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Temporal trends in bisphenol A exposure in the United States from 2003–2012 and factors associated with BPA exposure: Spot samples and urine dilution complicate data interpretation

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ABSTRACT

Nationally representative data on urinary levels of BPA and its metabolites in the United States from the 2003–2004 to 2011–2012 National Health and Nutrition Examination Surveys (NHANES) were used to estimate daily BPA intakes and examine temporal trends. Additionally, NHANES data on lifestyle/demographic/dietary factors previously reported to be associated with BPA exposures were examined to assess the resiliency of the reported associations (whether the association is maintained across the five surveys). Finally, various approaches for addressing issues with the use of BPA concentration data from spot urine samples were examined for their effect on trends and associations. Three approaches were assessed here: (i) use of generic literature-based 24-h urine excretion volumes, (ii) use of creatinine adjustments, and (iii) use of individual urine flow rate data from NHANES. Based on 2011–2012 NHANES urinary BPA data and assumptions described in this paper, the median daily intake for the overall population is approximately 25 ng/kg day; median intake estimates were approximately two to three orders of magnitude below current health-based guidance values. Estimates of daily BPA intake have decreased significantly compared to those from the 2003–2004 NHANES. Estimates of associations between lifestyle/demographic/dietary factors and BPA exposure revealed inconsistencies related to both NHANES survey year and the three approaches listed above; these results demonstrate the difficulties in interpreting urinary BPA data, despite efforts to account for urine dilution and translation of spot sample data to 24-h data. The results further underscore the importance of continued research on how to best utilize urinary measures of environmental chemicals in exposure research. Until a consensus is achieved regarding the best biomonitoring approaches for assessing exposures to short-lived chemicals using urine samples, research on factors associated with BPA exposures should include – and report results from - assessments using both volume-based urinary BPA and creatinine-adjusted urinary BPA data.

1. Introduction

Bisphenol A (BPA, CAS no. 80-05-7) has been the subject of a large and ever increasing number of scientific publications, with a simple PubMed search on the term “bisphenol A” yielding almost 9000 publications; over 300 of these are review publications. Research on BPA has included toxicity evaluations (reviewed extensively; see, for example, EFSA (2015), FDA (2014a) and Hengstler et al. (2011)), epidemiological assessments (reviewed in LaKind et al., 2014a), toxicokinetics/toxicodynamics (Hengstler et al., 2011) and exposure assessments (reviews for this aspect of the BPA literature include topics such as BPA migration from polycarbonate [Hoekstra and Simoneau, 2013] and dietary and non-dietary sources of exposure [Geens et al., 2012]).

A major source of data for human exposure to BPA is the biennial National Health and Nutrition Examination Survey (NHANES). The US Centers for Disease Control and Prevention's (CDC) National Center for Environmental Health provides data on urinary BPA for a nationally representative sample of the United States (US). Five NHANES surveys with data on BPA are now available, covering the time period from 2003 to 2012 (Calafat et al., 2008; CDC, 2006a,

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2009, 2011a, 2011b, 2014). These data have been mined extensively in efforts to explore temporal trends in human exposures to BPA (e.g., LaKind et al., 2012), factors influencing human exposure (LaKind and Naiman, 2011; McKinney et al., 2014; Tyrrell et al., 2013) and associations between exposure and various health outcomes (reviewed in LaKind et al., 2014a).

During the years associated with the release of the surveys' data (2003–2012), there has been a substantial amount of negative media and public attention paid to general population exposures to BPA, resulting in the introduction to the market of many "BPA-free" products (Caliendo, 2012). In addition, the Food and Drug Administration (FDA) no longer allows BPA-based polycarbonate resins to be used for manufacture of baby bottles and sippy cups (FDA, 2014b) and 11 states no longer permit use of BPA in infant feeding containers (http://www.consumerreports.org/cro/news/2011/10/california-joins-10-other-states-in-banning-bpa-from-infant-feeding-containers/index.htm). It is therefore possible that overall background human exposure to BPA has declined since 2003. While NHANES data cannot be used to examine the effect of the FDA action (urinary BPA data are not collected for children under six years of age), the general potential impact of public awareness on BPA exposures may be observable. If a decline is observed, it may be possible to use factors reported to be associated with urinary BPA levels to better understand which segments of the overall population are experiencing those decreases and why.

Various lifestyle, demographic and dietary factors have been reported to be associated with urinary BPA concentrations, including tobacco smoke exposure (Braun et al., 2011; Geens et al., 2014), family educational level (Covaci et al., 2015), canned foods (Covaci et al., 2015), household income (Geens et al., 2014; LaKind and Naiman, 2011), race/ethnicity, consumption of soda, school lunches and meals not prepared at home, and age and gender (LaKind and Naiman, 2011). Data on various demographic and lifestyle factors are available from NHANES. However, while the NHANES database includes information on aspects of the US population's diet (considered to be the major contributor to BPA exposure), due to the rapid metabolism and excretion of BPA, only those data capturing exposures occurring within the approximately 24-h prior to urine sample collection are relevant to such an exploration. This limits the NHANES dietary assessments to only a few food/drink items (LaKind and Naiman, 2011).

Because the urine samples used to measure urinary BPA are spot samples – as opposed to 24-h samples – it is generally recognized that a method is needed for addressing the variation associated with effect of urine dilution on the volume-based BPA concentrations. The most common method is to adjust the urinary volume measure (ng BPA/ml urine) with urinary creatinine concentrations (Barr et al., 2005), which are also reported in the NHANES datasets. However, this introduces complications to the interpretation of results of NHANES-based research which are not yet fully understood (Christensen et al., 2014; Garde et al., 2004; Weaver et al., 2015). Urinary creatinine levels themselves are variable and can be affected by age, sex, race/ethnicity, body mass index, fat-free mass, time of day of collection of urine samples (Barr et al., 2005), exercise (Calles-Escandon et al., 1984), diet (Neubert and Remer, 1998) and health (Tynkevich et al., 2014). The choice of exposure metric (e.g., unadjusted versus creatinine-adjusted) can introduce bias and can modify outcomes of analyses in environmental epidemiology studies (Christensen et al., 2014; Goodman et al., 2014). Thus, it has been recommended that results of analyses using urinary measures of environmental chemicals be reported for both adjusted and unadjusted concentrations (LaKind et al., 2014b; Weaver et al., 2015).

The urinary BPA data from spot samples can also be converted to 24-h estimates using three different approaches. The first is to use generic 24-h urine excretion values to convert volume-based urinary BPA levels (ng/ml) to daily BPA excretion (ng/day). The second is to use generic 24-h creatinine excretion values to convert creatinine-adjusted urinary BPA levels (ng/mg creatinine) to daily BPA excretion (ng/day). For the 2009–2010 and 2011–2012 NHANES datasets, urinary flow rate data are also available. According to the CDC, "the urine flow rate is a more accurate calculation used to determine urine analyte concentrations, especially exposure to environmental chemicals" (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/UCFLOW_F.htm). Thus, for two of the NHANES surveys, urine flow rate data can be used as another approach for converting volume-based urinary BPA levels in spot samples to daily BPA excretion.

In this paper, we explore the following questions:

(1) Is there any evidence that the US population exposure to BPA has declined during the period 2003–2012? We examine temporal trends for urinary BPA levels (both volume-based and creatinine-adjusted) and for daily BPA intake (ng/kg day). Daily intakes are determined using both volume-based urinary BPA concentrations and creatinine-adjusted BPA concentrations. Finally, we compare the intake results from the 2009–2010 and 2011–2012 NHANES data with intakes estimated using NHANES urinary flow data. By using these different methods, we can assess whether the approaches have an effect on the temporal trend analyses.
(2) Do the five NHANES surveys provide evidence that previously-identified lifestyle/demographic/dietary factors associated with BPA exposures (Braun et al., 2011; Covaci et al., 2015; Geens et al., 2014; LaKind and Naiman, 2011) are consistently observed? We explore consistency of associations across the five surveys using urinary BPA concentration data (volume-based and creatinine-adjusted).

2. Methods

2.1. NHANES data

The CDC's National Center for Health Statistics data files for NHANES 2003–2004 to 2011–2012 are publicly available (CDC, 2006a, 2009, 2011a, 2011b, 2014). The BPA data (NHANES variable URXBPH, ng/ml) are from a subsample of NHANES participants. Total BPA, after hydrolysis of conjugated metabolites, was measured in urine samples, with the method limit of detection (LOD) given as 0.4 ng/ml for all survey years. In the data analyses, measures below the detection limit were assigned a value of the LOD divided by the square root of 2 (CDC, 2006a). The sample population includes males and females ages 6 to 60+ years. The total number of participants with urinary BPA data for the subsample in each survey (and percent of the measurements below the LOD) is: 2003–2004 – 2517 (6.5%); 2005–2006 – 2548 (7.1%); 2007–2008 – 2604 (6.3%); 2009–2010 – 2749 (8.0%), 2011–2012 – 2489 (10.3%).

To estimate various population (and population subgroup) quantities such as means and percentiles, weighted means and percentiles were calculated using the NHANES two-year weights provided by CDC (as described in the NHANES analytic guidelines [CDC, 2006b]). The calculations of point estimates and confidence intervals were performed using R (R Core Team, 2014) with confidence intervals obtained using the R survey package (Lumley, 2004, 2014).

2.2. Estimating urinary BPA concentrations

We estimated both volume-based (unadjusted) and creatinine-adjusted population metrics as recommended by LaKind et al.

(2014b). For creatinine-adjusted levels, we divided each individual's urinary BPA level (ng/ml) by their creatinine level (NHANES variable URXUCR, mg/dL) and a unit adjustment of 0.01 to derive a creatinine-adjusted BPA concentration (μg/gr creatinine). No participants were excluded based on their creatinine levels.

2.3. Estimating population BPA daily intake

Excretion of ingested BPA into urine, mainly as the glucuronide conjugate, is essentially complete in 24 h (Dekant and Völkel, 2008; Teeguarden et al., 2011); thus, total urinary BPA (sum of the concentrations of BPA metabolites plus the parent compound in urine) in a 24-h urine sample approximates the BPA intake from the previous 24 h (LaKind and Naiman, 2008). While NHANES provides data almost exclusively for spot samples, Christensen et al. (2012) found that spot urinary concentrations of BPA were fairly comparable to corresponding 24-h average concentrations obtained from a similar population indicating that "spot samples can be used to characterize population distributions of intakes," with caution needed for data at the tail of the distribution. The approach of using spot urinary BPA data to estimate daily intakes of BPA in the US has been described previously (LaKind and Naiman, 2008, 2011; LaKind et al., 2012). In brief, daily BPA intake (ng/day) was estimated by multiplying the urinary BPA concentrations (ng/ml) by generic (ICRP, 2002) 24-h urinary output volume (ml/day). Age- and gender-based generic values for urinary output (ICRP, 2002) were used to create piecewise linear functions, one for males and one for females, giving urinary output as a function of age. These generic 24-h urinary excretion volume data are generally consistent with other urinary output volumes in the published literature (see LaKind and Naiman (2008) for a review of the published literature).

Daily intakes were then adjusted for body weight (ng/kg day) using individual body weights reported in the NHANES databases (Eq. (1)). Individuals with missing body weight data were excluded from the analyses.

$$\text{Urinary BPA (ng/ml)} \times \text{urinary output (ml/day)/body weight (kg)} = \text{ng BPA/kg–day} \quad (1)$$

We performed parallel analyses using creatinine-adjusted urinary BPA concentrations in combination with generic daily creatinine excretion values (ICRP, 2002) (Eq. (2)). We used the age- and gender-based daily creatinine excretion values (ICRP, 2002) to create piecewise linear functions, one for males and one for females, giving creatinine output as a function of age.

$$\text{Urinary BPA, creatinine–adj (ng/mg creatinine)} \times \text{creatinine output (mg/dy)/body weight (kg)} = \text{ng BPA/kg–day} \quad (2)$$

Using these approaches, distributions of intakes representative of the US population were determined for (i) all participants, (ii) participants by the following age groups: 6–11 years, 12–19 years, 20–39 years, 40–59 years, and 60+ years, (iii) participants by gender, and (iv) participants by race/ethnicity.

Finally, daily intakes based on individual urine flow rate were determined for the more recent NHANES surveys (2009–2010 and 2011–2012) by multiplying the urinary BPA concentration (ng/ml) for each participant by their urine averaged flow rates (ml/min) and by 1440 min/day (http://wwwn.cdc.gov/nchs/nhanes/2009-2010/UCFLOW_F.htm; http://wwwn.cdc.gov/nchs/nhanes/2011-2012/UCFLOW_G.htm), and dividing by each participant's body weight (Eq. (3)).

$$\text{Urinary BPA (ng/ml)} \times \text{urine flow rate (ml/min)} \times 1440 \text{ min/day/body weight (kg)} = \text{ng BPA/kg–day} \quad (3)$$

2.4. Associations between lifestyle/demographic/dietary factors and urinary BPA concentrations or BPA daily intake

We identified lifestyle/demographic/dietary factors that were available for at least three of the five surveys from either Laboratory files or from the Demographics, Examination, and Questionnaire files. For exposure via ingestion, two questions were specifically related to consumption of packaged food/drink that also focused on recent exposures (thus addressing the issue of BPA's short physiologic half-life): school lunches and meals obtained from outside the home. Information on demographics and smoking were also available for multiple NHANES surveys. The NHANES variable names, ages for which data were collected, and URLs for this information are given in Table 1. For education, analyses were conducted for adults only because for younger individuals school level is roughly a proxy for age.

In order to determine whether there is an association between BPA concentration and a predictor variable of interest, we fit regression models with log urinary BPA or log creatinine-adjusted urinary BPA as the response variable, taking into account the complex survey design, and tested for significant associations using the estimated regression coefficients and their standard errors. We also examined associations with BPA daily intakes as the response variable, using the three methods described above: intakes estimated with generic (ICRP, 2002) values for 24-h urinary excretion; intake based on creatinine-adjusted urinary BPA, and BPA concentrations adjusted for individual urine flow rate (for NHANES 2009–2010 and 2011–2012 survey data only). All of the calculations were carried out in R using the survey package (Lumley, 2004, 2014; R Core Team, 2014). Identical results were obtained using Stata 13, using the svy prefix for the regress command (StataCorp, 2013).

Predictor variables can be taken to be categorical or continuous. The categorical variables are: gender, ethnicity, and smoking status. The continuous variables are: numbers of school lunches, numbers of meals prepared away from home, income, age, education level, and number of cigarettes in the past 5 days.

In some cases, a continuous predictor variable was found to be considerably skewed (meals prepared away from home and number of cigarettes smoked). For these cases, regression models were also fit using log-transformations of the predictor variable. These transformations did not change the results in any substantial way (results not shown).

The above tests of association refer to individual two-year surveys. We are also interested in whether evidence of association between BPA and a particular dietary, lifestyle, or demographic factor emerges when tests over multiple surveys are combined. For the purpose of pooling over multiple surveys, we report what we refer to as an overall p-value for testing the null hypothesis of no association over all available surveys against the alternative of association over some of the available surveys using Fisher's method for combining independent p-values (Fisher, 1925). Here, if p-values $p_1, \ldots, p_n$ are obtained in n independent surveys, then an overall p-value is given by the tail probability for the χ^2distribution with $2n$ degrees of freedom at the value:

Table 1
NHANES variables used to examine associations with urinary BPA, variable names, age ranges for available data, and URL.

Variable	NHANES variable name	Data age range	URL
Demographics:			
Age (years)	RIDAGEYR	0 years+	http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/DEMO_c.htm
Education	DMDEDUC2	20 years+	http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/DEMO_D.htm
Gender	RIAGENDR	0 years+	http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/demo_e.htm
Household income	INDHHINC	0 years+	http://www.cdc.gov/nchs/nhanes/nhanes2009-2010/DEMO_F.htm
Ethnicity	RIDRETH1	0 years+	http://wwwn.cdc.gov/nchs/nhanes/2011-2012/DEMO_G.htm
Food:			
Meals away from home[a]	DBD091 or DBD895	1 years+	http://wwwn.cdc.gov/nchs/nhanes/2005-2006/DBQ_D.htm http://www.cdc.gov/nchs/nhanes/nhanes2007-2008/DBQ_E.htm http://www.cdc.gov/nchs/nhanes/nhanes2009-2010/DBQ_F.htm
School lunches[b]	DBD381	1 years+	
Smoking: Do you now smoke cigarettes? Every day, some days, not at all	SMQ040	20 years+	http://wwwn.cdc.gov/nchs/nhanes/2003-2004/SMQ_C.htm http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/SMQ_D.htm http://wwwn.cdc.gov/nchs/nhanes/2007-2008/SMQ_E.htm http://wwwn.cdc.gov/nchs/nhanes/2009-2010/SMQ_F.htm http://wwwn.cdc.gov/nchs/nhanes/2011-2012/SMQ_G.htm
Number of cigarettes smoked per day, past 5 days	SMQ720	12 years+	http://wwwn.cdc.gov/nchs/nhanes/2003-2004/SMQMEC_C.htm http://wwwn.cdc.gov/nchs/nhanes/2005-2006/SMQRTU_D.htm http://wwwn.cdc.gov/nchs/nhanes/2007-2008/SMQRTU_E.htm http://wwwn.cdc.gov/nchs/nhanes/2009-2010/SMQRTU_F.htm http://wwwn.cdc.gov/nchs/nhanes/2011-2012/SMQRTU_G.htm

[a] The language for the variable for meals away from home for the 2005–2006 survey (DBD091-# of times/week eat meals not from a home) was modified slightly for 2007–2008 and 2009–2010 (DBD895 – number of meals not home prepared).
[b] # times/week get school lunch.

$$-2\sum_{i=1}^{n}\ln(p_i)$$

3. Results

3.1. Temporal trends in BPA exposure in the US from 2003–2012

Urinary BPA: Percentiles and means of the NHANES urinary BPA data (unadjusted and creatinine-adjusted) for surveys from 2003 to 2010 have been reported by CDC (http://www.cdc.gov/exposurereport/) and published elsewhere (LaKind and Naiman, 2008, 2011; LaKind et al., 2012). Descriptive information for the 2011–2012 survey data is given in Table 2.

Geometric mean urinary BPA levels for the overall US population declined significantly from 2.64 ng/ml (95% CIs: 2.38, 2.94) (http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Sep2013.pdf) in 2003–2004 to 1.5 ng/ml (95% CIs 1.4, 1.6) in 2011–2012. A similar trend was observed for creatinine-adjusted urinary BPA measures with overall levels significantly declining from 2003–2004 (GM; 95% CI: 2.5; 2.3–2.7 μg/g creatinine) to 2011–2012 (GM; 95% CI: 1.66; 1.56–1.76 μg/g creatinine). In addition, from the 2003–2004 survey to the 2011–2012 survey, the percentage of BPA measures below the detection limit increased from 6.5% to 10.3%.

BPA Daily Intake: Percentiles and means were estimated for BPA daily intakes for the five NHANES surveys based on individual urinary BPA data and individual body weight data as described in the previous section. Intakes for 2003–2010 have been published previously (LaKind and Naiman, 2008, 2011; LaKind et al., 2012). Table 3 gives results for 2011–2012 by total population, age group, gender and race/ethnicity. For 2011–2012, median BPA intakes were higher for males than females. Median BPA intakes were similar across age groups; the highest intakes were for the 6–11 and 12–19 years age groups, but these intakes did not differ significantly from the other age groups. These age-related intake differences are generally consistent with those noted for the 2003–2004 and 2005–2006 NHANES surveys reported by LaKind and Naiman (2008, 2011). For the 2007–2008 NHANES survey, the highest intakes were in the 12–19 year age group.

Adjusting for creatinine, 40–59 year olds in the 2011–2012 survey had higher intakes compared to other adults and adolescents (Table 3), although the difference was not significant. Intakes for males are higher than for females, but the difference was not significant.

While intake estimates using NHANES urinary flow rate data cannot be used to examine temporal trends (as these data are only available for 2009–2010 and 2011–2012), they can be used to evaluate whether this approach yields intake estimates that vary widely from the generic-based and creatinine-adjusted estimates. Table 3 shows median intakes for 2011–2012 estimated from the individual flow rate data; use of individual urine flow rate data does not have a significant impact on estimates of median population intake as compared to the two other approaches for estimating daily intake.

Median BPA intakes and 95% CIs for the overall US population from 2003–2004 through 2011–2012 NHANES surveys are shown in Fig. 1. Over this time period, there has been an observable decline in BPA intakes for both unadjusted and creatinine-adjusted concentrations. While differences between adjacent surveys are generally not statistically significantly different (with an exception being from 2003–2004 to 2005–2006), across the overall time period the decline has been significant.

3.2. Associations between urinary BPA and lifestyle/demographic/dietary factors

The results of the assessment of associations between NHANES lifestyle/demographic/dietary factors and urinary BPA data are described here and summarized in Table 4. If a variable was not examined for a given survey or if data have not been released, those survey years are excluded from the tables.

3.2.1. Dietary exposure

School lunches, meals away from home: For school lunches (data available for 2005–2006, 2007–2008, 2009–2010), the associations were positive but only significant for unadjusted BPA data from the

Table 2
Volume-based urinary BPA (ng/ml) and creatinine-adjusted (μg/g creatinine) BPA concentrations from the 2011–2012 NHANES survey, with additional data by age, gender, and race/ethnicity. 95% confidence intervals are in parentheses.

2011–2012: BPA (ng/ml)													
	All	Male	Female	Age 6–11 year	Age 12–19 year	Age 20–39 year	Age 40–59 year	Age 60+year	Mexican-American	Other-Hispanic	Non-Hispanic Black	Non-Hispanic White	Other
25th %ile	0.7 (0.7, 0.8)	0.8 (0.7, 0.9)	0.6 (0.6, 0.7)	0.8 (0.6, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)	0.7 (0.5, 0.9)	0.6 (0.5, 0.7)	0.7 (0.6, 0.8)	0.7 (0.6, 0.9)	0.7 (0.6, 0.8)	1.1 (1.0, 1.3)	0.6 (0.4, 0.7)
50th %ile	1.4 (1.3, 1.5)	1.5 (1.4, 1.7)	1.3 (1.1, 1.5)	1.5 (1.3, 1.7)	1.7 (1.3, 2.1)	1.5 (1.3, 1.7)	1.4 (1.2, 1.7)	1.2 (1.1, 1.3)	1.4 (1.2, 1.5)	1.5 (1.1, 1.9)	1.3 (1.2, 1.5)	2.1 (1.9, 2.4)	1.1 (1.0, 1.4)
75th %ile	3.0 (2.7, 3.3)	3.2 (2.7, 3.7)	2.8 (2.4, 3.2)	3.1 (2.7, 3.5)	3.3 (2.9, 4.0)	2.9 (2.5, 3.4)	3.1 (2.7, 3.5)	2.6 (2.0, 3.1)	2.8 (2.4, 3.0)	2.7 (1.9, 5.1)	2.9 (2.6, 3.2)	4.1 (3.5, 4.6)	2.3 (1.8, 3.1)
95th %ile	9.4 (7.8, 11.2)	9.5 (8.1, 11.6)	8.5 (7.1, 13.3)	8.5 (7.0, 40.6)	9.9 (7.8, 13.4)	10.6 (8.0, 14.9)	9.6 (6.5, 14.0)	7.4 (5.4, 14.0)	7.6 (6.5, 9.6)	10.4 (6.7, 74.7)	8.9 (7.3, 13.6)	11.3 (8.4, 14.7)	7.4 (4.9, 17.3)
Mean	3.3 (2.8, 3.7)	3.6 (2.9, 4.4)	2.9 (2.2, 3.6)	3.6 (2.4, 4.8)	3.3 (2.3, 4.3)	3.0 (2.6, 3.4)	3.6 (2.0, 5.2)	2.9 (1.6, 4.2)	3.0 (1.9, 4.2)	2.8 (1.5, 4.1)	3.3 (2.4, 4.1)	3.9 (3.3, 4.5)	2.7 (1.8, 3.6)
GM	1.5 (1.4, 1.6)	1.6 (1.5, 1.8)	1.4 (1.3, 1.5)	1.6 (1.4, 1.8)	1.7 (1.4, 2.0)	1.6 (1.4, 1.8)	1.5 (1.3, 1.7)	1.3 (1.2, 1.5)	1.4 (1.3, 1.6)	1.5 (1.1, 2.1)	1.5 (1.4, 1.6)	2.1 (1.9, 2.4)	1.2 (1.1, 1.4)
Count	2489	1259	1230	396	388	623	553	529	310	235	813	661	418
2011–2012: BPA (μg/g creatinine)													
	All	Male	Female	Age 6–11 year	Age 12–19 year	Age 20–39 year	Age 40–59 year	Age 60+year	Mexican-American	Other-Hispanic	Non-Hispanic Black	Non-Hispanic White	Other
25th %ile	1.0 (0.9, 1.0)	0.8 (0.8, 0.9)	1.1 (1.0, 1.2)	1.3 (1.1, 1.4)	0.9 (0.8, 1.0)	1.0 (0.9, 1.0)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	0.9 (0.9, 1.0)	1.0 (0.7, 1.2)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.8 (0.7, 1.0)
50th %ile	1.6 (1.5, 1.7)	1.4 (1.2, 1.6)	1.8 (1.6, 2.0)	2.0 (1.8, 2.1)	1.5 (1.2, 1.9)	1.5 (1.3, 1.6)	1.7 (1.4, 1.9)	1.6 (1.4, 1.8)	1.5 (1.3, 1.6)	1.5 (1.2, 1.9)	1.6 (1.5, 1.8)	1.5 (1.3, 1.7)	1.5 (1.3, 1.7)
75th %ile	2.9 (2.7, 3.0)	2.6 (2.2, 2.9)	2.9 (2.8, 3.2)	3.3 (3.0, 3.8)	2.9 (2.3, 3.2)	2.6 (2.0, 2.9)	2.9 (2.7, 3.0)	2.9 (2.4, 3.3)	2.7 (2.4, 3.0)	2.9 (1.9, 4.2)	2.9 (2.7, 3.1)	2.6 (2.2, 3.1)	2.7 (2.1, 3.1)
95th %ile	8.2 (6.8, 11.0)	8.2 (6.5, 11.1)	8.1 (6.3, 11.3)	14.0 (8.3, 49.0)	8.3 (4.4, 89.9)	9.1 (5.6, 14.6)	7.7 (5.4, 20.3)	6.5 (5.3, 12.5)	7.2 (5.1,11.5)	8.0 (5.4, 62.2)	8.9 (6.5, 12.4)	7.2 (6.2, 10.8)	7.9 (5.0, 14.6)
Mean	3.0 (2.5, 3.6)	2.7 (2.4, 3.1)	3.3 (2.3, 4.3)	4.2 (3.0, 5.4)	2.7 (2.0, 3.3)	2.5 (2.1, 3.0)	3.5 (2.2, 4.8)	2.8 (2.0, 3.5)	2.6 (2.0, 3.1)	2.7 (1.5, 3.8)	3.0 (2.6, 3.5)	2.6 (2.2, 2.9)	5.1 (0.5, 9.6)
GM	1.7 (1.6, 1.8)	1.5 (1.4, 1.7)	1.9 (1.8, 2.1)	2.3 (2.0, 2.6)	1.6 (1.5, 1.9)	1.6 (1.5, 1.8)	1.7 (1.6, 1.9)	1.7 (1.5, 1.9)	1.6 (1.5, 1.8)	1.7 (1.3, 2.2)	1.8 (1.7, 1.9)	1.7 (1.5, 1.8)	1.6 (1.4, 1.8)
Count	2487	1258	1229	395	388	622	553	529	310	235	811	661	418

Table 3
BPA intakes (ng/kg day) in the US based on urinary BPA and creatinine-adjusted BPA concentrations from the 2011–2012 NHANES survey, with additional data by age, gender and race/ethnicity. 95% confidence intervals are in parentheses.

2011–2012: generic volume-based BPA intake (ng/kg day)													
	All	Male	Female	Age 6–11 year	Age 12–19 year	Age 20–39 year	Age 40–59 year	Age 60+	Mexican-American	Other-Hispanic	Non-Hispanic Black	Non-Hispanic White	Other
25th %ile	12.4 (11.6, 13.6)	14.4 (12.7, 16.9)	11.3 (9.7, 12.3)	13.9 (9.9, 16.7)	13.3 (11.3, 17.0)	13.8 (11.7, 16.4)	11.7 (9.5, 14.8)	11.0 (9.3, 12.2)	12.8 (10.9, 15.2)	14.2 (10.8, 16.2)	11.7 (10.9, 12.9)	16.7 (14.7, 18.7)	11.6 (9.4, 14.1)
50th %ile	24.9 (23.6, 27.3)	27.8 (25.3, 31.8)	22.1 (19.2, 25.0)	30.5 (23.4, 34.6)	30.8 (25.3, 37.6)	25.8 (23.5, 30.3)	23.7 (20.7, 27.8)	23.6 (18.6, 26.2)	25.3 (22.4, 30.3)	26.5 (19.4, 32.1)	24.3 (22.2, 25.8)	33.1 (29.8, 38.8)	21.7 (20.1, 25.0)
75th %ile	51.7 (47.8, 59.7)	59.5 (50.5, 67.4)	47.5 (40.9, 52.7)	56.8 (51.0, 67.2)	62.2 (52.0, 77.7)	50.6 (46.1, 60.3)	50.3 (45.6, 62.2)	45.2 (36.9, 54.8)	51.0 (42.9, 62.2)	49.7 (32.1, 111)	50.9 (46.1, 58.6)	67.8 (57.1, 77.2)	44.6 (35.8, 59.4)
95th %ile	165 (150, 205)	182 (158, 206)	160 (132, 208)	197 (148, 443)	221 (146, 277)	189 (146, 256)	156 (110, 208)	141 (105, 238)	145 (116, 216)	186 (126, 430)	162 (143, 208)	208 (168, 244)	160 (94.8, 484)
Mean	59.3 (49.7, 68.9)	71.5 (54.2, 88.8)	47.5 (38.1, 57.0)	67.4 (49.6, 85.3)	68.3 (42.7, 93.9)	53.4 (45.4, 61.3)	65.5 (27.0, 104)	49.5 (31.8, 67.3)	61.0 (26.6, 95.4)	55.0 (31.3, 78.8)	58.9 (40.5, 77.4)	65.7 (53.7, 77.7)	56.6 (34.2, 79.0)
GM	26.8 (25.1, 28.6)	30.5 (27.8, 33.5)	23.6 (21.4, 26.1)	30.4 (27.0, 34.2)	31.0 (26.0, 36.9)	28.0 (25.3, 31.1)	25.4 (21.6, 29.8)	23.6 (20.9, 26.8)	26.6 (23.5, 30.2)	27.9 (20.5, 38.0)	25.7 (23.9, 27.7)	34.2 (29.7, 39.2)	24.4 (20.8, 28.7)
Count	2460	1248	1212	395	384	616	544	521	305	234	801	656	405
2011–2012: creatinine-adjusted BPA intake (ng/kg day)													
	All	Male	Female	Age 6–11	Age 12–19	Age 20–39	Age 40–59	Age 60+	Mexican-American	Other-Hispanic	Non-Hispanic Black	Non-Hispanic White	Other
25th %ile	15.0 (13.9, 16.0)	15.4 (14.0, 17.4)	14.3 (13.1, 15.8)	18.7 (16.2, 20.4)	14.1 (12.6, 16.4)	15.5 (13.8, 16.9)	14.1 (11.4, 17.1)	14.8 (13.4, 16.4)	15.2 (13.1, 17.4)	15.5 (12.5, 19.2)	15.0 (13.7, 16.9)	13.8 (11.9, 15.0)	14.5 (11.9, 18.2)
50th %ile	26.1 (24.3, 27.9)	27.3 (24.3, 30.3)	25.0 (22.8, 27.8)	34.0 (29.9, 37.9)	26.1 (20.9, 33.6)	24.3 (23.1, 25.7)	27.1 (22.8, 29.8)	25.0 (22.0, 28.9)	26.2 (23.3, 29.0)	24.7 (19.3, 34.4)	26.8 (24.4, 29.3)	21.9 (19.4, 25.7)	27.7 (23.2, 30.8)
75th %ile	48.0 (43.7, 53.3)	52.3 (44.1, 58.1)	45.8 (41.4, 52.7)	61.6 (52.3, 72.7)	51.8 (43.3, 64.8)	41.2 (37.7, 44.3)	49.0 (40.5, 57.4)	54.7 (42.9, 58.6)	47.7 (39.7, 56.5)	46.3 (37.7, 68.5)	50.8 (45.6, 56.2)	42.0 (34.3, 50.9)	47.0 (37.1, 61.7)
95th %ile	151 (111, 187)	167 (140, 203)	118 (96.9, 170)	240 (149, 577)	183 (105, 308)	150 (103, 223)	106 (91.9, 202)	112 (92.3, 238)	111 (93.4, 183)	133 (90.1,1240)	157 (110, 193)	133 (97.8, 214)	156 (90.2, 326)
Mean	48.4 (43.5, 53.2)	54.4 (48.1, 60.7)	42.6 (36.5, 48.6)	69.0 (49.8, 88.1)	53.1 (37.2, 69.0)	42.9 (36.6, 49.2)	47.8 (31.8, 63.9)	45.3 (35.9, 54.8)	48.1 (29.4, 66.7)	47.3 (27.5, 67.1)	50.0 (42.3, 57.7)	41.2 (33.9, 48.5)	49.6 (35.9, 63.3)
GM	28.4 (26.7, 30.3)	29.8 (27.4, 32.5)	27.1 (24.9, 29.5)	36.9 (32.4, 42.2)	29.2 (24.9, 34.2)	27.0 (24.9, 29.4)	27.5 (24.7, 30.6)	28.2 (25.1, 31.7)	27.8 (25.3, 30.4)	28.8 (22.3, 37.2)	29.3 (27.3, 31.4)	24.7 (21.6, 28.3)	28.3 (24.4, 32.8)
Count	2458	1247	1211	394	384	615	544	521	305	234	799	656	405
2011–2012: urine flow rate-based BPA intake (ng/kg day)													
50th %ile	23.4 (22.0, 25.6)	24.7 (22.7, 27.9)	22.4 (20.7, 25.3)	35.5 (30.3, 49.1)	28.9 (24.3, 36.1)	23.7 (21.8, 27.1)	22.7 (18.9, 27.1)	17.7 (15.6, 21.5)	23.3 (21, 26.5)	23.5 (18.6, 30.5)	23 (21.5, 25.9)	24.3 (22.0, 29.1)	22.9 (18.2, 29.6)
Count	2316	1174	1142	337	358	599	520	502	289	218	771	607	375

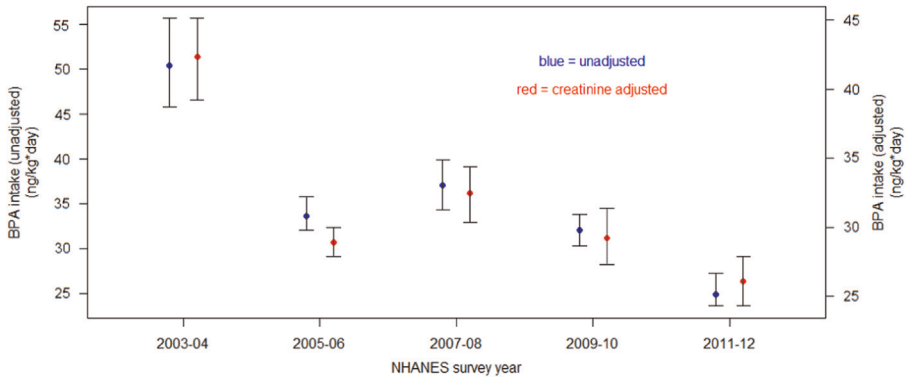

Fig. 1. Median BPA intakes (ng/kg day) and 95% CIs for the overall US population from 2003–2004 through 2011–2012 NHANES surveys. Blue=intakes based on unadjusted concentrations; Red=intakes based on creatinine-adjusted concentrations.

2009–2010 survey. The overall *p*-values were .15 for unadjusted BPA and .31 for adjusted BPA, consistent with the results from individual surveys. Meals away from home were consistently positively and significantly associated with urinary BPA levels across surveys (data were available for 2005–2006, 2007–2008, 2009–2010) (the overall *p*-value was .00017). However, when urinary BPA was creatinine-adjusted, the results were no longer significant for any survey year (overall *p*-value of .71).

3.2.2. *Lifestyle/demographic factors*

Income: Income was consistently inversely associated with urinary BPA (both adjusted and unadjusted). The results reached significance only for 2003–2004, 2005–2006 and 2011–2012 (the overall *p*-values were 5.4×10^{-5} for unadjusted BPA and 2×10^{-4} for creatinine-adjusted BPA).

Age: Age was consistently significantly negatively correlated ($p < .05$) with unadjusted urinary BPA across all five surveys. However, after adjusting BPA with creatinine, the direction of the correlation became inconsistent across surveys and the results were no longer significant (2009–2010 borderline significant). This is consistent with the overall *p*-value $< .00001$ for unadjusted BPA and .17 for creatinine-adjusted BPA.

Race/ethnicity: Using non-Hispanic Whites as the reference group, only Blacks had consistently significantly higher urinary BPA levels across surveys ($p < .001$) for unadjusted urinary BPA; the results were no longer significant when creatinine-adjusted BPA levels were used and the direction of association was reversed for four of the five surveys. Mexican-Americans had higher urinary BPA levels compared to non-Hispanic Whites across all surveys for unadjusted BPA but results did not achieve significance; the direction of the association changed after creatinine adjustment. Hispanics also had higher urinary BPA levels compared to non-Hispanic Whites across surveys but results were statistically significant only for 2009–2010; results were all non-significant after adjusting for creatinine. The overall *p*-values for Black/non-Hispanic White difference are $< .00001$ for unadjusted BPA and .04 for creatinine-adjusted BPA.

Gender: For unadjusted urinary BPA, males had higher levels compared to females across all surveys and results were significant (borderline significant for 2011–2012). However, when analyses were conducted using creatinine-adjusted BPA, the opposite results were obtained: females had consistently significantly higher levels of BPA than males (overall *p*-value of .000024 for unadjusted BPA and $< .00001$ for adjusted BPA).

Education: For four of the five survey years, education was inversely associated with urinary BPA (both unadjusted and adjusted) but results were generally not significant. However, the overall *p*-value was .02 for unadjusted BPA; the *p*-value was .55 for creatinine-adjusted BPA.

Smoking: Associations between smoking and urinary BPA were assessed using two different smoking-related questions: does the participant smoke cigarettes now (with responses including every day, some days, or not at all) and number of cigarettes smoked over the previous five days. For the first question, using unadjusted urinary BPA, a positive association was observed for all survey years for those who reported smoking every day, compared to those who responded "not at all;" however, none of the results reached the level of significance. Yet the overall *p*-value for the test of association for daily smokers is .04 for unadjusted BPA. In contrast, when using creatinine-adjusted BPA levels in the analyses, for 2009–2010 the direction of the associations was indicative of a small but insignificant negative association while for 2003–2004, 2007–2008 and 2011–2012, a positive significant association ($p < .05$) was observed. The overall *p*-value for creatinine-adjusted BPA for daily smokers is .002.

For associations between number of cigarettes smoked in the past five days and either unadjusted or adjusted urinary BPA levels, the direction of the association was inconsistent across surveys and results did not reach significance.

We also conducted analyses of associations between BPA daily intake based on (i) the generic (ICRP, 2002) 24-h urine excretion volumes, (ii) generic (ICRP, 2002) 24-h creatinine excretion data, and (iii) 24-h urine excretion volumes for each individual from the NHANES urine flow rate data (2009–2010 and 2011–2012 only) and the same lifestyle/demographic/dietary variables given in Table 4 (results not shown). In general, as with the approach of using urinary BPA measures, we found various inconsistencies across methods.

4. Discussion

In this paper, we used the five NHANES surveys with urinary BPA levels to assess whether temporal trends in US population exposures were discernable. We further used these data to evaluate whether lifestyle/demographic/dietary factors previously reported to be associated with urinary BPA levels were consistently observed for the five surveys. We recognize that NHANES is a cross-sectional study and measured urinary BPA levels only reflect very recent exposures. We therefore were careful in our analyses of lifestyle/dietary association assessments to include only those NHANES variables that could be plausibly associated with exposures occurring within the previous 24-h period. Here, we discuss temporal trends, associations, and approaches for addressing issues stemming from the use of spot urine samples in these types of analyses.

Table 4
Associations between urinary BPA concentrations and lifestyle/demographic/dietary factors in the 2003–2012 NHANES data. Results are shown for both unadjusted urinary BPA and creatinine-adjusted urinary BPA. Coefficients (β), *p*-values and *N* are given. Significance (bolded) is at $p < .05$. Coefficients and *p* values are for log-transformed BPA.

School lunches									
	β (unadjusted)	*p*-Value (unadjusted)	β (adjusted)	*p*-Value (adjusted)	–	–	–	–	*N*[a]
Y05-06	0.007	0.86	0.027	0.46	–	–	–	–	521
Y07-08	0.031	0.47	0.04	0.23	–	–	–	–	304
Y09-10	0.093	**0.02**	0.038	0.26	–	–	–	–	318
Meals away									
	β (unadjusted)	*p*-Value (unadjusted)	β (adjusted)	*p*-Value (adjusted)	–	–	–	–	*N*
Y05-06	0.02	**0.02**	0.004	0.56	–	–	–	–	2168
Y07-08	0.03	**0.003**	0.003	0.67	–	–	–	–	2201
Y09-10	0.02	**0.02**	0.006	0.41	–	–	–	–	2322
Income									
	β (unadjusted)	*p*-Value (unadjusted)	β (adjusted)	*p*-Value (adjusted)	–	–	–	–	*N*
Y03-04	−0.048	**0.008**	−0.035	**0.005**	–	–	–	–	1392
Y05-06	−0.029	**0.03**	−0.023	**0.03**	–	–	–	–	2066
Y07-08	−0.018	0.11	−0.019	0.05	–	–	–	–	2045
Y09-10	−0.017	0.05	−0.009	0.34	–	–	–	–	2079
Y11-12	−0.035	**0.008**	−0.024	**0.02**	–	–	–	–	1872
Age									
	β (unadjusted)	*p*-Value (unadjusted)	β (adjusted)	*p*-Value (adjusted)	–	–	–	–	*N*
Y03-04	−0.01	**9.00E−05**	−0.001	0.12	–	–	–	–	1488
Y05-06	−0.01	**< 00001**	−0.001	0.25	–	–	–	–	2192
Y07-08	−0.01	**< 00001**	−0.0002	0.87	–	–	–	–	2215
Y09-10	−0.005	**0.008**	0.002	0.05	–	–	–	–	2334
Y11-12	−0.005	**0.02**	0.001	0.65	–	–	–	–	2093
Race/ethnicity (unadjusted for creatinine; non-Hispanic White as reference)									
	Mexican American		Black		Other		Hispanic		*N*
	β	*p*-Value	β	*p*-Value	β	*p*-Value	β	*p*-Value	
Y03-04	0.106	0.23	0.575	**7E−05**	−0.394	**0.01**	0.023	0.91	1488
Y05-06	0.194	0.08	0.366	**0.0003**	0.080	0.60	0.375	0.08	2192
Y07-08	0.045	0.45	0.272	**0.001**	−0.361	**0.03**	0.031	0.77	2215
Y09-10	0.108	0.12	0.377	**0.0002**	−0.189	0.43	0.322	**0.001**	2334
Y11-12	0.034	0.57	0.366	**8E−05**	−0.192	**0.03**	0.048	0.76	2093
Race/ethnicity (creatinine-adjusted, non-Hispanic White as reference)									
	Mexican American		Black		Other		Hispanic		*N*
	β	*p*-Value	β	*p*-Value	β	*p*-Value	β	*p*-Value	
Y03-04	−0.103	0.11	0.108	0.19	−0.282	**0.05**	0.091	0.60	1487
Y05-06	−0.010	0.89	−0.063	0.15	−0.014	0.92	0.102	0.49	2192
Y07-08	−0.054	0.31	−0.063	0.27	−0.177	0.12	−0.064	0.46	2215
Y09-10	−0.047	0.39	−0.096	0.09	−0.137	0.41	0.033	0.58	2334
Y11-12	−0.092	0.07	−0.0945	0.11	−0.167	**0.03**	−0.051	0.72	2092
Gender (female as reference)									
	β (unadjusted)	*p*-Value (unadjusted)	β (adjusted)	*p*-Value (adjusted)	–	–	–	–	*N*
Y03-04	0.186	**0.01**	−0.186	**0.01**	–	–	–	–	1488
Y05-06	0.187	**0.03**	−0.212	**0.0002**	–	–	–	–	2192
Y07-08	0.097	**0.01**	−0.263	**< 00001**	–	–	–	–	2215
Y09-10	0.099	**0.01**	−0.212	**5E-05**	–	–	–	–	2334
Y11-12	0.152	0.06	−0.266	**0.0004**	–	–	–	–	2093
Education (adults)									
	β (unadjusted)	*p*-Value (unadjusted)	β (adjusted)	*p*-Value (adjusted)	–	–	–	–	*N*
Y03-04	−0.068	**0.04**	−0.002	0.95	–	–	–	–	1488
Y05-06	−0.070	0.05	−0.022	0.37	–	–	–	–	1490
Y07-08	0.009	0.73	−0.001	0.96	–	–	–	–	1814
Y09-10	−0.016	0.54	0.032	0.21	–	–	–	–	1914
Y11-12	−0.067	**0.03**	−0.031	0.17	–	–	–	–	1705
Smoking[b]									
	β (smokes daily – unadjusted)	*p*-Value (smokes daily – unadjusted)	β (smokes daily – adjusted)	*p*-Value (smokes daily – adjusted)					*N*[c]
Y03-04	0.132	0.13	0.159	**0.03**	–	–	–	–	744
Y05-06	0.155	0.14	0.105	0.31	–	–	–	–	690
Y07-08	0.120	0.13	0.138	**0.006**	–	–	–	–	857
Y09-10	0.124	0.12	−0.002	0.97	–	–	–	–	918
Y11-12	0.125	0.29	0.138	**0.02**	–	–	–	–	723
Number of cigarettes smoked in past 5 days[d]									
	β (unadjusted)	*p*-Value (unadjusted)	β (adjusted)	*p*-Value (adjusted)	–	–	–	–	*N*
Y03-04	0.001	0.88	0.007	0.21	–	–	–	–	309
Y05-06	−0.01	0.28	−0.005	0.34	–	–	–	–	391
Y07-08	−0.003	0.53	0.001	0.75	–	–	–	–	427
Y09-10	−0.011	0.05	−0.003	0.44	–	–	–	–	429
Y11-12	−0.003	0.72	0.008	0.05	–	–	–	–	355

– = not relevant.

[a] *N* is for unadjusted BPA values. The sample size is the same for creatinine-adjusted analyses except that there was one fewer participant with relevant data for the 2003–2004 and 2011–2012 survey years.

[b] Participant was asked: Do you now smoke cigarettes? Possible responses include: every day, some days, not at all. Participants for this query were age 20 years and older. The reference group for the analysis was non-smokers.

[c] *N* values for unadjusted and creatinine-adjusted analyses are the same.

[d] Participants were age 12 and older.

4.1. Temporal trends

Using the most recent NHANES data from 2011–2012 along with the assumptions described in this paper, the median daily intake for the overall population is now approximately 25 ng/kg day. Fig. 1 shows the comparisons of daily median intakes of BPA across surveys from 2003–2004 to 2011–2012. While urinary BPA levels and BPA daily intakes from one survey period to the next may not differ significantly, the overall trend from 2003–2004 to 2001–2012 is downward and significant overall.

The median daily BPA intake estimate for men is statistically significantly higher than for women for unadjusted urinary BPA levels. For creatinine-adjusted levels, the median level for men remains higher but the difference is no longer significant. A general decrease in daily BPA intake with increasing age was also observed for unadjusted BPA intakes. However, intakes across age groups do not differ substantially from the overall population intake (less than a factor of 2) and the trend was less consistent for creatinine-adjusted BPA. For race/ethnicity, differences across groups are relatively small and intakes are similar to the general population (Table 3).

Existing health-based guidance values in the US and Europe can be compared to our estimates of daily intakes. The US Environmental Protection Agency (EPA, 2009) gives a value of 50 μg/kg day (50,000 ng/kg day) as the Reference Dose (RfD) while the European Food Safety Authority (EFSA, 2015) recently modified its Tolerable Daily Intake (TDI) to 4 μg/kg of bw/day (4000 ng/kg day). In addition, a provisional TDI of 25 μg/kg bw-day (25,000 ng/kg day) has been established by Health Canada (Health Canada, 2008). Median intake values in the US were below 35 ng/kg day for all groups analyzed (for both unadjusted and creatinine-adjusted estimates) and the 95th percentiles were at or below 240 ng/kg day (Table 3). Thus, median and 95th percentile intake estimates were approximately two to three orders of magnitude or one to two orders of magnitude below the current health-based guidance values, respectively. This is in concordance with EFSA's comparisons of highest estimates for total BPA exposures (for example, from diet, dust, cosmetics and thermal paper) to their new TDI (EFSA's exposure estimates were three to five times lower than the TDI) (EFSA, 2015).

Results should be interpreted with caution due to the limitations imposed by the underlying data and the methodology for estimating daily intake, and especially those estimates in the tails of the intake distributions because of the small numbers of individuals

Table 5
Geometric means (GM) for unadjusted urinary BPA, urinary creatinine, and creatinine-adjusted urinary BPA for males and females and for non-Hispanic Whites and Blacks from the 2011–2012 NHANES survey data. The ratio of geometric means for gender in the fourth row is a ratio of ratios, i.e. 0.8 = 1.1/1.47. The ratio of GMs for race is in the lower right corner of the table, i.e. 0.9 = 1.4/1.52.

	GM(BPA)	GM(.01 × CREAT)	GM(BPA_{adj})
Male	1.6	1.07	1.5
Female	1.4	0.73	1.9
Ratio	1.1	1.47	0.8 (ratio of ratios)
Non-Hispanic White	2.1	1.26	1.7
Black	1.5	0.828	1.8
Ratio	1.4	1.52	0.9 (ratio of ratios)

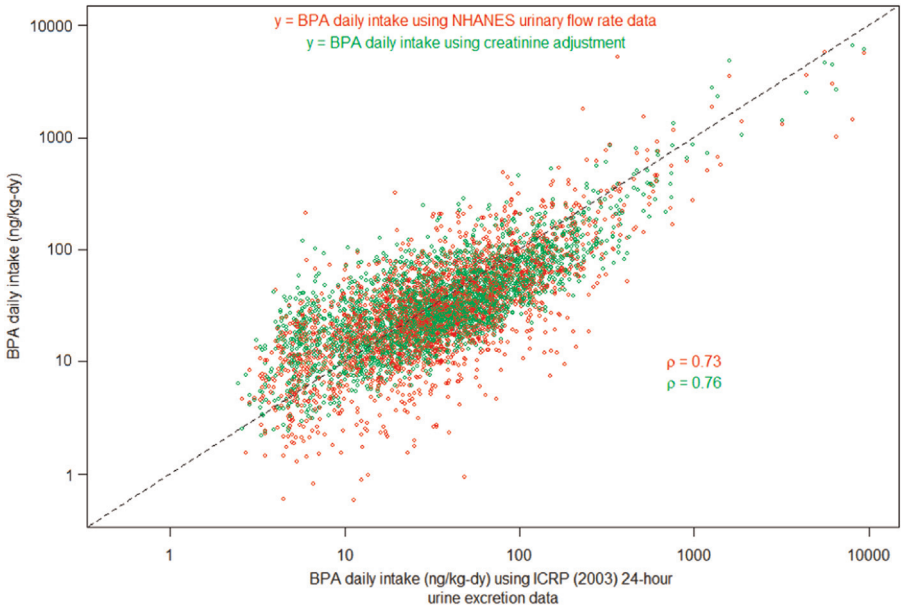

Fig. 2. Comparison of daily BPA intakes for 2009–2010 NHANES using three methods: BPA intake using 24-h urine excretion from generic (ICRP, 2002) data, BPA intakes estimated using creatinine-adjusted urinary BPA, and intakes estimated using urine flow rate-adjusted BPA concentrations. Dashed line corresponds to $y=x$.

Table 6
Comparison of 24-h urine volumes (ml/day) from the generic (ICRP, 2002) data with mean and median NHANES-based data by gender and age.

	6–11 years of age		12–19 years of age		20–39 years of age		40–59 years of age		60+ years of age	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Generic	600	600	1200	1200	1600	1200	1600	1200	1600	1200
2009–2010 NHANES-based mean (median)[a]	1037 (744)	1052 (756)	1273 (935)	1163 (829)	1928 (1326)	1511 (1004)	1669 (1201)	1424 (1078)	1381 (1086)	1250 (831)
2011–2012 NHANES-based mean (median)[a]	1251 (880)	1150 (904)	1696 (1056)	1271 (950)	1688 (1260)	1706 (1176)	1486 (1179)	1553 (1189)	1302 (996)	1564 (924)

[a] Value for each participant is the mean of up to three urine flow rate measurements.

represented by those tails (LaKind and Naiman, 2008, 2011).

4.2. Associations between BPA exposure and lifestyle/demographic/dietary characteristics

Results of assessments of associations between urinary BPA and lifestyle/demographic/dietary factors in some cases confirmed the results of earlier studies and in other cases contradicted those results. The five NHANES surveys therefore provide important information on the resiliency of reported associations.

In our earlier assessment of the relationship between smoking and urinary BPA from the 2005–2006 NHANES survey, we did not observe a significant association. Similarly, for all five two-year surveys examined here, none indicate a significant association between unadjusted urinary BPA and smoking. However, the *p*-value for the multiple test for association for daily smokers over the five periods based on Fisher's method for combining independent *p*-values is .04. This suggests an association between urinary BPA and smoking which is in accordance with some other reports (He et al., 2009; Arbuckle et al., 2015; Geens et al., 2014). It is not clear why the association did not hold when using number of cigarettes smoked over the previous five days but it is possible that smoking is a surrogate for some other type of behavior or demographic factor which would render the number of cigarettes smoked moot.

For the 2005–2006 survey, we reported a positive statistically significant association between urinary BPA and number of school lunches per week during the school year ($p=002$) and meals not prepared at home ($p=006$) (LaKind and Naiman, 2011). With five surveys now available, we are able to examine consistency of these associations. The results across surveys suggest that school lunches are not associated with urinary BPA measures. (While we had previously observed a significant positive association between school lunches and urinary BPA [LaKind and Naiman, 2011], the method used in that analysis would have been more likely to underestimate standard errors and *p*-values compared to the method used here.) Meals consumed away from home were consistently significantly associated with urinary BPA, but only when unadjusted urinary BPA concentrations were used in the analyses. Creatinine-adjusted urinary measures revealed no association with meals away from home. This underscores the importance of reporting results for both unadjusted and creatinine-adjusted concentrations.

In assessing BPA-lifestyle/demographic/dietary associations, one can also use daily intakes (as opposed to urinary BPA levels). Three methods for estimating intakes were used in this paper. These results were not uniformly consistent with those using urinary BPA as the dependent variable; some inconsistencies across methods (although not across surveys) may be explained by the impact of adjusting for urinary dilution.

4.3. Adjustments for urinary dilution

Due to difficulties in collecting 24-h urine samples, most biomonitoring studies use spot samples. Spot sample data can be used directly to provide volume-based concentrations (i.e., ng/ml BPA) or can be adjusted by an individual's urinary creatinine level (i.e., ng BPA/mg creatinine). While the latter approach is thought to provide a better measure of BPA exposure by correcting for dilution, it can also introduce complications to the interpretation of the data. In fact, whether or not one adjusts for urinary dilution with creatinine can have a substantial impact on assessments of associations between lifestyle/demographic/dietary factors and BPA exposure.

For example, age was significantly inversely associated with urinary BPA concentrations, but only for unadjusted BPA levels (Table 4). Similarly, the 2011–2012 concentration data in Table 2 reveal that geometric mean BPA levels are higher for men compared to women (1.6 vs 1.4 ng/ml, respectively) when levels are not adjusted but the reverse is true for creatinine-adjusted values (1.5 vs 1.9 μg/g creatinine, for men and women, respectively). Another example of the effect of creatinine-adjustment on association outcome is for race: the 2011–2012 concentration data (Table 2) reveal that geometric mean BPA levels are higher for non-Hispanic Whites compared to Blacks (2.1 vs 1.5 ng/ml, respectively) when levels are not adjusted but the reverse is true for creatinine-adjusted values (1.7 vs 1.8 μg/g creatinine, respectively). These reversals can be explained by recalling that:

$$\mathrm{BPA}_{adj} = \frac{\mathrm{BPA}}{.01 \times \mathrm{CREAT}}$$

Consequently, the geometric means satisfy:

$$\mathrm{GM}(\mathrm{BPA}_{adj}) = \frac{\mathrm{GM}(\mathrm{BPA})}{\mathrm{GM}(.01 \times \mathrm{CREAT})}$$

Focusing on the gender example, the ratio of male to female creatinine-adjusted urinary BPA levels can be expressed as a ratio of ratios (the lower right hand corner of Table 5):

$$\frac{\mathrm{GM}(\mathrm{BPA}_{adj}|\mathrm{male})}{\mathrm{GM}(\mathrm{BPA}_{adj}|\mathrm{female})} = \frac{\mathrm{GM}(\mathrm{BPA}|\mathrm{male})}{\mathrm{GM}(\mathrm{BPA}|\mathrm{female})} \Big/ \frac{\mathrm{GM}(.01 \times \mathrm{CREAT}|\mathrm{male})}{\mathrm{GM}(.01 \times \mathrm{CREAT}|\mathrm{female})}$$

As shown in the table of geometric means (Table 5), the ratio of geometric means for male vs. female is 1.1, which is greater than 1, indicating that males tend to have higher BPA levels than females. However, the ratio of geometric means for adjusted BPA levels is 0.8, which is less than 1, indicating that adjusted levels tend to be lower for males than females. This is explained by the fact that the ratio of creatinine geometric means (1.47) is greater than the ratio of BPA geometric means (1.1).

This also explains why non-Hispanic Whites tend to have higher urinary BPA levels compared to Blacks, but tend to have lower creatinine-adjusted BPA levels (Table 5).

If as a first approximation it is assumed that the BPA and creatinine values are jointly bivariate log-normally distributed, the above reasoning further explains the reversals observed for the medians for males/females and non-Hispanic Whites/Blacks.

Consideration of the impact of urinary dilution is important when using urinary biomonitoring data to estimate exposure across segments of the population, but there are complications related to creatinine adjustments that cannot be ignored. Many studies report results for only unadjusted or only creatinine-adjusted urinary chemical measures. This exercise demonstrates the importance of using and reporting on both measures (LaKind et al., 2014b; Weaver et al., 2015).

Consideration of urinary dilution is also important when estimating intakes of chemicals based on urinary biomonitoring data. We used three different approaches to estimate daily BPA intake: (i) generic (ICRP, 2002) 24-h urine excretion volumes, (ii) generic (ICRP, 2002) 24 h creatinine excretion data, and (iii) 24-h urine excretion volumes for each individual using NHANES urine flow rate data (2009–2010 and 2011–2012, only). The first and third approaches are both attempts to convert data from a spot sample to an estimate of daily urinary excretion using a volume-based approach, with information on the volume of urine excreted over a 24-h period. We might hypothesize that the NHANES-based data on urine flow rate would provide an improved estimate over generic literature-based 24-h urinary excretion or creatinine excretion values. To test this assumption, we used the three approaches to estimate intakes using the 2009–2010 urinary BPA data. As shown in Fig. 2, while for an individual, the approach used would potentially have a large effect on the intake estimate, for the overall population, intakes estimated with the three approaches are highly correlated.

Comparisons of generic 24-h urine excretion volumes (ICRP,

2002) and those derived from the NHANES data are shown in Table 6. The mean NHANES-based 24-h urinary volumes are generally higher than the generic values for children and adults from 20–59 years of age. However, these differences do not result in substantial changes to the distributions of daily intake of BPA.

The inconsistencies in associations between factors thought to be associated with BPA exposure and BPA intakes - despite the high correlations for intakes regardless of the method used to estimate those intakes - demonstrates the difficulties in interpreting urinary BPA data. Our results underscore the importance of continued research on how to best utilize urinary measures of environmental chemicals in exposure research in order to improve our ability to interpret the data resulting from these studies. While it is outside the scope of this paper to develop and offer a study design that would resolve this issue, we believe that studies beyond the types currently being conducted are needed to better understand the implications of intra- and interindividual variability in creatinine excretion (see, for example, Fortin et al., 2008) – as well as further studies on the influence of generic versus measured urinary excretion rates on interpretation of biomonitoring data. Until these types of information are available, we recommend that biomonitoring studies including urinary measures of environmental chemicals provide results based on both adjusted and unadjusted approaches.

In summary, BPA exposures in the US have declined during the time period from 2003 to 2012. Further, until a consensus is achieved regarding the best biomonitoring approaches for assessing exposures to short-lived chemicals using spot urine samples, efforts to understand factors associated with BPA exposures should include assessments using both volume-based and creatinine-adjusted urinary BPA levels and intake estimates.

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