Human biomonitoring of bisphenol A along pregnancy: An exposure reconstruction of the EXHES-Spain cohort

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ABSTRACT

This study was aimed at reconstructing the exposure to bisphenol (BPA) of 60 pregnant women from the EXHES-Spain cohort. A biomonitoring study was conducted by determining BPA levels in urine samples over the three trimesters of pregnancy. Moreover, the correlations between BPA levels and the role of different potential exposure sources, with special emphasis on the dietary intake, were also studied. Urine samples were subjected to dispersive liquid-liquid microextraction and the subsequent analysis via gas chromatography-mass spectrometry. BPA was detected in 76% of the urine samples. A significant decrease of urinary BPA levels was observed along pregnancy, as mean concentrations of creatinine-adjusted BPA were 4.64, 4.84 and 2.51 µg/g in the first, second and third trimester, respectively. This decrease was essentially associated with changes in the dietary habits of the pregnant women, including a lower intake of canned food and drinks. However, the potential role of other pregnancy-related biochemical or physiological factors should not be disregarded. Very interestingly, significant differences in urine BPA levels were found according to the fruit consumption pattern, as women who ate more citrus fruits showed lower BPA concentrations in urine. The reconstructed exposure to BPA was estimated in 0.072, 0.069 and 0.038 µg BPA/kg of body weight/day in the first, second and third trimesters, respectively. These values are far below the temporary tolerable daily intake (t-TDI) established by the EFSA.

Keywords: bisphenol A; biomonitoring; pregnant women; exposure reconstruction; urine.

1. Introduction

Bisphenol A (BPA) is a monomer widely used in polycarbonate synthesis, plasticizer in the production of epoxy resins, an additive to eliminate the excess of hydrochloric acid during the production of polyvinyl chloride (PVC) (Konieczna et al., 2015). BPA is not only used in the fabrication of plastics to be in direct contact with food, such as food containers or baby bottles, but also in inner coatings of cans and jar caps (Fiege et al., 2012; Acconcia et al., 2015). Even though polycarbonates and epoxy resins account for the 95% of the total production of BPA (Careghini et al., 2015), other materials, like dental sealants or thermal paper, may contain BPA (Ma et al., 2019).

Diet is the main pathway of exposure to BPA (Martínez et al., 2018, González et al., 2020a, Gys et al., 2020). However, dust inhalation or dermal absorption should not be disregarded as other potential routes of exposure (Geens et al., 2012; Mustieles et al., 2020). Once BPA is ingested, it suffers a rapid process of glucuronidation in the liver, followed by its excretion through urine (Ma et al., 2019). Most of the BPA ingested is actually excreted through the urine within 24 h (Csanády et al., 2002; Martínez et al., 2018; Thayer et al., 2015), although it can be partly accumulated in fat tissues (Bellavia et al., 2018; Casas et al., 2013). In any case, it has been largely agreed that urine is the most suitable biomonitoring tool to assess the exposure to BPA (Genuis et al., 2012; González et al., 2020b).

BPA is a well-known endocrine disruptor interfering in the downregulation of the endocrine system by binding to the oestrogens receptors (Kim and Park, 2019). The exposure to BPA is a topic of concern because it might lead to several adverse health effects such as obesity, metabolic disorders, altered reproduction and neurodevelopment, and cancer (Seachrist et al., 2016; Wang et al., 2017; Dumitrascu et al., 2020; Ma et al., 2019; Martínez et al., 2020a; Mustieles et al., 2020).

BPA exposure during pregnancy has a direct negative impact on maternal, foetal, and neonatal outcomes. Unconjugated BPA, as well as BPA-G at a smaller proportion, are able to cross the human placenta (Ginsberg and Rice, 2009; Balakrishnan et al., 2010). Moreover, because foetuses do not own a completely developed glucuronidation system, BPA is accumulated (Fenichel et al., 2013). Perinatal exposure to BPA has been linked to low birth weight (Huo et al., 2015), and to birth length and head circumference

(Lee et al., 2014; Snijder et al., 2013). In turn, developmental defects (i.e.: anogenital distance, nervous system abnormalities, chromosomal anomalies) and recurrent miscarriage has been also reported (Miao et al., 2011 and Guida et al., 2015). On the other hand, the potential effect of BPA on preeclampsia and gestational diabetes mellitus is a topic of recent concern, but as current research is very limited, results are still inconclusive (Pergialiotis et al., 2018).

This study was aimed at performing a biomonitoring study of BPA levels in urine samples from 60 pregnant women recruited within the EXHES-Spain cohort. The associations between maternal exposure to BPA with lifestyle habits and personal data were also explored.

2. Materials and methods

2.1. Study population

The study population comprised a group of pregnant women from the European Exposure and Health Examination Survey (EXHES-Spain) Spanish cohort (Martínez et al., 2020b), which was recruited during the first trimester of pregnancy as part of the Health and Environment-wide Associations based on large population surveys (HEALS) project (Bocca et al., 2019). The recruitment of pregnant women started in March 2016, being here included 60 pregnant women and their newborn children. Women were informed of the study during their first visit, around the 12^{th} gestational weeks (GW), at the Hospital Sant Joan in Reus (Catalonia, Spain). Details of recruitment protocols were previously described (Martínez et al., 2017, 2018). This study was approved by the Ethical Committee of Clinical Research of the Hospital (No 16-04-28/4aclaproj2), and the written informed consent was obtained from the participants. The characteristics of the EXHES-Spain cohort are summarized in Table 1.

2.2. Sampling and data acquisition

One hundred seventy-nine urine samples from 60 pregnant women recruited within the EXHES-Spain cohort were collected during their three trimesters of pregnancy.

Samples were obtained at approximately the 12th, 20th and 32nd GW. One of the 180 original samples, corresponding to a subject in her second trimester, was lost. Urine samples were properly stored at -80 ºC until analysis.

Women were requested to fill up different questionnaires about their lifestyle. Questions included data about diet, education, annual income, marital status, physical characteristics (i.e., height and weight), country of origin, as well as use of personal care products (PCPs) and cleaning products. In addition, other potential risk factors of BPA exposure (e.g., smoking and drinking habits, profession, etc.) were also taken into consideration. More information regarding questionnaires was given elsewhere (Martínez et al., 2017). After the delivery, data regarding anthropometric measurements of the babies, including weight, length, head circumference, as well as weight of placenta and width of umbilical cord, were recorded.

2.3. Analytical determination of BPA

2.3.1. Standards and reagents

BPA (99% purity) and $_{d16}$-bisphenol A (BPA_{d16}; 98 atom % D), were purchased from Sigma-Aldrich (West Chester, PA, USA) and Cambridge Isotope Laboratories, Inc. (Tewksbury, MA, USA), respectively. BPA_{d16} at a concentration of 1 ppm was used as internal standard (IS). Methanol from QCA (Tarragona, Spain) was used to prepare the different dilutions of BPA and BPA_{d16}. Acetonitrile (MeCN, >99% purity), acetic anhydride (AA, >99% purity) and tetrachloroethylene (T4CE, >99% purity), as well as β-glucuronidase (Type 1 from Helix pomatia, ≥3000,000 U/g solid glucuronidase and ≥10,000U/g solid sulfatase), were purchased from Sigma Aldrich-Merck (Darmstadt, Germany). Potassium carbonate (K_2CO_3, 99% purity) was purchased from PanReac AppliChem ITW Reagents (Barcelona, Spain). Glacial acetic acid and ammonium acetate were both purchased from Sigma-Aldrich, while acetone and methanol for washing was provided by Merck Millipore (Darmstadt, Germany).

2.3.2. Instrumentation

A gas chromatograph 6890 (Agilent, Little Falls, DE, USA) equipped with a Combi-PAL autosampler (CTC Analytics, Zwingen, Switzerland) and a mass selective detector (5975B, Agilent) with an electron ionization (EI) chamber, was used for data collection. The separation was performed on a DB-5MS column (30 m × 0.25 mm I.D. × 0.25 µm film thickness; J&W Scientific, Folsom, CA, USA). Chromatographic and detection specifications have been described elsewhere (González et al., 2019).

2.3.3. Quality control/quality assurance

To prevent any background contamination, all plastic materials were avoided, while glassware was previously baked for 1 h at 300 °C and then washed with acetone. Prior to the analytical procedure, samples were spiked with standards to evaluate different analytical performances, such as linearity, sensitivity, precision and accuracy (EC, 2017). Linearity was assessed through multilevel matrix-matched calibration with eleven calibration levels. Calibration curves were built by the least-squares linear regression model, plotting the peak area ratios of the target compound and IS versus the concentration of each target substance. In order to guarantee no contamination, a blank extract (free of BPA) was injected in each batch of samples. Furthermore, methanol was also injected between samples. Detection limits were calculated using low level points to achieve signal-to-noise ratios of 3. In turn, the quantification limits were established as the lowest concentration with acceptable accuracy and precision, corresponding to the lowest calibration level of the calibration curve. The limit of quantification (LOQ) was set at 0.1 µg/L , while the limit of detection (LOD) was set at 0.03 µg/L.

2.3.4. BPA extraction

The detailed methodology for BPA determination in urine samples was previously reported (González et al., 2019). Briefly, urine samples were defrosted until achieving room temperature followed by the transference of 5 mL of urine to a vial. Then, 100 µL of β-glucuronidase solution (20,000 U/mL in 1M ammonium acetate buffer pH 5.0) were added, and the mixture was incubated at 37ºC overnight. After cooling at room temperature, samples were transferred to a glass tube with conical bottom followed by the addition of the following mixture: 300 µL of K_2CO_3 (23%) (to achieve pH>10), 50 µL of BPA_{d16} (1ppm), 1325 µL of MeCN, 85 µL of T4CE and 125 µL of AA. Then, all the tubes were shaken and centrifuged for 10 min at 1800 rpm and 4 °C. Finally, 70 µL of the lower phase were transferred to a 100 µL insert, being 1 µL injected into the GC-MS. Finally, BPA concentrations in urine were adjusted according to the content of creatinine, which was analysed using a Cobas Mira automatic analyser (Roche Pharmaceuticals, Basel, Switzerland).

2.4. Exposure reconstruction

Reverse dosimetry simulations were performed to back-calculate the daily intake of BPA, according to measured urinary concentrations. The external exposure to BPA was estimated by applying using reverse dosimetry using a pregnancy-physiologically based pharmacokinetic (PBPK) model developed by Sharma et al. (2018). The PBPK model was coded in R, and solved using the R deSolve integration program GNU MCSim 6.2 (Bois and Maszle, 1997). A Markov Chain Monte Carlo (MCMC) method was used to estimate the probability distribution of cumulative daily BPA exposure for each individual subject. Since reconstructing daily doses from spot urine biomarker measurements at random time points proves are quite complex, the exposure profiles simulated for this cohort required a simplification. Therefore, a few assumptions were considered. Ingestion was assumed as the only exposure pathway of BPA. In turn, the contributions of dermal absorption from PCPs and air inhalation to the total aggregated exposure to BPA were considered as negligible (Martínez et al., 2018, Sharma et al., 2018). To reconstruct the BPA cumulative daily exposure, the spot BPA urine concentration was converted into cumulative BPA urine concentration by applying the following equation (Eq. 1), adapted from Mann and Gerber (2010):

$$\text{Cumulative BPA urine conc.} = \left(\frac{\text{Spot BPA urine conc.}}{\text{Spot creatinine}}\right) \times \text{total urinary creatinine} \qquad \text{(Eq. 1)}$$

Where cumulative BPA urine concentration is the individual total urine elimination of BPA in within a period of 24 h (in µg BPA/day), spot BPA urine concentration is the measured BPA concentration in each individual spot urine (in µg/L), spot creatinine is the measured creatinine concentration (in g/L), and total urinary creatinine is the total amount of creatinine excreted for 24 h by a woman, according to data from the scientific literature (in g/day).

Because of the dynamic changes in the renal blood flow and the glomerular filtration rate, the serum creatinine concentrations undergo some changes during pregnancy (Wiles et al., 2018; Odutayo et al., 2012). The mean value for serum creatinine in pregnancy has been reported to range 77%-84% compared to data from non-pregnant female (Wiles et al., 2019). The daily creatinine excretion for adult women was considered to be 21, 18 and 16 mg/kg body weight (bw)/day, associated with a body mass index (BMI) of <25 kg/m^2, 25-30 kg/m^2, and >30 kg/m^2, respectively (Koppen et al., 2019). The creatinine total amount for each individual was adjusted accordingly, considering both the BMI and the corresponding trimester reduction.

The health risks associated to the dietary intake of BPA were also characterized. The reconstructed exposure to BPA was compared to the temporary tolerable daily intake (t-TDI) set by the European Food Safety Authority (EFSA, 2015).

2.5. Statistical analysis

Data treatment was performed using the statistical package IBM SPSS (v. 26). Statistically significant differences of urinary BPA concentrations according to the characteristics and habits of the cohort were set at a level of significance of 0.05 ($p < 0.05$). The Levene test was used to compare the homogeneity of variances. Subsequently, the significance of the data was computed by an analysis of variance (ANOVA). For calculation purposes, when the concentration of BPA in urine was under the LOD, a value of LOD/2 was considered for that subject.

3. Results and discussion

3.1. Urinary BPA concentrations

The concentration of BPA in urine from 60 pregnant women from the EXHES-Spain cohort are summarized in Table 2. BPA was detected in 76% of the samples. Mean BPA levels were 2.85, 2.77 and 1.86 µg/L in the first (T1), second (T2) and third (T3) trimester, respectively. When considering the amount of creatinine, adjusted BPA mean levels were 4.64, 4.84 and 2.51 µg/g creatinine in T1, T2 and T3, respectively. No changes of BPA urinary levels were noted between the 12^{th} and 20^{th} GW. In turn, a significant decrease ($p<0.05$) of BPA concentrations was observed in the last trimester of pregnancy with respect to previous two. In T3, the urinary BPA levels in pregnant women were 46% and 48% lower than in T1 and T2, respectively. This reduction may be associated with changes of dietary habits during pregnancy (Quirós-Alcalá et al., 2013). The dietary habits of pregnant women notably changed after the 20^{th} GW. Thus, consumption patterns showed a decrease of the intake of canned or plastic-packaged foods and canned drinks (5%), meat (5%), fish (15%), fast food (2%), legumes (8%) and ready-to-eat food (3%). Contrastingly, pregnant women reported an increase of the consumption of dairy products (5%) as well as fruits and vegetables (2%) by the end of their pregnancy (T3). Since canned food is the major contributor to the dietary exposure to BPA (Lorber et al., 2015; González et al., 2020a), a lower intake of canned foods and drinks would be definitively related to the decrease of BPA levels in T3. Finally, a decrease in the smoking habits was noticed along pregnancy. Up to 32% of the participants smoked in T1, but these levels dropped to 15% and 8% in T2 and T3, respectively. It has been reported that smoking is a risk factor for high urinary BPA levels (Berman et al., 2014). However, although a slight decrease in the smoking habits was detected, no significant correlations between smoking and BPA levels were found in the present study.

Urine samples from three different participants (No. 481 (T1), 518 (T2) and 517 (T3)) were considerably high (17.7, 44.2 and 192 µg/L, respectively) in comparison to mean levels of each trimester (2.85, 2.77 and 1.86 µg/L, respectively). Food consumption patterns of these three women were linked to unhealthy lifestyles that are not representative of the cohort and clearly enhance the exposure to BPA. Since BPA accounts for 25% of the weight of cigarette filters (Braun et al., 2011), smoking is a key factor influencing BPA exposure (Berman et al., 2014). Moreover, the increase of body fat makes easier the accumulation of BPA. The positive association between BPA urinary levels and BMI has been observed in different studies (Bellavia et al., 2018; Casas et al., 2013). Therefore, in order to avoid an overestimation of urinary BPA concentrations of the cohort, these data were excluded from any further statistical analysis.

BPA levels in urine samples from pregnant women reported in a number of countries are summarized in Table 3. The current concentrations of urinary BPA in pregnant women living in Reus/Tarragona are similar to that previously found in other Spanish investigations (Casas et al., 2013, 2016; Valvi et al., 2013). Huang et al. (2019) observed 2-fold higher concentrations of BPA in urine samples from 850 pregnant women living in Wuhan, China than those here reported. Interestingly, BPA levels also decreased when comparing data from the first and third trimesters of pregnancy (Huang et al., 2019). In Puerto Rico, the geometric mean concentrations of BPA in urine samples from pregnant women living in Puerto Rico were 2.16, 2.07 and 1.78 µg/L in T1, T2 and T3, respectively, thus denoting a slight decrease along the pregnancy (Aker et al., 2019). However, our data are still slightly higher than those previously reported by several researchers in the scientific literature. In general, unadjusted urinary BPA concentrations of pregnant women are typically below 2 µg/L, irrespective of the country, according to data from the USA, the Netherlands, Mexico, Iran and several areas of China (Phillippat et al., 2013; Quirós-Alcalá et al., 2013; Jamal et al., 2020; Guo et al., 2020; Zhou et al., 2020; Hou et al., 2021).

3.2. Correlation of BPA levels with cohort characteristics and dietary habits

No significant relationships were found between BPA levels in urine of pregnant women and the following newborn characteristics: weight, length, head circumference, weight of placenta, and width of umbilical cord. Furthermore, no associations could be observed between the burdens of BPA and the maternal characteristics. This lack of associations could be explained by the relatively low number of participants compared to other studies in which significant relationships had been found (Berman et al., 2014; Snijder et al., 2013). It must be highlighted that the present study was focused on analysing the temporal changes of urinary BPA concentrations along the pregnancy, being more important the acquisition of data from each trimester than increasing the number of volunteers. From a logistic point of view, all the urine samples were collected in the morning, therefore eliminating the potential influence of sampling timing on BPA levels (Mahalingaiah et al., 2008).

Regarding dietary habits, a significant correlation ($p<0.05$) was found between the consumption of citrus fruits and creatinine-unadjusted levels of BPA in urine. Women consuming less than one piece of citrus fruits a day showed significantly ($p<0.05$) higher mean levels of urinary BPA than women eating at least one piece or more per day (4.08 vs. 2.23 µg/L). Fresh fruits and vegetables are two of the food groups with the lowest concentration of BPA (Liao and Kannan, 2013; Sakhi et al., 2014; Chen et al., 2016). Consequently, people with consumption patterns based on a high intake of fresh or unpacked fruits and vegetables, are more likely to reduce the exposure to BPA. In addition, fruit consumption is usually associated with healthy habits, diet and lifestyle; therefore, fruit consumption might be a good indicator of exposure to BPA. Braun et al. (2011) proved that strict vegetarians have lower levels of BPA compared to non-vegetarians.

Although no specific literature has been found regarding the relationships between low urinary BPA and fruit consumption, some studies seem to confirm this association. Rudel et al. (2011) performed a dietary intervention intended to reduce the dietary exposure to BPA and other metabolites, being fruit included. A reduction of BPA levels during the intervention was reported, meaning that fruit -among other healthy food- contributed to the reduction of BPA levels. In conclusion, it is reasonable that the regular consumption of fruit has a beneficial effect on health by reducing exposure to BPA. However, additional research is needed to further elucidate the real impact of fruits and vegetables consumption not only on urinary BPA levels but also on the health effects for pregnant women and foetuses.

3.3. BPA exposure reconstruction

The estimated exposure to BPA along the pregnancy, according to data calculated for the participants from the EXHES-Spain cohort, is depicted in Figure 1. Mean intake values were estimated in 0.072, 0.069 and 0.038 µg/kg bw/day in T1, T2 and T3, with maximum values of 0.262, 0.505, and 0.256 µg/kg bw/day, respectively. As above-mentioned, food consumption is the main exposure pathway to BPA, especially when consuming canned and plastic-packaged foodstuffs. The reduction of the biological burdens of BPA throughout the pregnancy would be consequent of a lower dietary intake of BPA. This is especially relevant in the last trimester of pregnancy, when other dietary and lifestyle factors, such as a higher consumption of fruits, may play an additional role. In any case, the current exposure to BPA for the pregnant women living in Tarragona is far below the t-TDI set at 4 µg/kg bw/day by the EFSA (2015). Even the daily exposure of those volunteers who showed very high urinary BPA concentration (No. 481, 517 and 518) did not exceed this threshold, as their BPA exposure was estimated in 2.01, 1.50 and 0.67 µg/kg bw/day, respectively.

Notwithstanding, it must be highlighted that low dose effects of BPA should be also taken into consideration (Jenkins et al., 2011; Li et al., 2020). In addition, the actual exposure to BPA might be underestimated due to several reasons. On one hand, the normalisation of BPA levels for creatinine is not an accurate data treatment methodology when analysing values from pregnant women, as creatinine metabolism and excretion change during the gestation. For this reason, another method for correcting the urine dilution, such as specific gravity, could be more appropriate, thus improving the reconstructed exposure (Braun et al., 2011). On the other hand, the values of daily creatinine excretion, extracted from the scientific literature (Koppen et al., 2019), correspond to the general population of adult women. At this moment, no daily creatinine excretion values have been reported for pregnant women. In any case, from a perspective of health risk assessment, our results are similar to those previously reported in a number of countries, where specific cohorts of pregnant women were not exposed to levels higher than the t-TDI (Cao et al., 2011; Chen et al., 2016; Mariscal-Arcas et al., 2009).

Recently, our laboratory performed a biomonitoring study of BPA and other analogues by analysing spot urine and blood samples from adults of a cohort who followed a diet based on a high consumption of canned food (González et al., 2020b). A duplicate diet study was carried out, being compared the results of two populations groups (canned-diet and control). The dietary intake of BPA by the adults consuming foodstuffs either canned or packaged in plastic was estimated in 0.110-0111 µg/kg bw/day, while the exposure by the people eating fresh or glass-packaged food was calculated in 0.027-0.041 µg/kg bw/day. In the present study, the estimated exposure to BPA by the EXHES-Spain cohort pregnant women was estimated in 0.072 and 0.069 µg/kg bw/day in the T1 and T2, respectively. These values would fall exactly in the middle of the BPA exposure when comparing a diet fully based on canned foodstuffs with a diet free of canned food. In turn, the BPA daily intake in T3 was calculated in 0.038 µg/kg bw/day, which falls well into the range of exposure by the control group in that biomonitoring study (González et al., 2020b). These results fully agree with the information obtained in the questionnaires, as a decrease of the intake of canned or plastic-packaged foods and canned drinks was reported.

4. Conclusions

A biomonitoring study was performed to determine the levels of BPA in urine samples from 60 pregnant women recruited within the EXHES-Spain cohort along the three trimesters of pregnancy. BPA was detected in 76% of the samples, whose creatinine-adjusted BPA mean concentrations were 4.64, 4.84 and 2.51 µg/g in T1, T2 and T3, respectively. A decrease of urinary BPA levels was found with time, being the levels of BPA in T3 significantly reduced compared with those found in T1 and T2. No significant relationships were reported between BPA levels and most maternal or newborn characteristics. The only exception was the consumption of citrus fruits, which was significantly associated with a decrease of urinary BPA levels. Furthermore, the reduction of BPA values in urine was related to some changes of consumption patterns, including the reduction of the intake of canned food and drinks. Biomonitoring results were used to reconstruct the exposure to BPA. According to the scientific literature, food consumption was assumed to be the main exposure pathway to this chemical. However, it must be highlighted that, in the present study, significant correlations could be only found between BPA levels and intake of citrus fruits. According to the estimations, none of the pregnant women showed an exposure level higher than the t-TDI set by the EFSA.

One of the limitations of the study is the relatively short number of participants, as only 60 pregnant women were included. Therefore, the role of other potential factors in the BPA exposure, including the consumption of specific foodstuffs and other lifestyle habits, could not be studied in detail. In any case, additional research on BPA and other bisphenol analogues is needed to understand well their toxicity mechanisms but also the effects on the development of foetuses *in utero* as well as the implications of the perinatal exposure to BPA. From a public health perspective, there must be a clear message addressed to pregnant women, emphasizing the importance of having a healthy diet. Furthermore, an increase of the intake of vegetables and fruits, especially citrus, and a decrease of the consumption of canned food and drinks, are two key factors to minimize the exposure to BPA.

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Table 1

Characteristics of the pregnant women from the EXHES-Spain cohort

Characteristics of the cohort (n=60)	%	Characteristics of the cohort (n=60)	%
Maternal age at delivery (years)		**Maternal pre-pregnancy BMI***	
<20	0	Underweight (<19 kg/m^2)	2
20-29	20	Normal (19–25 kg/m^2)	47
30-39	68	Overweight (>25 kg/m^2)	29
>40	12	Obese (>30 kg/m^2)	22
Twin pregnancy	5	**Maternal pregnancy BMI***	
Maternal smoking		Underweight (<19 kg/m^2)	0
Never smoke	66	Normal (19–25 kg/m^2)	30
Not during pregnancy	7	Overweight (>25 kg/m^2)	35
During pregnancy	27	Obese (>30 kg/m^2)	35
Maternal education		**Water consumption before pregnancy**	
Primary	19		
Secondary	30	Tap water	2
University	51	Bottled water	87
Annual income		Both	11
<19,000€	22	**Water consumption during pregnancy**	
19,000-35,000€	56		
>35,000€	22	Tap water	0
Maternal job related to		Bottled water	89
Medical devices	23	Both	11
Thermal paper	18	**Eat organic products**	
Dust	39	Never	39
No apparent risk	8	Hardly ever	30
Cleaning products	5	Sometimes	27
Unemployed	7	Very often	4
Maternal country of origin		**Type of milk**	
Spain	76	Whole	23
Rest of Europe	9	Semi-skimmed	58
South America	10	Skimmed	19
Asia	2		
Africa	3		

BMI: Body mass index

Table 2

Creatinine-unadjusted (µg/L) and -adjusted (µg/g creatinine) concentrations of BPA in samples of urine from women of the EXHES-Spain cohort along the pregnancy.

Trimester	Creatinine	% detected	Mean ± SD	Range	P5	P50	P95
1st Trimester (n=60)	Unadjusted	88	2.85 ± 3.12	<LOD-20.2	<LOD	2.33	6.96
	Adjusted	88	4.64± 3.97	<LOD -16.6	<LOD	3.96	14.0
2nd Trimester (n=59)	Unadjusted	78	2.77 ± 3.11	<LOD-17.0	<LOD	2.04	8.34
	Adjusted	78	4.84± 6.20	<LOD -35.1	<LOD	3.57	16.4
3rd Trimester (n=60)	Unadjusted	62	1.86 ± 2.46	<LOD-11.8	<LOD	1.10	6.95
	Adjusted	62	2.51 ± 3.36	<LOD -17.3	<LOD	1.89	6.46

SD: Standard deviation; LOD: limit of detection. P5, P50 and P95: 5th, 50th, and 95th percentile, respectively.

Table 3. BPA urine levels during pregnancy in different studies from the scientific literature.

Ref	Number of samples	Country	Trim.		Mean ± SD GM (95% CI) GM (SD) Mean; GM	Range	P5	P25	P50	P75	P95
Quirós-Alcalá et al., 2013	407	Mexico	T1	U	0.9 (2.8)	-	-	0.5	1.0	1.7	-
				C	1.1 (2.4)	-	-	0.6	1.1	1.8	-
	459		T2	U	1.0 (2.6)	-	-	0.5	1.0	1.8	-
				C	1.1 (2.4)	-	-	0.7	1.1	1.8	-
Philippat et al., 2013	71	USA	T1	U	-	-	< LOD	-	0.6	-	0.7
			T2	U	-	-	< LOD	-	1.8	-	9.5
			T3	U	-	-	< LOD	-	1.2	-	5.0
Valvi et al., 2013	402	Spain	T1	U	2.1 (2.6)	0.1-122.8	0.5	1.2	2.0	3.6	12.1
				C	2.6 (2.3)	0.2-138	0.8	1.5	2.4	4.2	12.9
			T3	U	1.8 (2.7)	<LOD-103.7	0.3	1.0	1.8	3.2	8.9
				C	2.0 (2.3)	0.2-102.6	0.5	1.2	2.0	3.1	6.6
Casas et al., 2013	479	Spain	T1	U	2.1 (2.7)	0.1-122.28	0.4	1.2	2.0	3.6	11.9
				C	2.6 (2.3)	0.2-138	0.7	1.5	2.3	4.1	11.9
			T3	U	1.8 (2.7)	0.1-103.7	0.3	1.0	1.8	3.2	8.5
				C	2.0 (2.3)	0.1-102.6	0.5	1.3	2.0	3.1	7.1
Casas et al., 2016	470	Spain	T1	U	2.3 (2.1, 2.4)	0.3–61.8	-	-	-	-	-
			T3	C	2.6 (2.4, 2.8)	0.3–69.4	-	-	-	-	-
Liu et al., 2018	467	Canada	T2	U	1.23 (1.11, 1.36)	-	-	0.59	1.19	2.34	8.20
				C	1.68 (1.55, 1.83)	-	-	0.88	1.56	2.80	9.57
Huang et al., 2019	850	China	T1	U	8.94; 2.19	-	< LOD	0.08	1.14	3.51	20.47
				SG	13.04; 0.81	-	< LOD	0.13	1.47	4.00	26.95
			T2	U	5.66; 2.07	-	< LOD	0.13	1.25	3.59	17.72
				SG	8.38; 0.96	-	0.02	0.19	1.71	4.47	24.01
			T3	U	5.70; 2.00	-	< LOD	0.25	1.23	3.31	17.94
				SG	8.76; 2.91	-	< LOD	0.35	1.72	4.90	27.42
Aker et al., 2019	922	Puerto Rico	T1	U	2.16 (2.49)	-	-	1.21	2.09	3.68	-
			T2	U	2.07 (2.69)	-	-	1.10	2.01	3.71	-
			T3	U	1.78 (2.40)	-	-	1.00	1.71	3.09	-
Hu et al., 2019	845	China	T1	U	0.8 (0.7, 0.9)	-	-	0.1	-	3.4	-
			T2	U	0.9 (0.7, 1.0)	-	-	0.2	-	3.8	-
			T3	U	1.0 (0.8, 1.1)	-	-	0.3	-	4.4	-
Li et al., 2019	941	China	T1	U	-	-	-	0.14	1.14	3.48	-
				SG	-	-	-	0.31	1.46	3.90	-
			T2	U	-	-	-	0.14	1.25	3.54	-
				SG	-	-	-	0.34	1.43	3.78	-
			T3	U	-	-	-	0.19	1.18	3.29	-
				SG	-	-	-	0.36	1.35	4.00	-
Zhou et al., 2020	322	China	T3	U	-;0.81	-	-	0.37	0.96	2.12	-
				C	-;0.95	-	-	0.46	1.02	2.45	-
Jamal et al., 2020	189	Iran	T1	U	1.46 ± 0.93			0.85	1.27	1.88	-
Guo et al., 2020	386	China	T3	U	-	0.16-224	-	0.60	1.75	16.1	-
				C	-	0.16-480	-	1.04	2.88	27.1	-
Derakhshan et al., 2021	1267	The Netherlands	T1	U	1.61	<LOD-21.0	-	-	-	-	-
			T2	U	1.47	<LOD-21.2	-	-	-	-	-

			T3	U	1.65	<LOD-20.5	-	-	-	-	-
Hou et al., 2021	390	China	T2	U	0.58 (0.53, 0.63)	0.11-14.58	0.21	0.33	0.51	0.88	2.76
				C	0.73 (0.67, 0.79)	0.09-26.75	0.23	0.41	0.62	1.10	3.69
Present study	60	Spain	T1	U	2.85 ± 3.12	<LOD-20.2	<LOD	1.13	2.33	3.76	6.96
				C	4.64± 3.97	<LOD -16.6	<LOD	2.04	3.96	5.45	14.0
	59		T2	U	2.77 ± 3.11	<LOD-17.0	<LOD	0.68	2.04	3.59	8.34
				C	4.84± 6.20	<LOD -35.1	<LOD	1.48	3.57	5.28	16.4
	60		T3	U	1.86 ± 2.46	<LOD-11.8	<LOD	<LOD	1.10	2.43	6.95
				C	2.51 ± 3.36	<LOD -17.3	<LOD	<LOD	1.89	3.24	6.46

T1, T2, T3: First, second and third trimester of pregnancy, respectively. C: Creatinine adjusted (µg /g crea); SG: Specific gravity corrected (µg /L); U: Unadjusted (µg /L); LOD: limit of detection; GM: geometric mean; 95% CI: confidence interval of GM. P5: 5th percentile; P25: 25th percentile; P50: 50th percentile; P75: 75th percentile; P95: 95th percentile. Results expressed in: GM ± SD, GM (95% CI), Mean ± SD, Mean; GM, Range, P5, P25, P50, P75, P95.

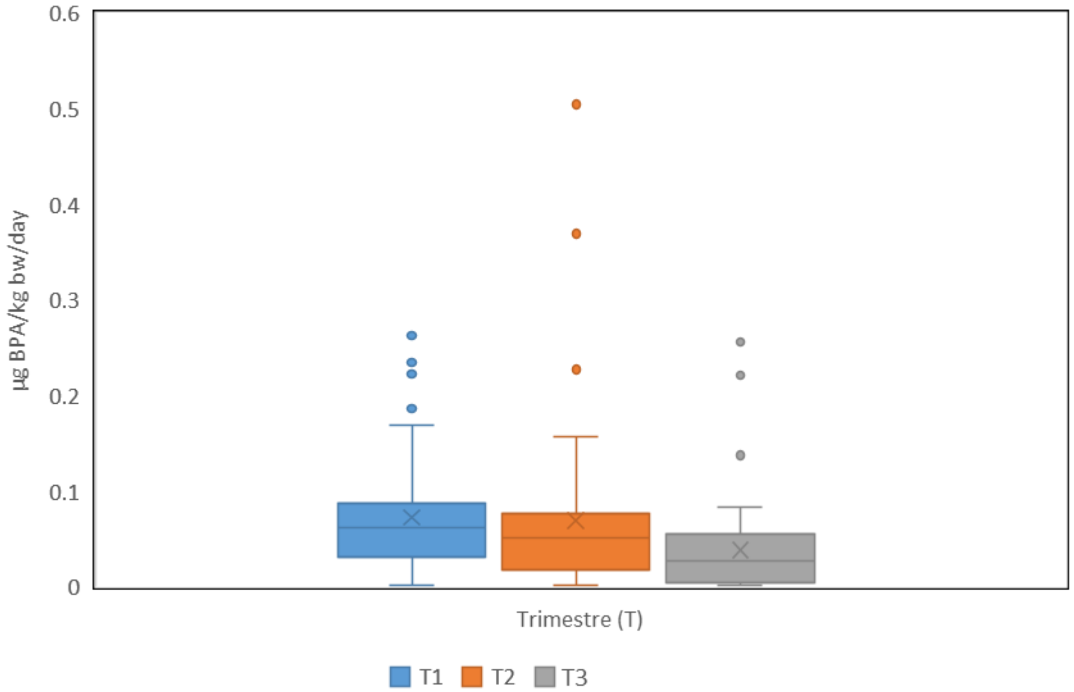

Figure 1. Estimated BPA exposure along pregnancy for 60 pregnant women of the EXHES-Spain cohort.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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