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Biomonitoring of co-exposure to bisphenols by consumers of canned foodstuffs

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ABSTRACT

For non-occupationally exposed adults, dietary intake is the main route of exposure to bisphenols (BPs), with canned foodstuffs playing a key role. This study was aimed at biomonitoring bisphenol A (BPA) and 5 more BP analogues (BPB, BPE, BPF, BPAF and BPZ) in spot urine and blood samples of a cohort of adults, who followed a diet based on a high consumption of canned food. To the best of our knowledge, this is the first study aimed at assessing the co-exposure of BP analogues in food and biological samples after a two-day duplicate diet study. The estimated total dietary exposure was 0.37 and 0.045 μg/kg body weight/day, for the canned-diet and control groups, respectively. BPA was the compound with the highest concentration in urine in comparison with the values of the remaining BP analogues. A high detection rate of BPA was noted in urine for both groups, 96% for the canned-diet group and 90% for the control group, while in blood it could be only quantified in 6% of the samples. The identification of other analogues was hardly related to diet, so it could be the result of other potential exposure sources, such as personal care products (PCPs) or air inhalation. After 2 days, the excretion of BPA was considerably higher in the canned-diet group subjects than those in the control group (7.02 vs. 1.89 μg/day), confirming that diet and canned foodstuffs are the main route of exposure to BPA. Anyhow, the temporary tolerable daily intake (t-TDI) established by the EFSA was not exceeded, even by those consumers with a diet rich in canned food. Moreover, spot urine samples provided accurate information about exposure and excretion of BPA, being the 4 h, instead of 24 h, the optimal sampling interval, when the collection of spot urine samples is not possible.

1. Introduction

Human biomonitoring is an analysis method widely used to measure concentrations of chemical substances and metabolites in biological tissues (Albertini et al., 2006; Ibarluzea et al., 2016). It is a good tool to assess exposure to environmental pollutants and to identify potential risks for human health. Traditionally, a number of biological matrices, including blood, urine, hair and breast milk, among others, have been used for human biomonitoring (Ashrap et al., 2018; Esplugas et al., 2019, in press; Ibarluzea et al., 2016; Katsikantami et al., 2016; Nadal et al., 2019; Quinete et al., 2016; Schuhmacher et al., 2019; Song et al., 2018; Velázquez-Gómez and Lacorte, 2019).

In recent years, the biomonitoring of endocrine disruptors has been increasing (Cullen et al., 2017; Karrer et al., 2020; Rodríguez-Gómez et al., 2017; Tordjman et al., 2016; Vela-Soria et al., 2016). Specifically, many efforts have been made to assess the occurrence of bisphenols (BPs) in biological matrices. BPs are a family of organic compounds that have a hydroxyl residue directly bound to an aromatic ring, obtained by the condensation of a phenol with a ketone or an aldehyde (Corrales et al., 2015; Geens et al., 2012; Michałowicz, 2014). They are of great concern due to the similar structure to the natural oestrogen 17β-estradiol, so they can interfere with the normal function of the endocrine system (Björnsdotter et al., 2017; Rochester, 2013; Usman and Ahmad, 2016). The main causes of exposure to BPs are diabetes, obesity, developmental problems, and infertility, among others (Diamanti-Kandarakis et al., 2009; Rochester, 2013). Bisphenol A (BPA) is the most used analogue among the 24 BPs described in the literature (Pelch et al., 2017). BPs are not persistent in the human body, being usually excreted through urine around 6 h after ingestion (Oh et al., 2018; Thayer et al., 2015). Although BPs are not bioaccumulative, human exposure is ubiquitous. BPs are contained in many daily-life products, such as coatings for food packaging, metal jar lids, automobile parts,

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thermal paper, dental sealants, toys, household appliances, adhesive plastics and clothes (Vandenberg et al., 2007; Chen et al., 2016a; Kang et al., 2006; Freire et al., 2019; Xue et al., 2017).

BPs have been found in trace amounts in a wide range of samples, including food (Choi et al., 2018; Cunha et al., 2012; Fattore et al., 2015; González et al., 2019a; Liao and Kannan, 2014), biological tissues (Cunha and Fernandes, 2010; Genuis et al., 2012; González et al., 2019b; Kolatorova Sosvorova et al., 2017; Martínez et al., 2019; Morgan et al., 2018; Tzatzarakis et al., 2015), as well as in different environmental compartments (Česen et al., 2018; Hu et al., 2019; Jin and Zhu, 2016; Liao et al., 2012; Liu et al., 2017).

Some studies about occupational exposure to BPA has been published, specifically for workers in the manufacture of polycarbonate plastics or handling thermal paper (Kouidhi et al., 2017; Ndaw et al., 2016, 2018). On the other hand, for non-occupationally exposed adults, the exposure to BPA occurs mainly through the diet, which means more than 99% of the total exposure (Martínez et al., 2017, 2018). Specifically, canned food is the food product that contains higher levels of BP due to the lining that protects the foodstuff from the tin. Therefore, the consumption of this type of food is the major contributor to BPs exposure to the general population (González et al.,2019a).

After ingestion, unconjugated BPs are quickly metabolized in the liver, transformed into an inactive form (conjugated), and subsequently excreted through urine (Gramec Skledar and Peterlin Mašič, 2016). In turn, although the contribution of other routes of exposure (i.e.: dermal, inhalation) is minor, its relative importance should not be ignored (Geens et al., 2012; Lu et al., 2018; Porras et al., 2014; von Goetz et al., 2017). Taking into account that dietary intake is the most important route of exposure to this BPs, the monitoring of these chemicals in food, as well as the exposure assessment, should be periodically performed for public health protection. To date, many investigations have already been focused on assessing the dietary exposure to BPA (Abou Omar et al., 2017; Chen et al., 2016b; Teeguarden et al., 2011), but the knowledge on the occurrence and co-exposure of other BP analogues is scarce (Husøy et al., 2019).

The present study was aimed at assessing the levels of BPA and 5 more BP analogues in blood and urine samples of an adult cohort of population, who followed a diet with a high content of canned food. The dietary intake of these BP analogues was also estimated and compared with previous values (González et al., 2019a). To the best of our knowledge, this is the first time that the dietary co-exposure to 6 BP analogues is assessed by means of a duplicate diet study, considering two perspectives: the occurrence of BPs in both, food (intake) and biological matrices (excretion). Previous investigations were basically focused on the single exposure to BPA.

2. Materials and methods

2.1. Standards and chemicals

BPA (99% purity), BPB (98% purity), BPF (98% purity), BPE (98% purity), BPAF (98% purity), and BPZ (99% purity) were purchased from Sigma-Aldrich (West Chester, PA, USA). The internal standard, d_{16}-bisphenol A ($BPAd_{16}$; 98 atom % D) was purchased from Cambridge Isotope Laboratories, Inc. (Tewksbury, MA, USA). Individual standard solutions and internal standards were prepared in methanol (HPLC grade from Sigma-Aldrich) at concentrations of 1000 μg/L and storage in amber glass vials at 4 °C. Acetonitrile (MeCN, gradient grade for HPLC), acetic anhydride (AA; > 99% purity) and tetrachloroethylene (T4CE, > 99% purity) were acquired from Sigma-Aldrich. Potassium carbonate (analytical grade) was obtained from Panreac Quimica (Barcelona, Catalonia, Spain). β-Glucuronidase (Type 1 from *Helix pomatia*, 100,000 U/g solid glucuronidase) was purchased from Sigma-Aldrich.

2.2. Instrumental equipment

BP analyses were performed in 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. 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., 2019b).

2.3. Quality control

The quality control of the analysis was performed by analysing blanks (urine and blood free of analytes) in each batch of 10 samples. Glass vials were used in extraction procedure in order to reduce possible bisphenol contamination. The storage tubes were tested using serum with non-detectable BPA levels and maintained in the same conditions as samples.

Blank samples were spiked with both native and internal standards and allowed to equilibrate for 1 h before extraction in order to evaluate linearity, linear range, sensitivity, precision and accuracy, according to EU guidelines (European Commission, 2017). A multilevel matrix-matched calibration with nine calibration levels, was generated by the least squares' linear regression model. The peak area ratios of each target analyte, as well as the internal standard vs. the concentration of each target compound, were plotted. 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 assayed with acceptable accuracy and precision, corresponding to the lowest calibration level of the calibration curve.

Confirmation criteria of target analytes were based on EU guidelines (European Commission, 2017), being defined as it follows: (i) at least three ions must be monitored for the analyte and two ions for the internal standard.; (ii) one ion will be identified as the target ion and the remaining ions will be qualifier ions; (iii) the relative retention time of the analyte must correspond to that of the calibration solution at a tolerance of ± 0.5%, and (iv) the S/N for each diagnostic ion must be > 3.

2.4. Study population

A 2-day duplicate diet study was performed to assess exposure to BPs of adults mainly consuming canned foodstuffs. The participants were recruited from the staff of the Centre of Environmental, Food and Toxicological Technology (TecnATox, Reus/Tarragona, Spain). The selection of the participants included people with no previous pathologies, over 50 kg of weight and non-vegan. Up to 30 people were contacted and only 4 of them refused to participate. The allocation of the different diet was randomly done. Briefly, a cohort of 26 individuals was divided into two groups: (1) those following a potential high-BPA diet based on canned foodstuffs, (canned-diet), and (2) those following a BPA-free diet, made of fresh foodstuffs and food products packed in glass containers and other BP-free materials (control). Both groups of subjects followed a balanced diet, which was revised and approved by a dietitian. Food basket from the canned-diet group consisted of 68% canned food products, whose contribution to the total dietary ingestion was 52%. Additional details of the diet were previously given (González et al., 2019a). The cohort characteristics are described in Table 1. One of the participants (No. 19) was excluded from the study because he declared the consumption of food that was not in the provided food basket. Therefore, the cohort of the study consisted of 25 individuals. The study was approved by the Ethical Committee for Clinical Investigation of the Institut d'Investigació Sanitària Pere Virgili (IISPV, Reus/Tarragona, Spain, Ref. CEIm: 112/2018). A written informed consent was obtained from all the participants.

Table 1
Cohort characteristics (n = 25).

%	Canned-diet (n = 14)	Control (n = 11)
Sex		
Male	29	36
Female	71	64
Body Mass Index		
Underweight (< 19 kg/m^2)	0	0
Normal (19–25 kg/m^2)	64	45
Overweight (> 25 kg/m^2)	29	55
Obese (> 30 kg/m^2)	7	0
Smoking		
Yes	14	0
No	86	100

In order to complete the information about the cohort, food frequency and lifestyle questionnaires, as well as a journal to record the total volume of each urine sample, were filled up by each subject. Participants were also asked for noting any other activities with a potential exposure and excretion of BPs, as well as incidents occurred during the study. Moreover, participants were asked not to consume any canned food or packed in polycarbonate plastic the days before starting the duplicate diet study in order to avoid a initial high exposure to BPs.

2.5. Sample collection

Urine and blood samples were collected to further analyse the concentrations of BPs. During the whole 48-h study, each participant collected spot urine samples and the first void urine (FVU) of the third day. On the other hand, blood samples were extracted in heparin tubes during the first day of the study. Extraction was done at four time spots: 8 AM (fasting), 11 AM, 2 PM and 5 PM. Fasting samples were considered as a baseline exposure, while the schedule for the other blood extractions was designed taking into account that the maximum concentration of BPs in serum is reached 1 h after their intakes (Thayer et al., 2015; Oh et al., 2018). Firstly, 2 mL of whole blood were taken separately. Blood samples were then centrifuged at 1300 g for 10 min in order to obtain plasma and the red blood cell (RBC) fraction. All the biological samples were stored at −20 °C until analysis.

2.6. BPs analysis in urine

After collection, urine samples were thawed at room temperature and homogenized by vortex. The analysis of unconjugated BPs was performed following a previously developed method (González et al., 2019b). Five mL of sample were transferred to a glass tube with conical bottom and spiked with 50 μL of BPA_{d16}. Rapidly, 1325 μL of MeCN, 85 μL of T4CE and 125 μL of AA were added to the sample. Tubes were shaken and centrifuged for 10 min at 2500 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 equipment. In turn, for the determination of total (unconjugated + conjugated) BPs, 5 mL of sample were transferred to a clear vial, to which were added 100 μL of β-glucoronidase solution (20,000 U/mL in 1 M ammonium acetate buffer pH 5.0). The mixture was then incubated overnight at 37 °C in order to guarantee the hydrolysis. After cooling at room temperature, BPs were extracted as above stated.

2.7. BPs analysis in whole blood, RBC and plasma

The preparation of the samples and the extractive procedures were performed according to González et al. (2019b). Firstly, whole blood, RBC and plasma samples were thawed at room temperature and homogenized by vortex. For the analysis of unconjugated BPs, 1.5 mL of MeCN was added to 500 μL of samples of total blood, RBC and plasma. Each sample was firstly spiked with 40 μL of BPA_{d16}, kept at room temperature for 10 min, and then centrifuged at 3500 rpm for 4 min. Subsequently, 1 mL of sample was transferred to a clean vial, adding 85 μL of T4CE and 100 μL of AA to the sample. In a glass tube with conical bottom, 3 mL of deionized water and 300 μL of K2CO3 (to achieve a pH ≥ 10) were added. Rapidly, the sample was transferred to the glass tube and vortexed. Samples were then centrifuged at 2100 rpm for 4 min. Finally, 70 μL of the lower phase were transferred to a 100 μL insert, being 1 μL injected into the GC–MS system. In turn, for the analysis of total (unconjugated + conjugated) BPs, 1.5 mL of sample was transferred to a clean vial and 30 μL of β-glucoronidase solution (20,000 U/mL in 1 M ammonium acetate buffered to pH 5.0) were added. Samples were incubated overnight at 37 °C to guarantee the hydrolysis. After cooling at room temperature, BPs were extracted as previously described.

2.8. Calculation of BPs urinary elimination

Total BPs elimination was calculated for each individual by multiplying the BP analogue concentration of each spot urine sample (μg/mL) by the volume of the urine sample of the corresponding spot sample (mL). To calculate the elimination of BPs on a daily basis, the following assumptions were considered: (i) the first void urine (FVU) contained urine samples collected before the breakfast of the day 1; (ii) day 1 data included urine samples collected between the breakfast of day 1 and the breakfast of day 2; (iii) day 2 contained urine samples collected after the breakfast of day 2 until the FVU sample of day 3.

2.9. Statistical analysis

To detect and assess differences between canned-diet and control groups, as well as through time, the statistical package SPSS 20.0 was used. Firstly, a Kolmogorov-Smirnov test was applied to compare the homogeneity of the variances. Then, a Student's *t*-test was applied to determine statistical differences. The determination of BPs in urine was carried out as individual spot urine samples. However, to perform the calculations, urine samples were grouped in different time intervals to determine which is the most convenient interval when the collection of spot urine samples is not possible. To do so, urine samples were grouped as 4-h, 12-h and 24-h interval, meaning that 4-h interval grouping generated 13 time intervals during the two days (5:00–9:00 am, 9:00–13:00 pm, 13:00–17:00 pm, 17:00–21:00 pm, 21:00–1:00 am and 1:00–5:00 am for the two days), while 12-h interval generated 5 time intervals (5:00–17:00 pm and 17:00–5:00 am for the two days). Finally, 24-h interval only generated 1 time interval (5:00–5:00 am) and that was equivalent as if only one sample was collected during 24 h.

In turn, the effect of consuming canned food on the exposure to BPA was assessed by building a mixed effects linear model on: (i) the quantity of excreted BPA as a function of time; (ii) the dichotomous factor of ingestion of canned food as a fixed effect; and (iii) the baseline excretion of each participant as a random effect. This analysis was carried out by means of the statistical package R version 3.5.3.

3. Results and discussion

3.1. BPs in urine samples

3.1.1. Concentrations of BPA

Unconjugated BPA was found only in 19 out of 189 urine samples of the canned-diet group and 7 out of 138 urine samples of the control group. Hence, detection rates were only 10% and 5% for the canned-diet and control groups, respectively (Supplementary Material, Tables S1-S2). Mean concentrations of unconjugated BPA were similar in both groups, independently on the consumption of canned foodstuffs (0.21 vs. 0.12 μg/L for the canned-diet and control groups, respectively). Low detection rates of unconjugated BPA might be related to the fact that

Table 2
Mean levels of total BPA in urine (μg/L) in canned-diet and control groups during the study.

No. Participant	FVU	Day 1	Day 2
CANNED-DIET			
1	2.91	1.50	2.80
2	< 0.2	1.96	1.76
3	1.45	6.08	10.6
5	0.953	2.52	3.43
8	4.53	7.72	8.31
9	15.7	3.25	6.75
10	0.484	3.85	3.59
18	1.78	5.01	4.30
20	2.06	3.89	6.02
21	5.74	8.31	9.73
22	3.64	8.42	14.6
23	1.94	10.5	2.60
24	3.47	3.55	6.32
25	1.45	6.75	6.06
Mean	**3.29**[a]	**5.24**[**,b]	**6.21**[***,b]
Standard deviation	3.91	2.76	3.61
Geometric mean	2.43	3.31	4.51
CONTROL			
4	0.759	1.83	1.93
6	3.58	1.46	1.28
7	3.34	3.32	2.92
11	2.35	3.38	2.09
12	1.44	1.88	1.80
13	0.712	2.41	1.82
14	2.26	1.40	1.01
15	< 0.2	1.40	1.36
16	2.39	1.84	1.15
17	3.10	3.88	1.59
26	3.29	4.14	3.10
Mean	**2.11**[a]	**2.45**[a]	**1.82**[a]
Standard deviation	1.22	1.04	0.68
Geometric mean	2.03	1.72	1.57

*Asterisks indicate significant differences between canned-diet and control groups at **P < 0.01 and ***P < 0.001.
[abc]Different superscripts indicate significant differences between days (p < 0.05).
FVU: First void urine.
LOD: 0.07 μg/L; LOQ: 0.2 μg/L.

Table 3
Total BPA elimination and exposure for the canned-diet and control groups through the study.

No. Participant	Total BPA elimination (μg)			Total BPA exposure (μg/kg bw/day)		
	FVU	Day 1	Day 2	FVU	Day 1	Day 2
CANNED-DIET						
1	1.02	3.48	3.60	0.013	0.045	0.046
2	ND	3.10	3.49	ND	0.055	0.062
3	0.392	6.59	5.73	0.006	0.100	0.087
5	0.381	7.88	7.26	0.007	0.141	0.130
8	0.792	7.69	10.6	0.012	0.118	0.162
9	3.93	6.30	5.45	0.058	0.093	0.080
10	0.087	8.52	5.75	0.002	0.158	0.106
18	0.578	3.64	6.42	0.007	0.046	0.080
20	0.411	5.89	8.60	0.008	0.118	0.172
21	0.287	14.9	11.8	0.005	0.276	0.218
22	0.873	4.77	14.3	0.013	0.071	0.213
23	1.16	9.20	3.79	0.015	0.118	0.049
24	1.09	4.89	5.80	0.014	0.061	0.073
25	0.32	12.7	5.74	0.004	0.149	0.068
Mean	**0.809**[a]	**7.11**[***,b]	**7.02**[***,b]	**0.012**	**0.111**	**0.110**
St. Dev.	0.97	3.42	3.21	0.014	0.061	0.059
CONTROL						
4	0.076	2.19	2.25	0.001	0.035	0.036
6	1.07	2.73	2.10	0.016	0.040	0.030
7	1.09	4.17	3.34	0.012	0.048	0.038
11	0.470	3.42	1.61	0.008	0.057	0.027
12	0.303	1.97	1.05	0.004	0.029	0.015
13	0.107	1.75	1.38	0.002	0.025	0.020
14	0.589	1.97	0.50	0.011	0.037	0.009
15	ND	3.24	1.41	ND	0.044	0.019
16	0.359	2.54	1.48	0.005	0.036	0.021
17	0.496	3.31	2.36	0.009	0.060	0.043
26	1.31	3.92	3.26	0.014	0.043	0.036
Mean	**0.534**[a]	**2.84**[b]	**1.89**[c]	**0.008**	**0.041**	**0.027**
St. Dev.	0.444	0.831	0.879	0.006		0.011
				0.011		

***Asterisks indicate significant differences between canned-diet and control groups at P < 0.001.
[abc]Different superscripts indicate significant differences between days (p < 0.05).
FVU: First void urine.
LOD: 0.07 μg/L; LOQ: 0.2 μg/L

BPA is mostly eliminated in the conjugated form, because of its rapid conjugation upon intake (Völkel et al., 2002). In fact, our results are in good agreement with those reported in a German study, in which less than 15% of the urine samples showed unconjugated BPA levels (Koch et al., 2012).

As expected, a high detection rate of total BPA (unconjugated + conjugated) was observed in urine. Total BPA was found in 306 out of 327 urine samples (94%) of both canned-diet and control groups. Detection rate per diet group was 96% for the canned-diet group and 90% for the control group. The mean concentrations of total BPA per individual participant and per diet group (canned-diet and control) over the study are summarized in Table 2. The mean concentrations of total BPA in the FVU of exposed and control groups were similar (3.29 vs. 2.11 μg/L). Afterwards, the excretion of total BPA by the canned-diet population considerably increased in days 1 and 2 (5.24 and 6.21 μg/L, respectively). In contrast, the excretion of total BPA in the control group over the two days of the study was similar to their FVU, being 2.45 and 1.82 μg/l after 24 h and 48 h, respectively. The variability was substantially higher between individuals of the canned-diet group than in those of the control group. It was probably due to the increase of BPA ingestion and the inherently different metabolism of the participants.

Detection rate of the current study is in accordance with those found in other investigations. In Norway, Husøy et al., (2019) detected BPA in 96% of 24-h urine samples from 144 adult volunteers who kept detailed diaries on their food consumption, the use of personal care products and handling of cash receipts. In the USA, BPA was detected in 98% of urine samples from 50 adults aged between 19 and 50 (Morgan et al., 2018), while slightly lower detection rates to those here observed were previously reported in Portugal (85%) and China (84%) (Cunha and Fernandes, 2010; Zhang et al., 2013).

Regarding urinary BPA concentrations, the geometric mean (GM) of the control group (1.64 μg/L) is in agreement with the results reported by Covaci et al. (2015), who analysed the urinary concentrations of total BPA in six European countries (Belgium, Denmark, Luxembourg, Slovenia, Spain and Sweden). The GM of BPA levels ranged between 2.55 and 1.30 μg/L, with Belgium and Sweden showing the highest and lowest GM, respectively. For the control group, the current results would fit well within the range. Contrastingly, as a potentially high-BPA diet was designed, the GM of BPA in urine of the canned-diet group (3.73 μg/L) was notably higher than the data relative to 6 European countries (Covaci et al., 2015).

3.1.1.1. Amount of BPA excreted. The amount of total urinary BPA, estimated from the concentration of total BPA and the volume of urine, is shown in Table 3. Before the beginning of the study, all participants of both groups, canned-diet and control, excreted a similar amount of BPA (0.81 and 0.53 μg/day, respectively). Afterwards, people eating canned foodstuffs significantly increased the amount of total BPA excreted during the rest of the study (p < 0.001), with urine

amounts of 7.11 and 7.02 μg obtained in days 1 and 2, respectively. Unexpectedly, the control group also excreted a higher amount of total BPA through the study, reaching values of 2.84 μg and 1.89 μg after 24 h and 48 h, respectively. The analysis of total BPA levels in FVU samples in the first day confirmed that both groups were similarly exposed to BPA before starting the duplicate diet study. However, the excreted levels for the canned-diet group were remarkably higher than those corresponding to the control group. Consequently, it can be confirmed that the consumption of canned foodstuffs and food packed in polycarbonate plastics significantly increase the exposure to BPA.

The average daily exposure to BPA in the canned-diet and control groups is summarized in Table 3. The mean daily exposure to BPA of the canned-diet group was constant through the study: 0.11 μg/kg bw/day. This value is slightly lower than that calculated by Gonzalez et al. (2019a) for the same population, in which data on food frequencies and BPA concentrations in foodstuffs was taken into account (0.23 μg/kg bw/day in day 1, and 0.14 μg/kg bw/day in day 2). In contrast, no differences were found in the control group when comparing the current dietary exposure with that previously estimated (González et al., 2019a): 0.04 vs. 0.03 μg/kg bw/day, and 0.03 vs. 0.01 μg/kg bw/day in days 1 and 2, respectively. Differences in both estimated BPA exposures could be the result of BPA exposure through other routes, either individual or combined (e.g., dermal absorption, air inhalation, etc.), and/or the fact that BPA may be excreted through other routes, such as sweat (Genuis et al., 2012). Although BPA is mostly eliminated through urine, it must be remarked that BPA is a lipophilic compound and, consequently, it might be partly accumulated in adipose tissue (Artacho-Cordón et al., 2018).

In 2015, the European Food Safety Authority (EFSA) reduced the tolerable daily intake (TDI) of BPA from 50 to 4 μg/kg bw/day (EFSA, 2015). Considering this last value, none of the groups here evaluated would exceed the threshold value. However, it must be noticed that the EFSA-TDI is still temporary, being the EFSA updated assessment scheduled for 2020. Furthermore, it cannot be neglected that a number of studies have reported adverse effects of BPA - even at low doses - such as disturbed mammary gland development, changes in normal behavioural parameters, or interference in brain development and functions (Negri-Cesi, 2015; Rosenmai et al., 2014).

Finally, for the BPA exposure group, the values are similar to those reported during a 24-h high-dietary BPA exposure study performed in the United States with 20 volunteers, who consumed a diet rich in canned foods and juices (Teeguarden et al., 2011). The volunteers' average consumption of BPA, estimated from the urinary excretion of total BPA, was 0.27 μg/kg bw/day. On the other hand, the dietary exposure to BPA of the control group would be similar to other worldwide reported values. Huang et al. (2017) estimated the levels of human BPA exposure considering urinary concentrations. Results reported exposure ranges of 0.0079–0.065 μg/kg bw/day for people living in 30 countries, with Italy and Tunisia showing the maximum and minimum levels, respectively. However, these authors found that European countries showed relatively higher exposure levels, with Italy, Sweden, Denmark, France and Cyprus in the top five (Huang et al., 2017).

The total BPA elimination curve of each participant over the study is depicted in Fig. 1. Although participants who followed a diet rich in canned foods excreted higher amounts of total BPA than those in the control group, the elimination curve of both groups had a similar pattern, with a higher peak of BPA between 1 AM and 9 AM of day 2.

The comparison in the levels of total BPA excretion between both exposure groups, classified according to 4-, 12-, and 24-h intervals, are shown in Fig. 2. In general terms, the wider the interval is, the lower the sensitivity to exhibit changes during the duplicate diet study, being 4 h the optimal. The R^2 of each mixed model worsens as the interval increases, proving that the optimization of the model increases inversely with the time interval. Hence, the shorter the interval, the better the excretion of total BPA is modelled (Supplementary Material, Tables S3-S4). Consequently, these results clearly confirm that the BPA analysis of spot urine samples provides much more information than the determination of BPA in composite samples of urine. Moreover, when the collection of spot samples is not possible, urine samples should be collected in short intervals of at least 4 h or less. This is in contrast with the collection of urine samples carried out in other studies, where, although individual urine samples are collected, pools of urine considering higher time slots (6-h) or 24-h time slots are made (Husøy et al., 2019). Other authors only collect a few samples during the study, such as 2, 4 and 6 h after canned food intake (Peng et al., 2019). Also, other authors only collect one urine sample, being collected either as the first morning urine or as one sample during the day (Covaci et al., 2015; Buckley et al., 2019).

The comparison between the dietary intake and the excretion of total BPA is depicted in Fig. 3. During day 1, both groups showed similar levels of total BPA. However, at the night of day 1 and, especially in the morning of day 2, the difference between both groups clearly increased. This high peak might be related to the higher intake of BPA at dinner of day 1. Some canned foodstuffs consumed during that meal, such as squid and asparagus, showed relatively high levels of BPA (30.85 and 88.66 μg/kg, respectively). Furthermore, the concentration of BPA in corn was also important, irrespective of the packaging (10.65 and 4.21 μg/kg in canned and glass-packed corn) (González et al., 2019a). Therefore, the high peak of BPA in the canned-diet group could be attributed to these three food items, while the slight increase of BPA in the control group could be the result of the corn consumption.

It must be highlighted that the sample of canned asparagus consumed by the canned-diet population contained a BPA level that exceeded the specific migration limit of BPA (González et al., 2019a), set at 50 μg/kg by the EC (2018). On the other hand, the excretion curve of total BPA for the control group also showed a peak in the morning of day 2, which could be related to the intake of glass-packed corn containing BPA at a concentration of 4.21 μg/kg. Subsequently, the amount of excreted BPA decreased in both groups However the canned-diet group continued to excrete a higher amount of total BPA than those in the control group until the end of the study. The mixed model between canned-diet and control groups (Table 4) showed significant differences on the time-slots 1 AM–5 AM and 5 AM–9 AM of day 2 ($p < 0.001$), confirming the strong correlation between diet and BPA exposure. Finally, the mixed model explained up to 71% of the variability (σ^2), thus proving that the inter-individual variability (τ_{00}) only contributed 17%.

3.1.1.2. Levels of other BP analogues. Unconjugated BP analogues, other than BPA, were not detected in any of the urine samples from both, canned-diet and control groups. In turn, total BPAF, BPF and BPE could be quantified in some urine samples from individuals with a diet based on canned foodstuffs (Supplementary Material, Tables S1-S2). Traces of BPAF were found in two punctual samples (1.05 and 0.50 μg/L) of two canned-diet participants (No. 1 and 18). These subjects indicated they had been in contact with personal care products (PCPs), which have been identified as an additional exposure pathway of relative importance for some BPs (Lu et al., 2018).

Eight samples from four participants had quantifiable levels of BPF, with a mean concentration of 6.56 μg/L. It must be remarked that one of the volunteers (No. 23) had detectable amounts of BPF in two-thirds of his urine samples, with a mean concentration of 4.96 μg/L. According to his diary record, this subject had been handling thermal paper products, (i.e., bus tickets) and using PCPs, such as face cleansers, toothpaste or moisturizers, which potentially contain BPs (Lu et al., 2018; Rochester and Bolden, 2015).

BPE was also found in some specific samples of three participants, being the mean level of these 0.28 μg/L. Surprisingly, three of the five positive samples belonged to one single participant. However, exposure to BPE was unlikely to be linked to diet, since the food items that contained BPE (mushrooms and nuts) were consumed in the first day 1 of the duplicate diet study (González et al., 2019a), while BPE was

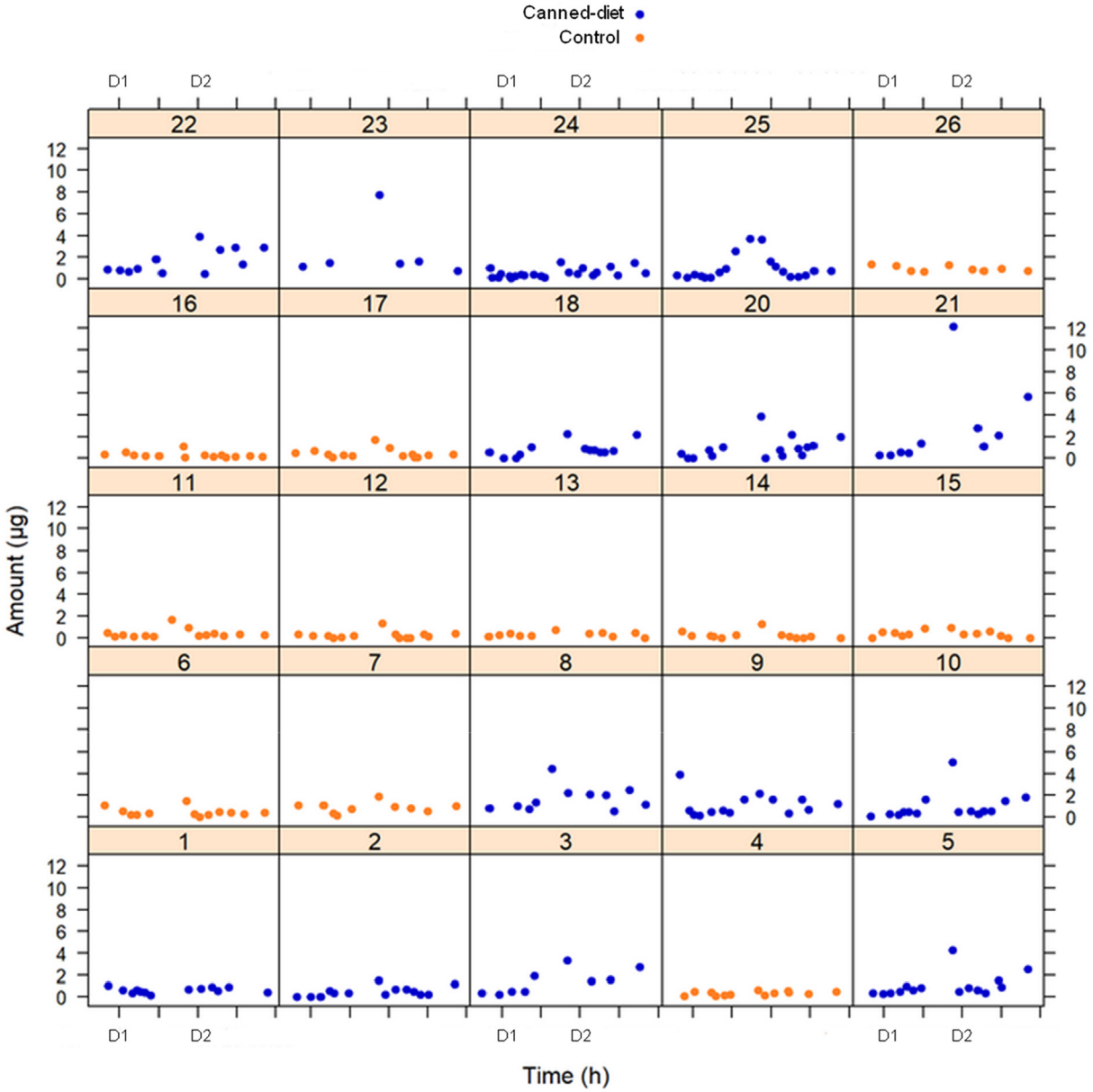

Fig. 1. Total urinary BPA (µg) elimination curve for individual participants of canned-diet and control groups during the 2-days duplicate diet study. D1: Day 1; D2: Day 2.

detected in urine samples of the second day. Unlike BPAF and BPF, no information on the occurrence of BPE in daily-life products is available in the scientific literature. Therefore, further research focused on determining sources and presence of BPE in market basket products is required.

3.2. BPs in blood samples

The concentrations of BPs in blood were determined as a complementary analysis to confirm whether BPs tend to remain in blood, or they are rapidly excreted through urine. Unfortunately, the detection rates of BPA and the remaining 5 BP analogues in 3 different blood matrices (whole blood, plasma and RBC) were extremely low (Supplementary Material, Tables S5-S10). Therefore, it would be hard to relate these concentrations to the dietary exposure of BPs. Briefly, total BPA was detected in the whole blood of 4 participants of the canned-diet group and 2 volunteers of the control group, while unconjugated BPA was only detected in a sample of an individual consuming canned foodstuffs. As the participant with the highest concentrations of BPA reported to smoke and take medication during the study, some interference might have occurred (He et al., 2009). In turn, BPAF was detected in the first blood sample of one participant belonging to the control group. Although BPs have been scarcely determined in whole blood, the current detection rates are much lower than those reported elsewhere (González et al., 2019b; Yamamoto et al., 2016, Zhang et al., 2013). Regarding the occurrence of BPs in plasma, total BPA was only found in three canned-diet participants, while total BPB was detected in two samples of the canned-diet group and one in the control group (first blood extraction). Once more, the current detection rates of BPs in plasma were notably lower than those previously reported in the scientific literature (Cambien et al., 2020; Wiraagni et al., 2019; Kolatorova Sosvorova et al., 2017). Finally, BPA and BPAF were only detected in one RBC sample – each analogue in a different RBC sample – of the control group belonging to two different participants, being these detection rates also lower than those recently reported in Chinese adults (Jin et al., 2018).

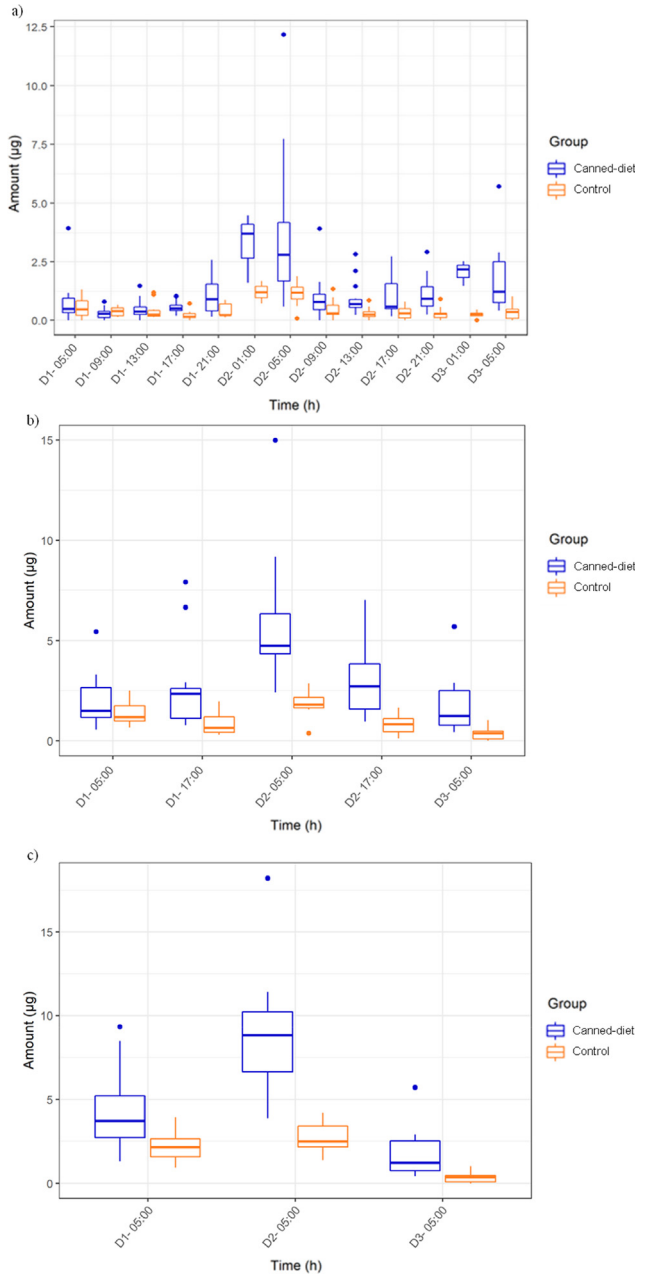

Fig. 2. Total BPA elimination for canned-diet and control groups considering (a) 4-h; (b) 12-h and (c) 24-h intervals during the duplicate diet study. D1: Day 1; D2: Day 2; D3: Day 3.

On one hand, our uncommonly low detection rates might be related to the fact that most of the above-mentioned studies were performed by means of LC-MS/MS. Anyhow, scarce results found in whole blood, plasma and fractions could be explained by the fact that BPA is a non-persistent compound in the body that is quickly metabolized. Consequently, the occurrence of BPA in blood may be several orders of magnitude lower than that in urine (Calafat et al., 2013), being concluded that blood is not a suitable biological matrix to assess the dietary exposure to BPs.

4. Conclusions

To the best of our knowledge, this is the first duplicate diet study assessing co-exposure to BPA and five more BP analogues from a double perspective. The dietary intake of BPs was estimated by analysing the food consumed during the duplicate diet study, while their excretion was evaluated by determining BPs in urine. Interestingly, spot urine samples, instead of 24 h composite samples, were collected and individually analysed. The results of the present investigation mean valuable information for future studies, as an optimal time-slot for urine sampling is also recommended. Additionally, BPs levels in three blood fractions were also determined as a complementary analysis.

Urine was confirmed to be the best matrix to assess the dietary exposure to BPs, especially BPA. Detection rates in urine reached up to 94%, while BPA could be only found in 6% of the blood samples. Trace levels of other BP analogues were found only promptly, but at much lower quantities than those of BPA. FVU indicated that both groups –canned-diet and control – were similarly exposed to BPA before starting the study, meaning that avoiding the consumption of canned food could reduce substantially the exposure to BPs. Afterwards, exposure to BPA of the participants following a canned foodstuffs-based diet, substantially increased through time, supporting that diet plays an essential role in the exposure to BPA. BPA is a compound with a relatively short half-life in the body, since a high dietary intake of BPA is consistent with a subsequent high BPA elimination through urine. Moreover, the sampling and analysis of spot urine samples allows a better sensitivity to detect slight changes, providing more accurate information than 24 h composite samples. If individual samples cannot be collected, urine should be sampled in short periods (every 4 h or less) to avoid any potential loss of information.

Although participants following a diet rich in canned food products were more exposed to BPA than those in the control group, the temporary TDI established by the EFSA was not exceeded. However, further actions are required to ensure human health protection because the exposure to BPs has been linked to adverse health effects, even at acceptable doses.

CRediT authorship contribution statement

Neus González: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Montse Marquès:** Conceptualization, Formal analysis, Supervision, Validation, Writing - review & editing. **Sara C. Cunha:** Data curation, Formal analysis, Investigation, Methodology. **José O. Fernandes:** Formal analysis, Supervision. **José L. Domingo:** Formal analysis, Supervision, Writing - original draft. **Martí Nadal:** Conceptualization, Funding acquisition, Project administration, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

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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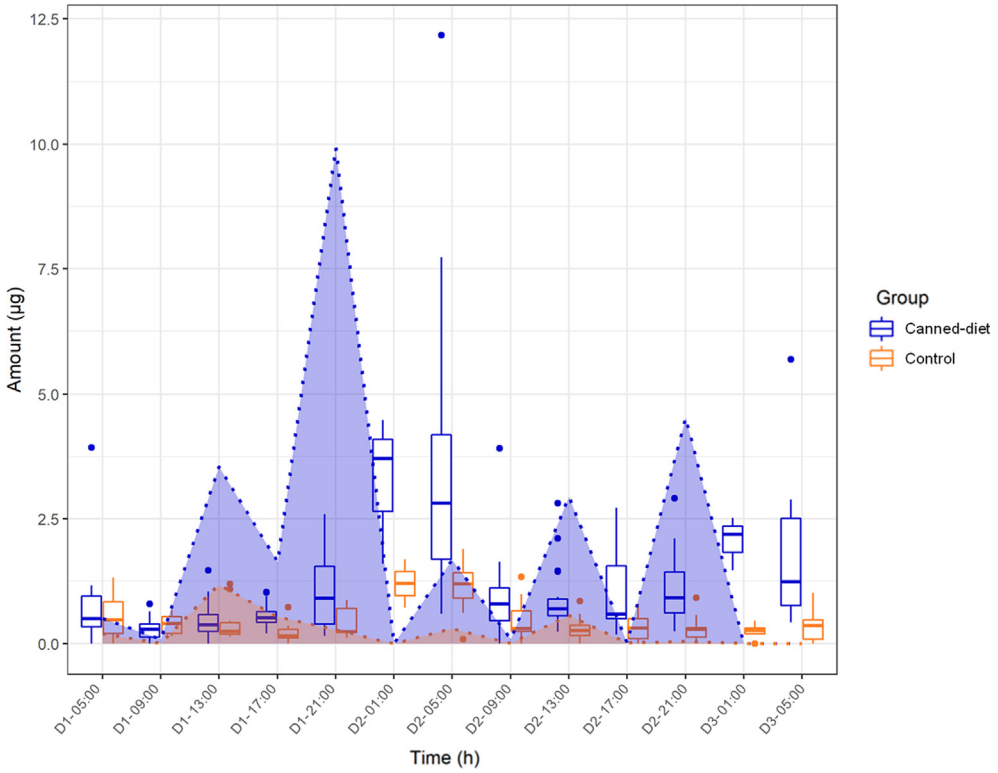

Fig. 3. Total BPA elimination plus dietary intake of BPA (in dots) for canned-diet and control groups during the duplicate diet study. D1: Day 1; D2: Day 2; D3: Day 3.

Table 4
Mixed model between canned-diet and control groups considering 4-hour intervals.

Predictors	Amount (µg)		
	Estimates	CI	*P*
Intercept	1.08	0.68–1.49	< **0.001**
Non-canned	−0.78	−1.15 to −0.40	< **0.001**
Day 1 09:00	−0.44	−0.90 to 0.01	0.056
Day 1 13:00	−0.29	−0.72 to 0.14	0.187
Day 1 17:00	−0.23	−0.68 to 0.21	0.297
Day 1 21:00	0.02	−0.47 to 0.50	0.947
Day 2 01:00	1.71	0.89 to 2.54	< **0.001**
Day 2 05:00	1.89	1.41–2.36	< **0.001**
Day 2 09:00	0.12	−0.35 to 0.59	0.613
Day 2 13:00	−0.03	−0.47 to 0.42	0.904
Day 2 17:00	−0.01	−0.45 to 0.43	0.974
Day 2 21:00	0.00	−0.46 to 0.46	0.997
Day 3 01:00	0.52	−0.20 to 1.24	0.158
Day 3 05:00	0.41	−0.06 to 0.88	0.090
Random effects			
σ^2	0.71		
τ_{00} person	0.17		
ICC person	0.19		
Observations	327		
Marginal R^2/Conditional R^2	0.355/0.477		

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105760.

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