Environment International 141 (2020) 105758

Contents lists available at ScienceDirect

Environment International

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

Different temporal trends of exposure to Bisphenol A among international travelers between Los Angeles and Beijing

Yan Lin[a], Xinghua Qiu[b,*], Jinming Liu[b], Chi-Hong Tseng[c], Patrick Allard[d], Jesus A. Araujo[a,c], Yifang Zhu[a,*]

[a] Department of Environmental Health Sciences, Jonathan and Karin Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA 90095, United States

[b] State Key Joint Laboratory for Environmental Simulation and Pollution Control, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing 100871, PR China

[c] Division of Cardiology, Department of Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA 90095, United States

[d] Institute for Society and Genetics, University of California, Los Angeles, Los Angeles, CA 90095, United States

A R T I C L E I N F O

Handling Editor: Lesa Aylward

Keywords:
Bisphenol A (BPA)
Exposure
Biomarker
Temporal trend
Regulatory policy

A B S T R A C T

Recent studies suggested a significant downward trend in population's exposure to bisphenol A (BPA) in the United States. However, the temporal trend of BPA exposure remains unclear in China - a populous country with substantial industrial activities but less efforts made to phase out BPA in consumer products. In addition, it is unclear to what extent a visit from the United States to China could affect human exposure to BPA. In this natural experiment, we measured the concentration of total BPA in 418 urine samples repeatedly collected from 55 Los Angeles residents before, during, and after they spent 10 weeks in Beijing from 2012 to 2017. We found that traveling from Los Angeles to Beijing led to a 2.91-fold (95% CI: 2.43 to 3.50) increase in urinary BPA levels, which fully returned to baseline after study participants came back to Los Angeles. From 2012 to 2017, urinary BPA concentrations decreased in Los Angeles by 25.5% per year (95% CI: −30.8% to −19.8%; $p < 0.001$) but did not change in Beijing ($p = 0.24$). Consequently, the concentration ratio of urinary BPA between Beijing and Los Angeles increased from 1.23 (95% CI: 0.82 to 1.85) in 2012 to 4.05 (95% CI: 2.75 to 5.97) in 2017. These results indicate that BPA exposures may increase among international travelers to China. Additional efforts are needed to reduce population's exposure to BPA in China.

1. Introduction

Bisphenol A (BPA) is primarily used to produce polycarbonate plastics and epoxy resins (Huang et al., 2012). It is widely present in consumer products such as baby feeding bottles, food containers, and thermal paper receipts (Morgan et al., 2018). BPA is among the highest production volume chemicals worldwide. The United States, in particular, has been one of the largest BPA manufacturers with a production capacity of 1.1 million tons in 2007 (Huang et al., 2012). In 2003–2004, the National Health and Nutrition Examination Survey (NHANES) identified ubiquitous exposure to BPA among the general population in the United States (Calafat et al., 2008). While recent toxicological and epidemiological evidence indicated BPA's adverse health effects at low doses (Richter et al., 2007; Rochester, 2013; Vandenberg et al., 2013, 2012), whether BPA at the current population exposure level would be a serious public health concern remains controversial (Bolt and Stewart, 2011).

As an endocrine disruptor, BPA may induce adverse developmental effects after exposures in early childhood - a major window of developmental vulnerability (Rochester, 2013). Thus, the use of BPA in baby feeding bottles has been prohibited in many countries including the United States and China (Chen et al., 2016a,b). However, comparable efforts to ban BPA in food containers and other consumer products are lacking and the exposure to BPA among adults remains prevalent. In 2014, the United States Food and Drug Administration concluded that BPA is safe at the current levels present in foods after reviewing ~ 300 studies published between 2009 and 2013 (Food and Drug Administration, 2014). Nevertheless, the BPA controversy is not thereby ended, given an increasing number of studies published after 2013 linking current levels of BPA exposures to adverse health effects

* Corresponding authors at: College of Environmental Sciences and Engineering, Peking University, Beijing 100871, PR China (X. Qiu). UCLA Fielding School of Public Health, 650 Charles E. Young Drive South, 51-295B CHS, Los Angeles, CA 90095, United States (Yifang Zhu).

E-mail addresses: xhqiu@pku.edu.cn (X. Qiu), yifang@ucla.edu (Y. Zhu).

https://doi.org/10.1016/j.envint.2020.105758
Received 21 February 2020; Received in revised form 13 April 2020; Accepted 21 April 2020
Available online 08 May 2020

such as birth outcomes (Ding et al., 2017; Huo et al., 2015) and cardiovascular disease - related factors (Lang et al., 2008; Zhang et al., 2016).

Despite the lack of nationwide enforcement to remove BPA in food containers and thermal paper receipts in the United States, 13 states and manufacturers have taken proactive roles to phase out BPA in consumer products (Ye et al., 2015). As a result, the exposure to BPA among the general population in the United States has decreased over time while exposure to BPA substitutes has become an emerging problem (Ye et al., 2015). On the other hand, the BPA production in Asia has increased rapidly in recent years, and reached 2.4 million tons in 2012, accounting for 53% of the global production (Merchant Research & Consulting Ltd, 2019), which may lead to a high level of BPA exposure in those countries (Zhang et al., 2011). Unlike in the United States, efforts to phase out BPA by manufacturers of consumer products in Asian countries have rarely been reported and the temporal trends of human exposure to BPA in China remain unclear.

In 2010, the University of California Los Angeles (UCLA) and Peking University (PKU) in Beijing, China, began a joint research program in which UCLA students visit Beijing for 10 weeks each summer. In our previous studies, we have shown that participants traveling from Los Angeles to Beijing exhibit increased urinary concentration of polycyclic aromatic hydrocarbons (PAHs) metabolites likely due to severe air pollution in Beijing (Lin et al., 2016, 2019), suggesting that the repeated measurement on travelers serve as an effective approach to evaluate the exposure to environmental chemicals in two different countries with individual variations well controlled. In this study, we recruited 55 UCLA students participating in this program from 2012 to 2017 and collected a total of 418 morning urine samples before (LA-before), during (Beijing), and after (LA-after) their 10-week visit to Beijing. With the measurement of urinary BPA concentrations, we aimed to (1) determine to what extent traveling from Los Angeles to Beijing would affect BPA exposures; and (2) compare the temporal trend of BPA exposures between the two cities.

2. Methods

2.1. Study participants

This study was built upon a joint research program between UCLA and PKU. This program supports ~ 15 UCLA students every year to visit PKU for ten weeks from mid-June to early-September for a full-time internship in a PKU lab matching students' research interest. Participants were recruited from this summer program in 2012, 2014, 2015, 2016, and 2017 via emails or on site at the program orientation held in early April (Lin et al., 2016, 2019). Most participants were accommodated in apartments on or near UCLA campus in Los Angeles and in hotels near the PKU campus in Beijing. Written informed consents were obtained from all participants with study purpose and risk explained. Demographic information and pre-existing health conditions were surveyed with a baseline questionnaire. The study was performed in accordance with guidelines and approval of the Institutional Review Boards of both UCLA and PKU.

2.2. Urine collection

For each participant, multiple morning urine samples with more than one-week intervals were collected in Los Angeles, Beijing, and in Los Angeles again. Urine collections were conducted either at study clinics of UCLA and PKU or at residual places at participants' convenience. All the collection was conducted on weekdays with the number of urine samples per participant at each phase shown in Table 1. Because previous studies have suggested short biological half-times of BPA after dietary exposures (i.e. ~ 6 h)(Thayer et al., 2015; Völkel et al., 2002), the urine samples were not collected until one week after the arrival at the new city to exclude the exposures from the previous city. Notably, a previous study reported significant declines in urinary BPA levels with increasing fasting time in the range of 4.5 – 8.5 h, which disappeared in the range of 8.5 – 24 h (Stahlhut et al., 2009). Therefore, participants were asked to fast for at least 8 h before sample collection so that the influence of fasting time on the difference in urinary BPA concentration between cities and years is diminished. Samples were collected with 90-mL polypropylene specimen containers and the aliquots were stored in 15-mL polypropylene centrifuge tubes (Fisher Scientific, Hampton, NH, USA) at −20 Celsius and kept away from light unless necessary. Urine samples collected in UCLA were transported to PKU for laboratory analysis through flight (~12 h) with dry ice. All the urine samples kept frozen throughout the transportation process. All the laboratory analysis was conducted within 16 months after the samples were collected.

2.3. Analytical method

Chemical standards of BPA and deuterium-labeled BPA (i.e. d_{16}-BPA), as well as β-glucuronidase-sulfatase were purchased from Sigma-Aldrich (St. Louis, MO, USA). All solvents used in this study were residue grade from Fisher Scientific (Hampton, NH, USA). We determined the total (conjugated + free) concentrations of BPA with a previously established method (Lin et al., 2019, 2016). Briefly, after spiked with d_{16}-BPA, two mL of urine were incubated with β-glucuronidase-sulfatase (Helix pomatia), followed by liquid–liquid extraction, diazomethane derivatization, and purification by silica gel column chromatography. Finally, samples were concentrated under a nitrogen stream and quantified by gas chromatography/mass spectrometry (Agilent 7890A-5975C). The estimated method limit of quantification (LOQ) was 11 pg/mL. The average (± standard deviation) recovery of d_{16}-BPA was 93.5 (± 25.4) %. The concentration of BPA in urine samples were corrected by the recovery of d_{16}-BPA. We have prepared 16 identical samples to monitor the method reproducibility and their relative standard deviations were 12.2 (± 17.3) %. Laboratory blank samples were prepared for each batch of urine samples, and the concentrations of BPA in blank samples were 3.9 (± 5.8) % of the average concentrations in urine samples. We also randomly selected six paired polypropylene containers and centrifuge tubes and screened for potential contaminations. The BPA concentrations in these blank samples were comparable to laboratory blanks and were 4.6 (± 5.7) % of the average concentrations in urine samples. Blank subtraction was not performed, and the BPA data were normalized by creatinine concentrations measured based on the Jaffe reaction (Toora and Rajagopal, 2002).

2.4. Daily intake Estimation.

We estimated BPA daily intakes (EDI, μg/kg body weight/day) in both cities based on a model described below (Lakind and Naiman, 2008; Zhang et al., 2013):

$$EDI = C_u \times V_u \times \frac{1}{W}$$

where C_u and V_u are the unadjusted concentrations of BPA (μg/mL) and urine excretion rate (L/day), respectively. According to previous studies, the average urine excretion rates of 1.6 and 1.2 L/day were assumed for the males and females, respectively (Lakind and Naiman, 2008; Zhang et al., 2013). W is the body weight (kg) and was obtained via the baseline questionnaires.

2.5. Statistical Analysis.

BPA was detected in 99.5% of the urine samples. For urine samples in which BPA was not detected, levels were assigned with 1/2 of the LOQ for statistical analysis. Because the distribution of BPA concentrations was right-skewed, geometric means with the interquartile

Table 1
Demographic information of study participants during 2012–2017.

	Total	2012	2014	2015	2016	2017	p_{trend} [a]
Number of subjects	55	10	14	13	8	10	
Designated number of samples per participant (LA-before/Beijing/LA-after)		3/5/3	1/5/3	2/3/2	2/3/2	2/3/2	
Actual number of samples collected (LA-before/Beijing/LA-after)	98/199/121	30/47/27	11/64/37	24/35/26	14/23/13	19/30/18	
Age (yr)	24.0 ± 7.8[b]	23.3 ± 5.8	23.3 ± 5.6	27.8 ± 13.6	22.6 ± 3.2	22.0 ± 2.7	0.86
BMI (kg/m^2)	21.3 ± 2.3	21.1 ± 1.4	21.7 ± 2.8	21.3 ± 2.1	20.1 ± 2.3	22.1 ± 2.4	0.62
Race (Asian/Others)	40/15	7/3	8/6	12/1	6/2	7/3	0.63
Sex (M/F)	27/28	4/6	9/5	3/10	3/5	8/2	0.34
Smoking (yes/no)	2/53	0/10	0/14	0/13	2/6	0/10	0.29

[a.] Temporal trends were tested by simple linear regressions for age and BMI, and logistic regressions for race, sex and smoking status;
[b.] Mean ± standard deviation

ranges (IQR) were reported by phase (i.e., LA-before, Beijing, and LA-after), city, and year. The difference in BPA concentrations between phases was evaluated with linear mixed effects models with participants as the random effects. Temporal trends of demographic variables were tested by linear or logistic regression models as appropriate. Temporal trends of BPA concentrations in each city were tested by linear regression controlled for age, sex, body mass index (BMI), race, and smoking status. Statistical significance was considered with a p-value < 0.05. All analyses were performed in statistical software R (www.r-project.org).

3. Results

Of 55 study participants (27 males and 28 females), the majority were Asian young non-smokers (Table 1). The average (± standard deviation) age and BMI were 24.0 (± 7.8) years and 21.3 (± 2.3) kg/m^2, respectively. None of participants have reported symptoms or history of heart disease, metabolic disorders, or symptoms of asthma, kidney disease, blood coagulation disorders, rheumatological diseases, or chronic inflammation during the previous 6 months, except for one who reported to have hypertension. No significant temporal trend was observed for age, BMI, race, sex, or smoking status from 2012 to 2017 (p greater than 0.05, Table 1). Urine samples were collected from 47 participants in all 3 study phases and from 8 participants in 2 study phases with absence in either LA-before or LA-after.

Over the entire study period, the geometric mean concentration of urinary BPA was 1.73 μg/g creatinine (IQR: 0.98–3.29) in Beijing, which is significantly higher than levels detected in LA-before (geometric mean: 0.53 μg/g creatinine; IQR: 0.25–0.96) or LA-after (geometric mean: 0.59 μg/g creatinine; IQR: 0.31–1.00). No significant difference was observed in the BPA levels between LA-before and LA-after ($p = 0.51$, Fig. 1A). These results suggest a 2.91-fold (95% CI: 2.43 to 3.50, $p < 0.001$) increase in exposure to BPA in Beijing as compared with Los Angeles (LA-before and LA-after). No significant correlation was observed between urinary BPA concentrations in Beijing and participants' time spent in Beijing ($p = 0.68$, Figure S1 of the Supplementary Materials).

From 2012 to 2017, the creatinine-adjusted levels of BPA in Los Angeles (LA-before and LA-after) were significantly decreased per year (-25.5%, 95% CI: −30.8% to −19.8%; $p < 0.001$, Fig. 1B), while no significant temporal trend was observed in Beijing (-5.0%, 95% CI: −12.9% to 3.6%; $p = 0.24$, Fig. 1C). These trends were consistent for unadjusted BPA concentrations when creatinine concentrations were controlled as a covariate (Table S1). The different trends of urinary BPA levels in Beijing and Los Angeles had resulted in a greater contrast of exposure to BPA between Beijing and Los Angeles, from 1.23 folds in 2012 (95% CI: 0.82 to 1.85; $p = 0.31$) to 4.05 folds in 2017 (95% CI: 2.75 to 5.97; $p < 0.001$) (Fig. 1D).

4. Discussion

In this study, we performed a natural experiment on Los Angeles residents who traveled to Beijing in a well-defined timeframe, which allowed us to directly compare the level and temporal trend of exposures to BPA between the two cities. We found that the urinary concentration of BPA was significantly lower in Los Angeles and decreased from 2012 to 2017, suggesting a successful reduction in population's exposure to BPA in the United States. In Beijing, however, the urinary BPA concentration was at relatively higher levels and did not change over time, suggesting that BPA remain an important environmental problem in China.

We compared the levels of urinary BPA in Los Angeles and Beijing to those among other healthy general population in the United States and China (Fig. 2). The temporal trend observed in our study aligns well with the long-term trends in both countries (i.e. 2006–2017), suggesting the relevance of our findings in two cities to the nationwide measures. Remarkably, the past decade witnessed continued increases in BPA production in both the United States and China (Greiner et al., 2004), while population's exposure decreased in the United States but did not change in China (Fig. 2). Thus, it is unlikely that national BPA productions drove the temporal trends of BPA exposure in either country.

We have identified national efforts to reduce BPA exposures in both countries (Fig. 2). In China, the regulation was mainly targeted at reducing the infant exposure by prohibiting the use of BPA in baby feeding bottles (Jiang et al., 2018), which might explain the lack of significant decline in urinary BPA levels in the non-infant population (Fig. 2). In contrast, extensive efforts were made by both government and manufacturers in the United States in 2009–2012, to phase out BPA in various consumer products including food packages and thermal receipts (Ye et al., 2015). Consequently, urinary BPA levels among general population have decreased since 2012 in the United States (Ye et al., 2015).

In addition to national regulatory policies, participants' behavioral changes may also contribute to the elevated levels of BPA exposures in Beijing. Results from our previous studies have suggested that travelers from Los Angeles to Beijing tended to spend more time at outdoors and less time cooking (Lin et al., 2016, 2019). Thus, they may have higher chance to eat fast food in Beijing as compared with Los Angeles and therefore were more likely exposed to BPA in food packages. Additionally, since participants were accommodated in hotels in Beijing, decorative materials consisting of epoxy resins (e.g., carpet and wallpapers) may also pose extra exposure risks (Ma et al., 2014). On the other hand, the inhalation of aerosols originated from waste incineration have been shown to increase BPA exposures (Song et al., 2019; Zhang et al., 2020), which should not be neglected in Beijing since we have previously identified significant contributions from waste incineration's to fine particles collected in PKU (Ma et al., 2018).

Our results showed that exposure to BPA could increase after a short-term travel to China, which might be relevant to more than 1.6

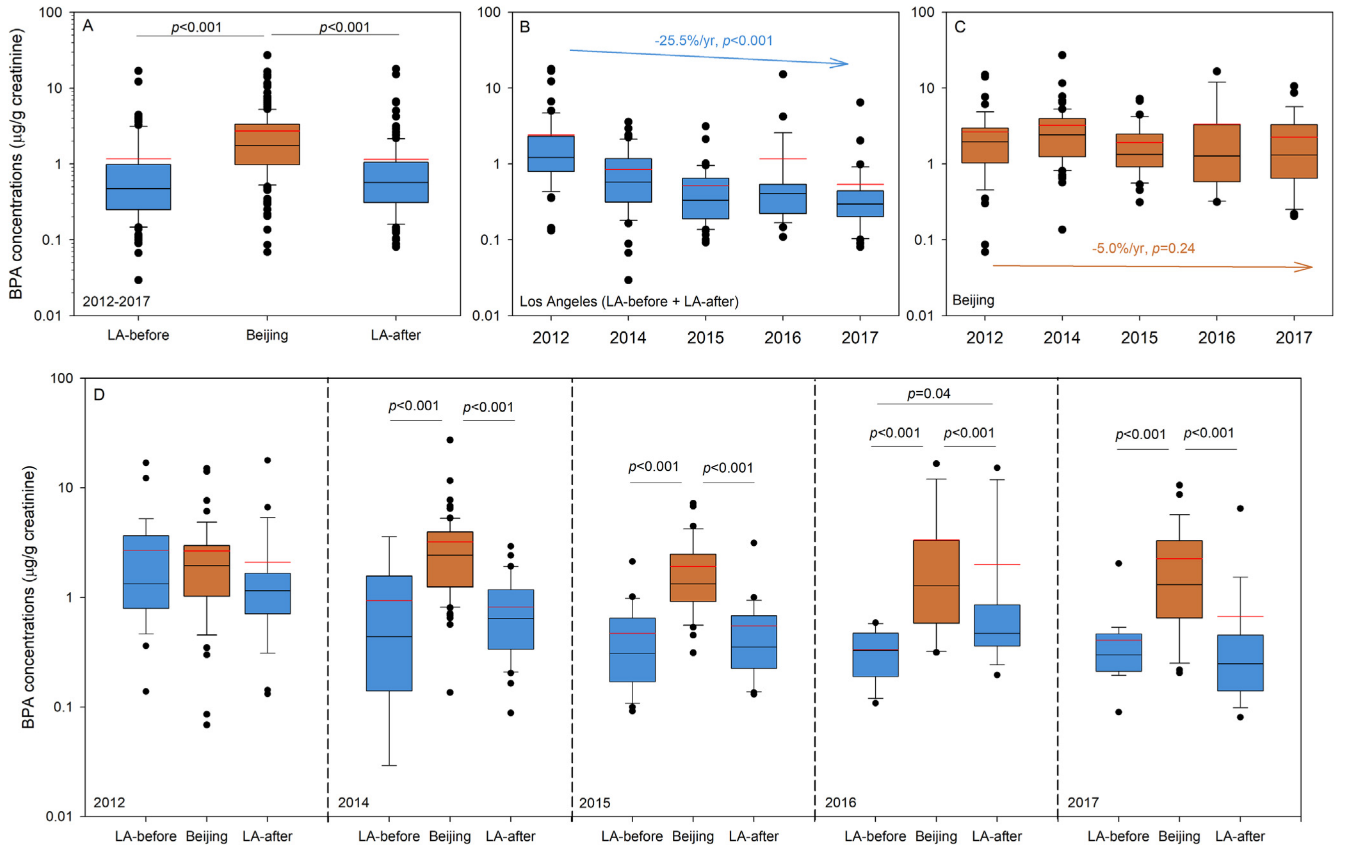

Fig. 1. Urinary concentration of BPA in LA-before, Beijing, and LA-after in the entire study period (Panel A) and in each year (Panel D) and as well as temporal trends of BPA concentrations in Los Angeles (Panel B) and Beijing (Panel C) from 2012 to 2017. Blue and orange boxes indicate data in Los Angeles and Beijing, respectively. The solid horizontal line represents the median, and the red horizontal line represents the mean. The box represents the 25^{th}-75^{th} percentiles, and the whiskers represent the 10^{th} and 90^{th} percentiles.

million United States residents who traveled to China each year (US Department of Commerce ITA Tourism Industries, 2018). Previous studies have suggested that BPA daily intakes were higher among population in Europe and Oceania as compared with other continents (Huang et al., 2018; Zhang et al., 2011). These studies also suggested comparable levels of BPA exposures in the United States and China, which is consistent with our results in 2012 (Huang et al., 2018). However, our results further indicated that with rapid declines in BPA exposures in the United States, Los Angeles residents who traveled to Beijing were exposed to significantly higher levels of BPA in 2014 – 2017. Albeit there is no evidence of adverse health effects of short-term BPA exposure in human, animal studies have shown that short-term exposure to BPA could induce metabolic disorders (Batista et al., 2012; Santos-Silva et al., 2018).

In recent years, while population's exposure to BPA has declined in the United States (Ye et al., 2015), there is an increasing concern about the exposure and toxicity of BPA substitutes (e.g. bisphenol S) (Y. Chen et al., 2016). In China, however, the transition from BPA to its substitutes may not be as fast as that in the United States, given the lack of significant declines in BPA exposures from 2012 to 2017 in Beijing. Moreover, recent evidence showed one order of magnitude higher urinary BPA levels as compared with bisphenol S in general population in China (Liao et al., 2012; Zhang et al., 2016), suggesting that BPA remains a marked public health concerns in China. Notably, albeit the study participants (mostly Asian American or Asian international students) lived in similar environments with local university students, precautions must be made before extrapolating our results to local residents, as the differences in lifestyles due to races, age groups, and travel itself are likely to modify the level of exposures. For example, a previous study has shown that BPA exposures among university students were associated with consumption of canned coffee or tea (Matsumoto et al., 2003), the level of which might differ between our study participants and local residents in Beijing. In addition, participants' exposure to BPA through food packages and decorative materials might also be higher than local residents as discussed above.

The EDI of BPA in both cities was estimated based on a previously established method assuming urine excretion rates of 1.6 L/day and 1.2 L/day for the males and females, respectively (Lakind and Naiman, 2008). The geometric mean (IQR) EDI was 11.5 ng/kg body weight/day (6.2 to 22.6) and 41.2 (21.7 to 97.1) in Los Angeles and Beijing, respectively. Albeit the higher exposure levels in Beijing, the maximum EDI of BPA was 738 ng/kg body weight/day, far less than the reference dose recommended by the United States Environmental Protection Agency (50 μg/kg body weight/day, oral exposure) (US Environmental Protection Agency). Nevertheless, it's important to note that fasting urine samples were collected in our study so that the EDIs are most likely underestimated due to diminished dietary contributions. In addition, recent studies have associated exposure to BPA at current levels in China to various clinical (e.g., type 2 diabetes (Ning et al., 2011) and low birth weight (Huo et al., 2015)) and pre-clinical endpoints (e.g., oxidative stress (Zhang et al., 2016) and sperm quality (Ji et al., 2018)). Thus, a more accurate estimation of BPA intakes among local residents and a better understanding of BPA's health effects is warranted before we can conclude the safety of BPA exposure levels in China.

The observed temporal trends of BPA exposures in this study appeared to be different from those of PAHs exposures, which was decreased in Beijing but not in Los Angeles as suggested in our previous study on the same population in 2014 and 2015 (Lin et al., 2019). These results may reflect different priorities for environmental regulatory actions in the United States (BPA) and China (PAHs and air pollution),

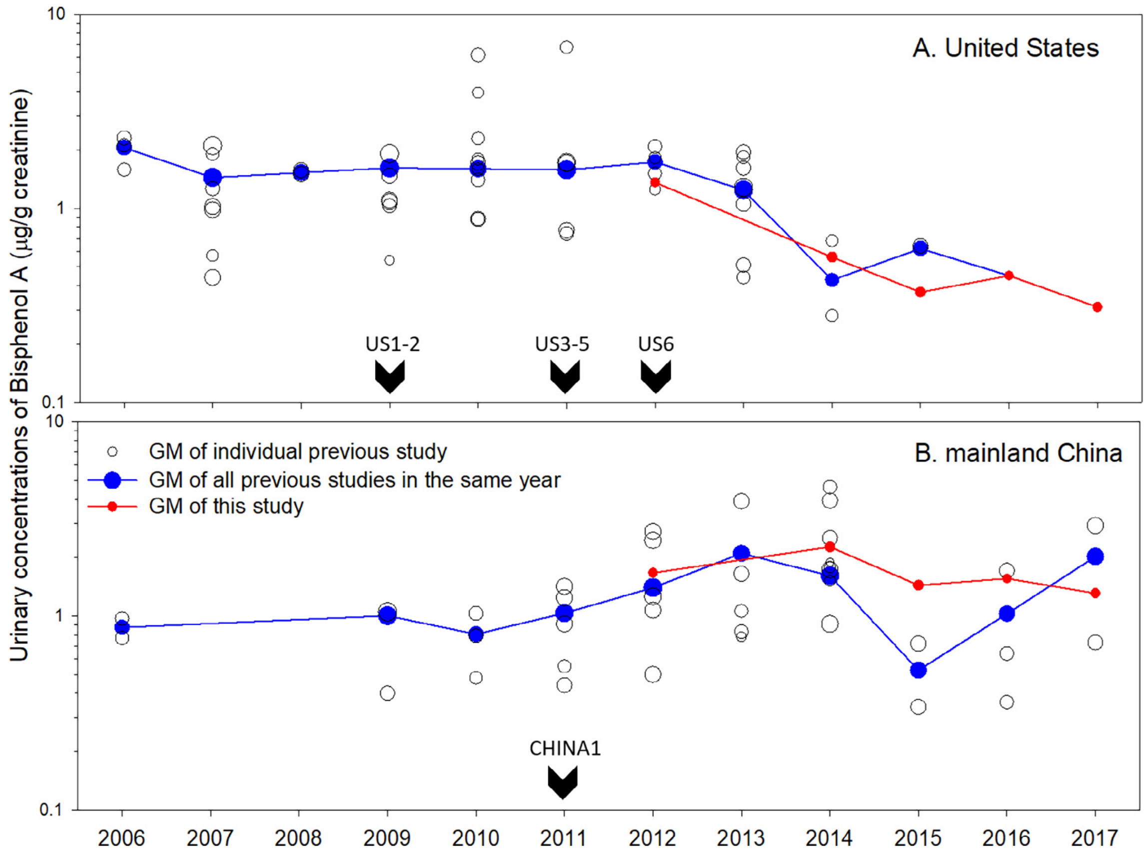

Fig. 2. Temporal trend of urinary BPA concentrations among general population and BPA regulatory policies in the United States (Panel A) and mainland China (Panel B) (US1: 13 states in U.S. enacted BPA restriction since 2009; US2: six large manufacturers stopped selling baby bottles containing BPA in U.S. since 2009; US3: U.S.'s largest manufacturer of thermal receipt stop using BPA in 2011; US4: major food package companies stopped using BPA in 2011; US5: FDA sent clear signs to industries about the transition out of BPA in 2011; US6: FDA banned BPA in baby bottles and children's drinking cup in 2012; CHINA1: Chinese government banned BPA in baby bottles in 2011. GM: geometric mean. White circle indicates median or mean level if GM is not reported by previous studies; blue circle indicates GM weighed by the number of population size. Circle areas are proportional to logarithmic population size. Inclusion and exclusion criteria of the studies is introduced in the Supplementary Materials and detailed information of each study is summarized in Table S2 of the Supplementary Materials).

in which the public health awareness is likely to play an essential role (Kiss, 2013; Sheehan et al., 2014). In the United States, the extensive debate of BPA safety in the past decades has brought substantial concerns to consumers about the use of BPA in consumer products (Kiss, 2013). This provides direct motivations for manufacturers to phase out BPA in their products albeit the lack of law enforcement, which largely contributed to the observed declines in BPA exposure. Similarly, the implementation of air pollution control policies in China was also partially motivated by the increasing public concerns of air pollution, after the frequent haze events in January 2013 (Sheehan et al., 2014).

Despite the unique experiment design, our study has several limitations. First, urine samples in different years were collected from different subjects so that the observed temporal trends were cross-sectional. However, despite an absence of significant temporal trends of participants' demographics (Table 1), we observed different temporal trends in urinary BPA levels between two cities in models adjusting demographic variables (Fig. 1). Thus, it is unlikely that the temporal trends of the exposure are confounded by the differences in participants. Second, the studied population might not be representative for the general population in the United States or China. However, the homogeneity in the study population may reduce the variability of urinary BPA levels due to social status and activity patterns, hence it is mostly likely that the change of environment drives the temporal trends in both cities. Finally, we did not survey activities that might lead to exposure to BPA, such as contact with receipts or the consumption of canned drinks. Notably, recent studies have suggested new BPA exposure pathways with different pharmacokinetics (Liu and Martin, 2017), such as dermal exposures via cloths (Wang et al., 2019). Thus, future studies are warranted to elucidate the contribution of different pathways to the elevated BPA exposure in China.

In summary, based on the measurement of urinary biomarkers, we found that healthy adults who traveled from Los Angeles to Beijing for 10 weeks were exposed to elevated levels of BPA. A significant downward trend of BPA exposures was observed in Los Angeles from 2012 to 2017 but not in Beijing. These results suggest that the United States' efforts to reduce population's exposure to BPA are effective, which are current lacking in China. Future studies are warranted to identify exposure pathways responsible for the elevated BPA exposures in China.

Acknowledgements

This work was supported by the National Institute of Environmental Health Sciences (NIEHS, 1R21ES024560 to YZ and JAA) and the National Natural Science Foundation of China (NSFC, 21876002, 21322705, and 41561144007 to XQ). We acknowledge the extensive support from the Joint Research Institute in Science and Engineering by Peking University and UCLA, especially Erin Hakim and Larissa Harrison for their assistance with recruitment. We thank Nu Yu for her assistance with sample collection. We also want to express our sincere appreciation to all volunteers who participated in our study. All the authors claim no potential conflict of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105758.

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