BW per day}$ (0.61 $\mu\text{g/kg BW per day}$). The mean total BPA urinary concentration among the exclusively formula-fed infants (13.1 $\mu\text{g/L}$) was lower than those exclusively fed breast milk (23.3 $\mu\text{g/L}$), a difference that did not reach statistical significance.

In the current study, multiple-birth infants, who have similar dietary sources, treatment levels, and surroundings, have more similar urinary BPA concentrations than infants from different mothers. Understanding that most of the variability came from between-family and very little from within-infant will aid in making appropriate power and sample size calculations in the design of future studies that involve clustering of infants within family.

CONCLUSIONS

This study provided detailed information on the duration of use of specific medical devices and estimation of the nutritional intake of BPA from either maternal milk or formula.

Urinary BPA concentrations were statistically higher as the number of medical devices used over the 3 days before evaluation increased, but they were not associated with the nutritional sources (breast milk or formula). Although median BPA exposures calculated from urinary concentrations were 16- to 32-fold higher for neonates in the NICU in comparison with children in the general population²⁴ or healthy infants,²¹ they were still below the US Environmental Protection Agency reference dose (RfD) (dose below which no adverse health effects should result from a lifetime of exposure). However, it is important to keep in mind that, although BPA concentrations were below the RfD, there is ongoing controversy regarding potential health risks of low-dose (ie, below RfD) exposures to BPA.²⁶ Finally, the degree of prematurity and gender remained strong significant independent predictors of urinary BPA concentrations even after adjustment for device use and nutritional exposure, indicating the need for additional research into other potential determinants in the NICU including the microenvironment of the isolette.

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