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Extraction and analysis of bisphenols and their derivatives in infant and toddler ready-to-feed meals by ultrasound-assisted membrane extraction followed by LC–MS/MS

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Abstract

This research developed an ultrasound-assisted membrane extraction coupled with liquid chromatography-tandem mass spectrometry method for the determination of nineteen bisphenols and their derivatives in infant and toddler ready-to-feed meals. The calibration curves for all analytes were linear in the tested range, and the limit of detection and limit of quantitation were in the range 0.27 to 0.79 ng/g and 0.80 to 2.4 ng/g, respectively. The recovery values were in the range of 76 to 138%. This method was successfully applied to determine the content of bisphenols in 56 real samples of ready-to-eat meals for infants and toddlers. All of the analytes were quantified in at least one sample in the range of 1.0-371.9 ng/g. Mean exposures to bisphenols were estimated to be 9.01-769.49 ng/kg bw/day for both female and male babies. The health risk assessment revealed hazard quotient < 1, indicating that consumption of ready-to-eat meals is unlikely to pose any health risks to babies, even at the highest concentrations found in this study.

Keywords: BPA analogues; endocrine-disrupting compounds; exposure assessment; liquid chromatography-tandem mass spectrometry; food security.

1. Introduction

Infants and toddlers are a particularly vulnerable population group. Due to the significantly higher food intake per kg of body weight than of adults, several times greater absorption from the gastrointestinal tract, faster metabolic processes and a not yet properly developed immune system, they are much more exposed to chemical stressors (Petrarca et al., 2016). For all these reasons, food manufacturers have to comply with specific requirements in terms of composition, labelling, and limits for contaminants, which are very stringent and are significantly lower compared than those of adult products. The European Commission has set up maximum permissible levels (MPLs) for some chemicals and contaminants, such as some elements (Pb, Cd, Hg, As), polycyclic aromatic hydrocarbons, mycotoxins and pesticides (European Commission, 2006). For other possible contaminants, such as those coming from technical processes, microbiological hazards, and food contact materials, specific regulations apply (Regulation, 2011, 2006, 2005). One of the most commonly identified food contaminants is bisphenol A (BPA) (Vilarinho et al., 2019). This compound is the starting monomer used on a large scale in the synthesis of polycarbonates, polysulfones, and polyesters. Moreover, BPA is also the core substrate for producing bisphenol A diglycidyl ether (BADGE), the main monomer used in epoxy resin, which has a wide variety of applications for food contact materials (Spagnuolo et al., 2017).

The results of studies conducted over many years have shown that both BPA and BADGE may have harmful effects on the human body, including endocrine activity and potential impact on the development of cancer (Michałowicz, 2014). BPA exposure, even at very low doses, has been linked to metabolic disorders, cardiovascular disease, reproductive problems, and neurological disorders, among others. For this reason, many countries have introduced restrictions on the use of this compound in the production of certain products, especially in goods intended for children (Almeida et al., 2018). In 2018, the European Commission lowered the specific migration limit (SML) of BPA from 0.6 to 0.05 mg/kg of food (Regulation, 2011). In addition, a ban of BPA in food contact varnished or coated materials and articles for infants and young children has been introduced

(Commission, 2018). Because of these strict laws, producers have started to replace BPA with other bisphenols (BPs) that have been suspected to be less harmful. BPF, BPS, BPB, BPE are among the most commonly used BPA analogues in the production of polycarbonates and epoxy resins (González et al., 2019; Ma et al., 2022).

Toxicological research has found that these potentially safer substitutes also have harmful toxicological profiles. It was found, inter alia, that BPS, BPF, and BPAF had oestrogenic activities similar to or even stronger than those of BPA (Jin et al., 2020). Moreover, some literature findings have indicated that analogues have greater neuroendocrine disruptive effects than BPA (Ullah et al., 2018). A previously conducted study showed that prenatal BPF exposure is associated with decreased cognitive function in children at 7 years (Bornehag et al., 2021). Additionally, the collective data to date suggest that BPS and BPF induce hormonal imbalances (Rosenfeld, 2017). Furthermore, it has been demonstrated that BPS, BPF, and BADGE are considered obesogens (Andújar et al., 2019). Despite studies of the leaching rates of BPA, the analogues are much less studied, even with strong evidence of the leaching of these compounds. Among others, BPA, BPB, BPE, BPF, BPS, BADGE, and BFDGE have been detected in canned beverages (Wang et al., 2021), packaged fruit, vegetables, meat, and fish samples (González et al., 2020; Lestido-Cardama et al., 2021; Russo et al., 2019; Szczepańska et al., 2020).

The Scopus database reports hundreds of papers using "migration", "analysis", "food" and "bisphenols" as keywords. It is surprising, however, that after adding the words "baby food" and "infant," the number of articles decreases drastically to just a few (search setting: from 2000 year). Published reports mainly concern the analysis of homemade meals (Hulin et al., 2014; Lee et al., 2019) and only one article concerns ready-to-eat meals. Different kinds of ready-to-eat plastic packaged baby food samples were analysed for quantification of BPA and its six substitutes, namely, BPF, BPS, BPAF, BPE, BPB, and BPP (García-Córcoles et al., 2018)

This small number of articles may be because mainstream research on food intended for infants and infants primarily focuses on the analysis of pesticides, mycotoxins, veterinary drugs and metals (Jeong et al., 2014; Ojuri et al., 2019; Parker et al., 2022; Santonicola et al., 2017).

Considering the high risk of negative health effects of BP substitutes it seems particularly necessary to conduct research aimed at monitoring the levels of these compounds. Therefore, the main object of this work was the analysis of BPA derivatives in a wide range of ready-to-eat packaged baby food samples. The first goal was to develop a method for the identification and quantification of ten bisphenols (BPA, BPBP, BPC, BPF, BPFL, BPG, BPM, BPP BPS, PBZ) and nine BADGEs (BADGE, BADGE·H₂O, BADGE·2H₂O, BADGE·HCl, BADGE·H₂O·HCl, BADGE·2HCl, BFDGE, BFDGE·2H₂O, BFDGE·2HCl) applicable to a wide range of baby food samples (fruit, meat and vegetable dishes) from different brands followed by liquid chromatography-tandem mass spectrometry. The second goal was to carry out exposure calculations and risk assessment. To the best of our knowledge, this is the first study to analyse such a large group of BPA derivatives in samples of various types of packaged baby food.

- 2. Materials and methods
- 2.1. Chemicals and materials

Analytical standards of BPA, BPBP, BPC, BPF, BPFL, BPG, BPM, BPP, BPS, PBZ, BADGE, BADGE·H₂O, BADGE·2H₂O, BADGE·HCl, BADGE·H₂O·HCl, BADGE·2HCl, BFDGE, BFDGE·2H₂O, and BFDGE·2HCl were purchased from Sigma–Aldrich (St. Louis, USA, 99% purity). Internal standard d₁₀-labelled BADGE and ¹³C-labelled BPA (ring-¹³C₁₂) were supplied by Cambridge Isotope Laboratories Inc. (Tewksbury, USA). Methanol (MeOH) was of LC–MS hypergrade purity and obtained from Merck KgaA (Darmstadt, Germany). Ammonium formate and ammonium hydroxide solution 32% were purchased from Sigma–Aldrich (St. Louis, USA). All reagents were of analytical purity grade. Ultrapure water was produced by an HLP5 Hydrolab system (Straszyn, Poland) equipped with an EDS-Pak Polisher (Sigma–Aldrich) to remove endocrine-disrupting compounds. Polypropylene (PP) flat membrane sheets (pore

size 0.1 μ m, wall thickness 100 μ m) were obtained from GVS Filter Technology (Roma, Italy). Syringe filters (nylon, 13 mm wide, 0.22 μ m) were purchased from Labfil ALWSCI (Hangzhou, China).

2.2. Samples

Overall, 56 ready-to-eat packaged infant and baby food samples, including soups, vegetable or meatvegetable dinners, fruit, and desserts, were purchased in a large grocery store in Gdańsk (Poland). The food samples varied according to the child's age and the type of packaging.

To facilitate subsequent statistical analysis, the samples were grouped into three categories based on the age of the target group: 4 to 6 months (group A), 7 to 12 months (group B), and 13 to 36 months (group C). Further details of these samples, including the packaging type, major components, fat content, and product weight, are provided in Table S1.

2.3. Preparation of standards and calibration

Each stock solution of BPs and BADGEs was prepared in MeOH (0.5 mg/mL). The working solution was obtained by mixing the stock solutions and diluting with MeOH and then employed to prepare calibration solutions and spiked samples. Internal standards (ISs) were prepared separately by dissolving the proper amount to obtain a stock solution at a concentration of 2.5 μ g/mL. All solutions were stored in a freezer at -20°C. Fresh calibration solutions were prepared for every batch of samples.

2.4. Sample preparation

To obtain homogeneity, after opening the package, the product was homogenized (3 min at 30.000 rpm, VWR VDI12 homogenizer, VWR International, Poland). Except for those that were analysed immediately after preparation, the samples were stored at -20°C. The extraction was carried out according to a previously developed procedure (Szczepańska et al., 2020) with slight modifications. The membrane bag was prepared by heat-sealing the two edges of a porous polypropylene

membrane sheet (1.5x1.5 cm²). One end was kept open for the filling of samples. After placing 0.5 g of food sample (spiked with working solution or real) and 2.5 µL of IS solutions, the remaining end was heat-sealed. The membrane bag was then placed in a glass vial, and 8 mL of MeOH was added. Then, the vial was subjected to an ultrasound bath (60 W), and the extraction was allowed to take place for 25 min. After this time, the membrane bag was removed from the vial, and the solvent was dried under a gentle nitrogen stream (35°C). Then, 1 mL of MeOH was added to the vial to reconstitute the analytes, and water was avoided according to our previous findings (Szczepańska et al., 2019). The residue was vortexed, filtered using syringe filters (nylon, 0.22 μ m) and transferred to chromatographic vials for further analysis. Each experiment was conducted in triplicate. Due to the complex matrices of the analysed samples and the possibility of the occurrence of matrix effects in this study, the preparation of spiked samples was necessary. During the preliminary studies, it was not possible to find a representative sample that could serve as a matrix for the spiking test. All samples analyzed in this research contained apple either as the main ingredient, close to main or remaining one, hence the choice of fresh apple that could serve as the sample matrix. Therefore, fresh apples were purchased at a local market. Approximately 100 g of each apple was pilled, milled and homogenized, and at all steps, the contact of the matrix with plastic material was reduced as much as possible to avoid contamination with bisphenols.

To obtain six-point calibration curves (1, 2, 5, 10, 20 and 50 ng/g), samples were divided into 10 g aliquot portions, and the working solution was added to each of them. In each sample, the IS concentration was kept at 20 ng/g. For each batch of samples, fresh calibration samples were prepared.

2.5. Chromatographic conditions

All analyses were performed with a Shimadzu triple quadrupole LC–MS/MS system (LCMS-8060, Shimadzu, Japan) equipped with an electrospray ionization source (ESI) working in positive and negative multiple reaction monitoring (MRM) mode. The optimum detection conditions are

presented in the electronic supplementary material (Table S2). The separation of target analytes was performed on a Phenomenex Kinetex EVO C18 (1.7 μ m, 100 Å, 100 mm x 2.1 mm). The flow rate was constant at 0.6 mL/min, and the injection volume was set to 1.0 μ L. Two chromatographic methods were applied to determine the analytes. BADGE, BADGE·H₂O, BADGE·2H₂O, BADGE·HCI, BADGE·H₂O·HCI, BADGE·2HCI, BFDGE, BFDGE·2H₂O, BFDGE·2HCI, BPBP, BPC, BPF, BPFL, BPG, BPM, BPM, and PBZ were separated using gradient elution. The mobile phase consisted of (A) water with 0.01% v/v ammonium hydroxide and (B) MeOH. The initial conditions of 30% B were maintained for 0.5 min, and then the content of MeOH was increased to 70% over 10 min and held for 4 min. Following this, the mobile phase composition was decreased to the starting conditions (30% B) over 20 min. After each analysis, the initial column conditions were restored over 5 min. The column oven temperature was kept at 50°C. To separate BPA and BPS, elution in isocratic mode was applied. The mobile phases were water (A) and (B) methanol without additives. Elution was carried out with mobile phases A and B at a ratio of 55/45 v/v. The total run time was 7.5 min. The column was kept at 45°C. Example chromatograms of standards are presented in Fig. 1.

<insert Figure 1. Example chromatograms of standards>

The minimization of possible contaminations was achieved through special care being taken in all steps of the applied procedure. All glassware was pre-cleaned using detergent, rinsed thoroughly with MilliQ water and MeOH and then heat treated (>350°C), and using of any plastic equipment was minimized. If it was not possible to use a substitute, only plastic accessories made of high-quality polypropylene were used. Moreover, Milli-Q system was equipped with EDS-Pak cartridge for removing endocrine disrupting compounds. What is more, according to findings by (Wilczewska et al., 2016), separate method using isocratic elution was used to determine BPA and BPS. 2.6. Infants and toddlers dietary intake and hazard risk

The estimated intake (EDI) of BPA and BADGE analogues for different age groups was calculated by equation (1) by combining the average body weight of the infants and toddlers, the infants'/toddlers' daily consumption of ready-to-eat meals and the average concentration of each detected compound.

$$EDI = \frac{C \cdot IR}{BW} \tag{1}$$

where:

EDI - estimated daily intake [ng/kg body weight/day],
C - concentration of identified compound in product [ng/g]
IR - average food consumption [g/day]
BW - average body weight [kg].

The average amount of ready-to-eat products consumed in this study was assumed to be one whole product per day, so the mass of the products (Table S1) was used for these calculations. In this work, EDI values were calculated for three age groups of infants at the ages of 6, 12 and 36 months. It was assumed that children of a certain age consume only products from a dedicated age group. For example, children at the age of 6 months consume products from group A, at the age of 12 months from group B, and at the age of 36 months from group C.

According to the WHO Child Growth Standards, it was assumed that the median body weight was 7.3 kg for female infants and 7.9 kg for male infants aged six months, 8.9 kg (female) and 9.6 kg (male) for those aged 12 months and 13.9 kg (female) and 14.3 kg (male) for those aged 36 months ("World Health Organization, Child growth standards, Weight-for-age," n.d.).

Furthermore, the hazard quotient (HQ) was calculated from equation (2):

$$HQ = \frac{EDI}{TDI}$$
(2)

where EDI is the estimated daily intake obtained from eq. 1 and TDI is the tolerable daily intake of compound. The following TDI values proposed by the European Food Safety Authority were used for the calculations: 4 µg/kg body weight/day for BPA and 150 µg/kg body weight/day for the sum of BADGE, BADGE·H₂O and BADGE·2H₂O. Because the TDI values for other BPA and BADGE analogues have not been established for the purposes of the calculations, it was assumed that the TDI value of BPA was employed for estimating the HQ values for all of the BPs (BPBP, BPC, BPF, BPFL, BPG, BPM, BPM, PBZ), and 150 µg/kg body weight/day was employed for the sum of chlorinated derivatives of BADGE (BADGE·HCl, BADGE·H₂O·HCl, BADGE·2HCl) and BFDGE (BFDGE·2H₂O, BFDGE·2HCl).

An HQ of <1 indicates that the xenobiotic ingestion dose through food consumption is lower than the reference dose, suggesting no expected adverse effects on humans. In contrast, adverse effects are possible if the HQ is > 1

Afterwards, the hazard index (HI) according to eq. 3 was calculated

$$HI = \sum_{i=k}^{n} THQ_1 \tag{3}$$

where HI is the sum of the individual THQi values obtained from equation 2.

The HI calculation assumes that the consumption of a particular food type would result in simultaneous exposure to several potentially toxic elements. In this study, it was assumed that the type of food consumed would be classified according to the age of the children, as described earlier, into groups A, B, and C. For the evaluation of the calculated values, it was assumed that HI < 1 means that there is no concern about health risk, HI \geq 1 indicates a potential health concern.

3. Results and discussion

3.1. Matrix selection and matrix influence

Most of the samples were based on a mix of either fruits or vegetables with the addition of meat and natural fruit juices. Thus, a matrix material was chosen based on the components of infant foods, and apple mousse was the matrix most suitable, corresponding to the composition of most of the samples. Apples were purchased at a local market and prepared according to section 2.4 Sample preparation. The apple matrix was prepared as described in sample preparation, including blank samples and spiked samples (n=3). In all blank samples of apple matrix, the content of analytes was below the LOD level. To minimize and to evaluated the influence of membrane bags, test samples were prepared without matrix/real samples. In all test matrix candidate samples, the content of analytes was below the LOD level (data not shown); hence, the influence of membrane material on real sample results should be treated as insignificant. Other possible influences on the results and contamination either with BADGE/BFDGE or bisphenols may come from plastic accessories and from used solvents. To minimize this influence, the solvents were of LC-MS grade, while in the case of samples, contact of standards and solutions with plastic utensils was minimized as much as possible. To reduce the influence of BPA and BPS as the two analytes that may produce nonreplicable results in gradient elution, the chromatographic method in isocratic mode was used, as proven and stated in research by Wilczewska et al. (Wilczewska et al., 2016).

3.2 Analytical figures of merit

The developed analytical method was evaluated in terms of LODs and LOQs, recoveries at three spiking levels and repeatability. All results are presented in Table S3. The contamination background was evaluated for milled apple; hence, all values were below the LOD level, and no correction was applied to real samples. The obtained calibration curves were linear in the designed range (1-50 ng/g), while the correlation coefficients were above 0.9939 for all the analytes. In most real samples, the content of analytes was in the lower range of calibration, and it was decided to apply the weighing factor 1/x for all calibration curves to increase accuracy for all the tested compounds. The values of LODs and LOQs were calculated based on weighed calibration curves made on matrix

matched samples of apple. The formulas used were as follows: LOD=(3.3×Sb)/a and LOQ=3×LOD, where *a* is the slope of the obtained calibration curves and *Sb* is the standard deviation of the intercept of the calibration curve (Konieczka and Namieśnik, 2018). The LOD values were in the range of 0.27-0.79 ng/g, while the LOQs values were in the range of 0.8-2.37 ng/g. The quantification of real samples was performed based on matrix matched calibration curves. To calculate the matrix effect (ME) the following equations was used to calculate *t-value* and estimated variance (Sp) based on two calibration curves, one on solvent and matrix matched (Slutsky, 1998).

$$t(b) = \frac{|b_s - b_m|}{\sqrt{sp^2 \left(1/\sum (X_{i,s} - \overline{X_s})^2 + 1/\sum (X_{i,m} - \overline{X_m})^2\right)}}$$
(4)
$$S_p^2 = \frac{(n_m - 2)S_s^2 + (n_a - 2)S_m^2}{n_s + n_m - 4}$$
(5)

Where *b* is the intercept of calibration curve, *X* the concentration, *n* the number of replicates (in this case n=18), *S* the standard deviation of slope, the indexes *s* and *m* correspond to solvent and to matrix matched calibration curves respectively. The calculated t values for each analyte was compared with the t-value from Student's distribution table (t_{crit} =2.04). Values above t_{crit} indicate that matrix effects are present for some analytes (Table S3), hence the need to use matrix matched calibration curves of all compounds in food samples.

For the recovery studies, spiked samples were prepared at three concentration levels: 5, 10 and 20 ng/g of apple at three repetitions (n=3) and were subjected to sample preparation procedures. The obtained recoveries for all analytes ranged from 76-135% for 5 ng/g, 79-138% for 10 ng/g and 81-129% for 20 ng/g. The RSD values for all spiked sample sets ranged from 0.5% to 6.9%.

3.3. Occurrence of BPA analogues in ready-to-eat baby food samples

The detection levels of the studied analytes in commercial ready-to-eat baby food samples are shown in Table 1. All of the bisphenols studied were detected and quantified in at least one sample. The concentrations of the detected analytes ranged from 1.00±0.11 ng/g for BPZ and BPP to 371.9±8.8 ng/g for BADGE·2HCI. The highest frequency was observed for BADGE·2HCI (69.6%), BPG,

(64.3%), BPP (64.3%), and BPZ (60.71%), while the lowest was observed for BFDGE· $2H_2O$ (3.57%), BFDGE (5.36%), BPF (5.36%) and BPA (7.14%). In the case of BPP, it seems that the obtained results are quite consistent with those published by García-Córcoles et al. (García-Córcoles et al., 2018) where BPP was detected and quantified in the majority of the analyzed samples. The detected BPP concentrations ranged from 1.00 ± 0.11 to 29.0 ± 2.2 (mean 6.91 ng/g) and from 4.1 to 7.7 (mean 5.96 ng/g) in our study and García-Córcoles et al., respectively. The slightly different level of content may be due to the difference in the number of samples analysed (56 vs. 15). In the case of BPG and BPZ, there is no literature data yet to compare our findings.

The low prevalence of BPA and thus high occurrence of other analogues is closely related to the regulation introduced in 2018 (Commission, 2018) prohibiting the migration of this compound from varnishes or coatings applied to materials and articles specifically intended to come into contact with infant formula and baby food, which prompted most manufacturers to replace BPA with other bisphenols. Similar results have been reported in (García-Córcoles et al., 2018). In 9 samples, the concentrations of BFDGE and its chloro- and hydroxy-derivatives were detected in the range of 1.12-3.28 ng/g. The presence of these compounds is somewhat surprising since, in 2005, the use of BFDGE was completely banned from food contact materials. However, in the literature, there are reports (published after 2015) in which the presence of these compounds at the ng level was also found in samples of packaged food, such as tuna (Fattore et al., 2015) and energy drinks It can be assumed that the contamination of food with these compounds took place at one of the stages of transport of raw materials, their storage or the production of ready-to-eat meals. In almost all the samples, with a single exception (sample ID. 5), at least one analyte was quantified. By analysing the obtained results in terms of the type of packaging in which the samples were stored, it can be seen that the analytes were most often identified in the samples stored in plastic pouches. In a sample of fruit-vegetable mousse stored in this packaging, as many as 16 out of 19 analysed compounds were identified (only BADGE 2HCl, BPA and BPS were not detected). Interestingly, the highest total amount of bisphenols (388 ng) was identified in a sample of vegetable mousse stored in a glass jar intended for children

over 4 months of age. Fig. 2 summarizes the relationships among the identified compounds and the type of packaging in which the food was stored in a Venn diagram. Diagram analysis revealed that BPS was only identified in samples stored in glass. In the case of samples stored in plastic pouches, BFDGE, BFDGE·2H₂O, BPF and BPM were unique. BADGE·2H₂O, BADGE·H₂O·HCl, BPC, BPFL, BPG, BPP, and BPZ were quantified in samples stored in each type of packaging studied. No particular correlations were found between the quantified compounds and the type of the analysed sample (mix of fruits, mix of vegetables, mix of fruits and vegetables, vegetables and meat).

<insert Figure 2. Venn diagram of analytes occurence with regard to sample packaging>

3.4. Estimated dietary intake and risk assessment

The average and 95th percentile concentrations for infant age groups were used to represent average- and high-exposure scenarios, respectively (Table 2). The highest average level of analyte found in samples from group A (n = 23) was found for BADGE- 2HCl (45.57 ng/g, with a 95th percentile value of 179.62 ng/g), followed by BADGE- HCl (17.17 ng/g), BPC (9.79 ng/g) and BPS (7,00 ng/g). In the case of samples from group B (n=25), the highest average level was quantified again for BADGE- 2HCl (40.28 ng/g with a 95th percentile value of 154.97 ng/g), followed by BADGE (16,39 ng/g), BPFL (15.08 ng/g) and BPC (9.24 ng/g). However, for samples from group C, the highest average concentration was found for BPFL (24,64 ng/g, with a 95th percentile value of 24.64 ng/g) and BADGE- 2H₂O (7.73 ng/g). The EDI values of bisphenol analogues via ready-to-eat baby food consumption according to the age of male (M) and female (F) infants/babies are summarized in Table 3. The mean EDI values of the studied compounds were in the range of 22.56-769,49 ng/kg b.w./day for females and 20.85–711,05 ng/kg b.w./day for males, 12.82-450.72 05 ng/kg b.w./day (F) and 11.93-417.85 ng/kg b.w./day (M) and 9.27-212.74 ng/kg b.w./day (F) and 9.01-206.79 ng/kg b.w./day (M) for groups A, B and C, respectively. The highest estimated dietary exposure in the 95th percentile was 3248.96 ng/kg b.w./day for BADGE- 2HCl in the food intended for the youngest group of children

(4-6 months, group A). This might be due to the lower body weight of younger infants in comparison to older infants. Similar findings were also described in other reports (Cirillo et al., 2015; Niu et al., 2015). The HQ and HI calculated for each compound are also displayed in Table 3. The highest HQ value was calculated as 0.03 (and 0.11 for the 95th percentile) for BPS in group A. Importantly, when all approaches, both the mean and 95th percentile, were taken into account, the HQ and HI values obtained for the studied compounds were found to be far below 1. The highest HI value was found to be 0.195 (0.482 for the high-exposure scenario) and 0.160 (0.470 for a high-exposure scenario) for infants between 6 and 12 and 4 and 6 months, respectively, which indicates that the exposure of these compounds presents no apparent risk to infants and children through the consumption of ready-to-eat meals. However, these data refer to the consumption of only one dose of the product, so it is obvious that consumption of more will increase the daily dietary exposure. Additionally, if a new EFSA draft opinion concerning the reduction of the BPA TDI value from 4 μ g/kg bw/day to 0.04 ng/kg bw/day is issued, it is highly likely that the HQ will be exceeded in the future (EFSA, 2021). We considered a probable future scenario for the dietary exposure assessment (Table S4). For a future scenario, HQ and HI values are significantly higher than those reported for the current TDI value (from tens of thousands to even hundreds of thousands of times). The findings of this simulation indicate that adverse health effects are possible. Given that the likelihood of such effects increases with increasing HI values, it can be assumed that the risk is very high. Moreover, it should be kept in mind that the diet of children, especially infants, is based mainly on milk consumption, so the daily consumption of xenobiotics is probably much higher. In particular, in the literature, one can find some reports about the presence of BPs both in breast milk and infant formula (Karsauliya et al., 2021; Niu et al., 2021; Sirot et al., 2021).

4. Conclusion

The developed method presents determination of a large group of BPA analogues in more than 50 samples of various types of packaged baby food and the comparison along with others similar was

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presented in table 4. Dietary exposure and health risk assessment was assessed on the basis of obtained results. The major compounds occurring in analysed samples were BADGE 2HCl, BPG and BPP. Low frequencies of detection were observed for BFDGE, BPF and BPA. The samples stored in packaging made from plastic showed a significantly higher number of quantified compounds than those stored in glass jars. The health risk assessment calculated for the obtained results (and the current TDI value for BPA) showed HQ values of less than one, hence ready-to-eat meals will unlikely pose any health risks to infants and toddlers even at the highest concentrations found in the present study. The limitations of the research are connected with the fact that two separate chromatographic methods should be run for such a set of analytes, there is a lack of proper reference material, and there is limited possibility for comparison with other findings. Furthermore, it must be taken into account that fruit/vegetable mousses, especially in the early months of life, constitute only a small portion of consumed food compared to milk (breastmilk/infant formula); thus, the daily intake of bisphenols may be significantly higher. The future study should focus on the determination of BPs dietary intake of a complex diet containing both ready-to-eat meals and ready-to-feed milk. Overall, our study provided key data on the next source of infant and baby exposure to BPA-related compounds. These findings can be used as inputs for total dietary intake estimates and risk assessments of children of various ages.

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Figure 1. Example chromatograms of standards

Figure 2. Venn diagram of analytes occurrence with regard to sample packaging





Sa									Analyte C	Concent	ration [ng,	/g] ± SD								
mp le ID	BAD GE	BAD GE∙ H₂O	BAD GE· 2H ₂ O	BAD GE- HCI	BAD GE- 2HCl	BAD GE· H ₂ O ·HCl	BFD GE	BFD GE∙ 2H₂ O	BFD GE· 2HC I	BPA	BPB P	BPC	BPF	BPFL	BPG	BP M	BPP	BPS	BPZ	Σ of ana lyte s
1	-	-	1.65 ±0.1	-	-	-	-	-	-	-	-	2.65 ±0.3	-	4.55 ±0.2 7	3.34 ±0.2	-	3.81 ±0.2	-	1.00 ±0.1	17. 0
2	-	1.73 ±0.2 7	2.55 ±0.2	-	8.04 ±0.4	1.85 ±0.1	-	-	-	-	-	-	-	-	-	-	-	-	-	14. 2
3	1.18 ±0.1	-	1.91 ±0.2	-	6.47 ±0.4	1.77 ±0.1	-	•	•	•	•	-	•	-	-	-	1.00 ±0.2	-	•	12. 3
4	-	-	1.59 ±0.1	-	-	-	-	-	-	-	1.25 ±0.3	2.95 ±0.1	-	4.58 ±0.1	2.94 ±0.5	-	3.49 ±0.3	-	1.03 ±0.2	17. 8
5	-	-	-	-		-	-		-		-	-		-	-		-	-	-	
6	-	-	-	-	2.05 ±0.2 7	-	-	-	-	-	2.76 ±0.3 0	-		-	3.36 ±0.2 5		1.03 ±0.1 6	-	1.36 ±0.1 7	10. 6
7	1.58 ±0.1 8	-	11.3 0±0. 79	-	7.72 ±0.3 8	3.25 ±0.4 0	-	-	-	-	-	-	-		-		-	36.0 ±3.2	2.40 ±0.4 4	62. 3
8	-	-	3.16 ±0.1 0	-	3.98 ±0.3 8	1.41 ±0.1 4	-	-	-	-	-	-	-	-		-	-	-	2.16 ±0.1 9	10. 7
9	-	-	1.27 ±0.0 6	-	371. 9±8. 8*	-	-	-	-	-	1.15 ±0.1 8	2.79 ±0.4 9	-	5.07 ±0.3 4	2.95 ±0.4 3	-	3.82 ±0.1 1	-	-	388
10	-	-	1.62 ±0.1 2	-	169. 5±4. 4*	-	-	-	-	-	1.11 ±0.2 5	-	•		1.33 ±0.2 7	-	1.35 ±0.2 1	-	-	175
11	1.16 ±0.3 8	-	1.54 ±0.1	-	127. 0±6. 9*	-	-	-	1.32 ±0.1 8	-	1.20 ±0.1	2.26 ±0.2	-	5.35 ±0.3 9	3.22 ±0.3	-	4.88 ±0.2 4	-	1.22 ±0.1	149
12	-	-	2.23 ±0.1	-	10.6 4±0.	2.16 ±0.1	-	•	-	2.51 ±0.3		-	-	-	-	-	-	1.72 ±0.1	-	19. 3
13	-	-	1.79 ±0.1	-	4.38 ±0.3	-	-	-	•	-		34.9 ±1.8	-	-	-	-	1.11 ±0.2	1.96 ±0.3	-	4.1
14	-	-	1.04 ±0.1	-	2.83 ±0.3	-	-	•	•		-	-	-	-	-	-	-	4.17 ±0.3	-	8.0
15	•	-	2.18 ±0.2	-	-	-	0	•	-	-	-	2.27 ±0.1	•	5.36 ±0.2	3.23 ±0.3	-	4.25 ±0.2	-	-	17. 3
16	-	1.85 ±0.1	15.3 ±1.0	-	4.40 ±0.3	2.59 ±0.2	.(5	-	1.28 ±0.2	-	-		-	-	-	1.03 ±0.2	2.93 ±0.2	6.72 ±0.7	36. 1
17	3.60 ±0.1	1.44 ±0.1	12.4 ±1.0	17.2 ±1.8	59.8 ±2.9	6.39 ±0.1	-	•	-	-	2.50 ±0.2	9.66 ±0.3	-	20.1 6±0.	18.8 ±1.2	1.34 ±0.1	17.3 5±1.	-	3.22 ±0.2	173 .9
18	-	-	-		3.76 ±0.3	-	-	•	-	-	-	-	-	-	-	-	1.08 ±0.1	-	1.09 ±0.1	5.9
19	-	-		·	2.52 ±0.2	-	-	•	-	•	2.09 ±0.2	-	-	-	2.54 ±0.4	-	3 1.17 ±0.1	-	-	8.3
20	-	-	•		62.1 ±3.1	-	-		-	-	2.26 ±0.4	-		-	4 2.99 ±0.1	-	-	-	1.13 ±0.1	68. 5
21	-		1.86 ±0.1	-	5.84 ±0.3	1.51 ±0.1	-	•	-	-	-	1.12 ±0.1	•	-	-	-	1.08 ±0.1	3.73 ±0.2	9 16.8 4±0.	32. 0
22	-	-	±0.0 0	-	6 2.43 ±0.2	-	-		-	-	-	29.4 ±1.6		-	-	-	-	7 2.40 ±0.3	36 1.72 ±0.2	36. 0
23	-	-	6.57 ±0.3	-	4 10.4 5±0.	2.38 ±0.2	•	•	-	•	-	-	-	•	-	-	1.01 ±0.1	8 3.08 ±0.3	8 1.39 ±0.1	25. 0
24	1.57 ±0.3	1.49 ±0.1	2 12.7 0±0.	5.28 ±0.1	79 58.7 ±1.8	7 6.63 ±0.3	-		-	-	3.27 ±0.5	18.2 8±0.		30.9 ±2.8	27.2 ±1.2	1.34 ±0.1	5 23.9 ±1.5	-	7 6.48 ±0.6	197 .6
25	-	-	-	-	* 5.58 ±0.1	9	-	•	-	-	-	65 -	-	-	-	7	1.02 ±0.2	-	5 1.05 ±0.1	7.7
26	3.22 ±0.1	3.33 ±0.2	14.6 ±1.6	2.30 ±0.1	8 240. 3±7.	4.26 ±0.1	-	•	-	-	2.18 ±0.3	12.0 8±0.	-	17.8 9±0.	14.2 ±1.0	1.13 ±0.8	2 19.8 ±1.8	-	5 2.44 ±0.3	337
27	2 1.54 ±0.1	5 1.59 ±0.1	9.82 ±0.8	9 3.42 ±0.5	5* 36.5 ±1.6	9 2.67 ±0.1	-	•	1.60 ±0.2	-	2 2.24 ±0.1	43 8.61 ±0.5	•	93 14.8 7±0.	10.1 8±0.	0 -	12.1 ±1.1	•	0 -	105
28	7 111. 5±2.	7 15.7 4±0.	0 13.0 ±1.2	1 5.48 ±0.6	53.0 ±2.6	7 5.15 ±0.3	1.3± 0.41	•	3 1.91 ±0.7	-	5 1.46 ±0.7	1 10.8 ±1.7	2.57 ±0.3	54 22.7 ±1.0	95 13.6 0±0.	-	12.1 ±0.8	-	1.06 ±0.1	271 .2
29	9* -	76 -	2.40 ±0.1	7	-	1	-	-	-	-	7 -	2.11 ±0.2	4	3.61 ±0.3	58 2.93 ±0.3	-	4 3.40 ±0.4 8	•	-	14. 5
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47 2.86 3.32 19.9 3.53 - 5.86 - - - 23.0 - 25.0 21.5 1.74 30.5 - 6.50 ±0.1 ±0.3 0±0. ±0.4 ±0.1 ±1.7 ±2.8 ±2.6 ±0.5 ±1.9 ±1.1 4 9 39 8 8 3 1	142
48 2.15 1.97 15.1 1.67 - 3.55 - - - 4.40 13.5 - 13.1 29.1 1.64 22.9 - 8.26 ±0.5 ±0.1 3±0. ±0.1 ±0.4 ±0.1 ±1.4 ±1.7 ±3.2 ±0.1 ±1.3 ±0.7 1 3 54 3 2 1 0 0 0	119
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54 4.69 12.5 6.31 3.02 10.4 5.85 - - 1.07 7.74 - 1.38 - - - 1.04 2.18 - ±0.2 2±0. ±0.3 ±0.3 1±0.4 ±0.3 ±0.2 ±0.6 ±0.2 ±0.2 ±0.1 2 2.78 4 8 55 1 4 6 1 9 1	56. 2
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-not detected * sample diluted to fall within the calibration curve range (in all cases 10x)

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	mea	95 th	frequenc	mea	95 th	frequenc	mea	95 th	frequenc
	n	percentii	У [%]	n	percentii	у [%]	n	percentii	у [%]
BADGE	1 88	3 30	17 39	163	е 7/ 9/	30	2 21	e 152	37 50
DADGE	1.00	5.50	17.55	9	74.54	52	5.51	4.52	57.50
$BADGE \cdot H_2O$	1.68	1.84	13.04	4.84	12.95	28	6.81	11.95	25.00
BADGE · 2H ₂ O	4.11	13.00	73.91	9.51	22.96	60	7.73	13.38	37.50
BADGE · HCl	17.1 7	16.58	4.35	3.42	5.41	32	3.02	3.02	12.50
BADGE· 2HCl	45.5 7	179.62	82.61	40.2 8	154.97	52	3.58	8.57	75.00
BADGE∙ H₂O∙HCl	2.59	6.54	39.13	4.99	14.42	48	3.66	5.67	37.50
BFDGE	-	-	0.00	1.26	1.26	12	-	-	0.00
BFDGE· 2H₂O	-	-	0.00	1.66	1.76	8	-	-	0.00
BFDGE· 2HCl	1.32	1.88	21.74	1.84	2.57	36	1.83	3.07	37.50
BPA	1.90	2.45	8.70	-	\mathbf{C}	0	6.95	7.66	25.00
BPBP	1.79	2.92	34.78	4.49	11.84	60	2.49	3.18	87.50
BPC	9.79	31.35	39.13	9.24	20.15	52	3.32	7.28	62.50
BPF	-	-	0.00	2.45	2.56	8	3.69	3.69	12.50
BPFL	7.51	27.65	26.09	15.0	27.98	44	24.6	24.64	12.50
PDC	4 47	21.20	12 10	8	22.22	76	4	15 22	97 E0
DPG	4.47	21.29	45.40	9	27.25	70	5.17	15.25	67.50
BPM	1.34	1.34	4.35	1.43	1.72	20	1.07	1.07	12.50
BPP	3.16	20.44	65.22	10.7	29.36	64	5.68	16.78	50.00
BPS	7.00	3 63	34 78	2 2 2 3	3 26	12	2 18	2 18	12 50
BP7	11.5	15.91	8.70	6.80	9.25	 24	7.60	8.23	25.00
BPS BPZ	7.00 11.5	3.63 15.91	34.78 8.70	2.23 6.80	3.26 9.25	12 24	2.18 7.60	2.18 8.23	12.50 25.00

Table 2. Concentration (mean and 95th percentile) and detection frequency of bisphenols in ready-to-eat meals for infant and toddlers collected in Gdańsk, Poland.

nd – not detected

* Only values above the LOQ were taken to calculate the mean and 95th percentile concentration.

Table 3. Estimated Daily Intake (EDI), Hazard Quotient (HQ) and Hazard Index (HI) of bisphenol analogues according to the age of male (M) and female (F) infants and toddlers.

analyte	parameter	age [months]									
			ô	1	2	36					
		F	М	F	М	F	М				
BADGE	EDI [ng/kg/b.w./day)										
	mean	29.10	26.89	181.82	168.56	38.40	37.32				
	(95th percentile)	(46.03)	(42.53)	(836.47)	(775.48)	(68.92)	(66.99)				
BADGE· H2O	EDI [ng/kg/b.w./day)										
	mean	27.04	24.99	52.32	48.51	-	100.96				
	(95th percentile)	(31.54)	(29.15)	(141.15)	(130.86)		(183.48)				

BADGE· 2H2O	EDI [ng/kg/b.w./day)						
	mean	66.68	62.38	117.53	108.96	80.56	78.30
	(95th percentile)	(207.10)	(191.37)	(301.52)	(279.54)	(120.09)	(116.73)
Σ BADGE, BADGE∙	HQ	0.001	0.001	0.002	0.002	0.001	0.001
H2O, BADGE· 2H2O	(95 th percentile)	(0.002)	(0.002)	(0.01)	(0.01)	(0.001)	(0.001)
BADGE· HCl	EDI [ng/kg/b.w./day)						
	mean	-	-	39.68	36.79	47.85	46.51
	(95th percentile)			(60.76)	(60.76)	(47.85)	(46.51)
BADGE · 2HCl	EDI [ng/kg/b.w./day)						
	mean	769.49	711.05	450.72	417.85	41.21	40.06
	(95th percentile)	(3248.96)	(3002.20)	(1608.96)	(1491.64)	(129.02)	(125.41)
BADGE· H2O·HCI	EDI [ng/kg/b.w./day)						
	mean	41.91	38.73	450.72	417.85	45.09	43.83
	(95th percentile)	(74.80)	(69.11)	(1608.96)	(1491.64)	(86.79)	(84.36)
Σ BADGE· HCl,	HQ	0.01	0.01	0.01	0.01	0.001	0.001
BADGE· 2HCl,	(95th percentile)	(0.02)	(0.02)	(0.02)	(0.02)	(0.002)	(0.002)
BADGE · H2O · HCl							
BFDGE	EDI [ng/kg/b.w./day)						
	mean	-	-	12.82	11.93	-	-
	(95th percentile)			(14.23)	(13.27)		
BFDGE· 2H2O	EDI [ng/kg/b.w./day)	-	-				-
	mean			14.92	13.83	-	
	(95th percentile)			(15.79)	(14.64)		
BFDGE· 2HCl	EDI [ng/kg/b.w./day)						
	mean	22.56	20.85	22.36	20.73	16.76	16.29
	(95th percentile)	(22.56)	(20.85)	(25.57)	(23.70)	(22.95)	(22.32)
Σ BFDGE, BFDGE∙	HQ	0.0002	0.0001	0.0003	0.0001	0.001	0.0001
2H2O, BADGE· 2HCl	(95th percentile)	(0.0002)	(0.0001)	(0.0003)	(0.0002)	(0.002)	(0.0001)
BPA	EDI [ng/kg/b.w./day)						
	mean	32.45	29.98	-	-	87.87	85.41
	(95th percentile)	(41.93)	(38.74)			(119.04)	(115.71)
	HQ	0.01	0.01	-	-	0.02	0.02
	(95th percentile)	(0.01)	(0.01)			(0.03)	(0.03)
BPBP	EDI [ng/kg/b.w./day)						
	mean	28.60	26.42	47.80	44.31	19.65	19.04
	(95th percentile)	(44.24)	(40.88)	(150.05)	(139.11)	(26.96)	(26.21)
	HQ	0.01	0.01	0.01	0.01	0.005	0.005
DDC	(95th percentile)	(0.01)	(0.01)	(0.04)	(0.03)	(0.01)	(0.01)
BPC	EDI [ng/kg/b.w./day)	150.07	147 70	112 17	104.02	20.04	20.22
	(OEth porcontilo)	159.67	147.72	(200 1E)	104.92	29.04 (62.15)	20.25
		(300.48)	(517.91)	(200.15)	(207.14)	0.01	(00.41)
	(95th percentile)	(0.14)	(0.13)	(0.03	(0.03	(0.01	(0.02)
RDF	EDI [ng/kg/h w /day)	(0.14)	(0.13)	(0.07)	(0.07)	(0.02)	(0.02)
DET	mean	_	_	2/ 95	23 13	21 82	30.94
	(95th percentile)			(28 52)	(26.44)	(31.83)	(30.94)
	HO	_	_	0.01	0.01	0.01	0.01
	(95th percentile)			(0.01)	(0.01)	(0.01)	(0.01)
BPFI	FDI [ng/kg/b.w./dav]			(0.01)	(0.01)	(0.01)	(0.01)
	mean	107.11	98.98	179.23	166.16	212.74	206.79
	(95th percentile)	(230.03)	(212.56)	(334.78)	(310.37)	(212.74)	(206.79)
	HQ	0.03	0.02	0.04	0.04	0.05	0.05
	(95th percentile)	(0.06)	(0.05)	(0.08)	(0.08)	(0.05)	(0.05)
BPG	EDI [ng/kg/b.w./day)	, , , , , , , , , , , , , , , , , , ,	· · ·	<i>、 ,</i>	ζ γ	()	. ,
	mean	66.07	61.05	126.80	118.61	42.31	41.08
	(95th percentile)	(167.80)	(155.06)	(345.16)	(319.99)	(129.90)	(126.26)
	HQ	0.02	0.02	0.03	0.03	0.01	0.01
	(95th percentile)	(0.04)	(0.04)	(0.09)	(0.08)	(0.03)	(0.03)
BPM	EDI [ng/kg/b.w./day)	-	-	-			
	mean			19.87	18.42	9.27	9.01
	(95th percentile)			(36.34)	(33.69)	(9.27)	(9.01)

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BPS	EDI [ng/kg/b.w./day)	()	()	()	()	()	()
RPS	(95th percentile) FDI [ng/kg/h w /day)	(0.03)	(0.03)	(0.10)	(0.09)	(0.04)	(0.04)
	mean	119.83	110.73	38.11	35.33	34.57	33.60
	(95th percentile)	(425.59)	(393.27)	(71.68)	(66.45)	(34.57)	(33.60)
	HQ	0.03	0.03	0.01	0.01	0.01	0.01
	(95th percentile)	(0.11)	(0.10)	(0.02)	(0.02)	(0.01)	(0.01)
BPZ	EDI [ng/kg/b.w./day)						
	mean	52.59	48.60	57.49	53.39	17.86	17.33
	(95th percentile)	(184.40)	(170.39)	(217.49)	(201.63)	(47.83)	(46.49)
	HQ	0.013	0.012	0.014	0.013	0.004	0.004
	(95th percentile)	(0.046)	(0.043)	(0.054)	(0.050)	(0.012)	(0.012)
	ні	0.160	0.148	0.195	0.181	0.135	0.132
	HI 95th	0.470	0.435	0.482	0.447	0.197	0.192

CRediT authorship contribution statement

Natalia Jatkowska: supervision, conceptualization, methodology, writing original draft, visualization, data curation; Paweł Kubica: writing - review & editing, visualization, validation, investigation, data curation, methodology

Declaration of interests

 \boxtimes 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.

□ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Bisphenols and their derivatives present in infant and toddler food
- Ultrasound-assisted membrane extraction of ready-to-eat meals samples
- Estimated intake and risk assessment of bisphenols and their derivatives
- Quantitation of bisphenols and diglicydyl ether derivatives in food samples