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Bisphenol A in Fluid and Powdered Milk Samples and Associated Child Dietary Exposures

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Abstract

Bisphenol A (BPA) is a synthetic chemical found in a wide range of consumer products and consumables that humans are exposed to. The aim of this study was to determine BPA contamination levels in 51 milk samples sold in the Rio de Janeiro Metropolitan Region, Brazil. Bisphenol A was detected (≥limit of detection, LOD) in five of the analyzed samples (9.8%) and quantified (≥limit of quantification, LOQ) in two (3.8%). The estimated daily intake (EDI) for children aged up to 12 months ranged from 24.95 to 97.72 ng/kg body weight/day, lower than the established European Union tolerable daily intake value. Recent evidence, however, suggests that even low doses of endocrine disruptors such as BPA may pose potential health risks, even more so when exposure occurs at such an early life stage.

Keywords

Bisphenol A, UHPLC-MS/MS, QuEChERS, Cow's Milk, Dietary Exposure Assessment

1. Introduction

Bisphenols are part of a class of diphenylalkane substances, and the major bisphenol compound, 2,2-bis(4-hydroxyphenyl) propane, CAS No. 80-05-7, popularly known as Bisphenol A (BPA), is one of the most prevalent chemicals currently marketed worldwide [1] [2] [3]. It is used mainly in the manufacture of resistant polycarbonate plastics and epoxy resins for metallic food coatings and beverage packaging. Packaging alterations caused by changes in temperature or pH are, however, sufficient for BPA migration from packaging to food contents [4] [5] [6] [7].

Bisphenol A is an environmental contaminant with the ability to disrupt natural hormone regulatory mechanisms in the human body following exposure. Several studies have demonstrated that BPA exposure is associated with adverse health effects, including endocrine disruption, various types of cancer, diabetes, increase susceptibility to gastric inflammation, damage to the colonic epithelium, obesity and cardiovascular and endocrine system diseases [8]-[15]. The European Food Safety Authority (EFSA) has established a temporary BPA tolerable daily intake (tTDI) of 4 μg/kg/body weight/day, and the European Union has increased restrictions on its use by fixing a specific migration limit of 0.05 $mg \cdot kg^{-1}$ into food from varnishes or coatings applied to food contact materials [16].

A study on BPA exposure from food and non-food sources for different human age groups carried out by the European Authority revealed that dietary sources are the most significant BPA exposure contributors, especially during early life stages [16]. Furthermore, due to the high number of contaminated foodstuffs detected worldwide [17] [18] [19], many analytical methods have been developed for different samples. In this regard, cow's milk is highly consumed worldwide, due to its nutritional benefits, also comprising a primary food item, especially for children, and is ingested by most populations during entire life periods. Daily BPA intakes can, therefore, be estimated by analyzing this food item [20] [21]. Bisphenol A has, in fact, been frequently researched in milk and its derivatives worldwide [22] [23]. Scarce studies, however, are available concerning the presence of BPA in food items [24] [25] [26] [27] [28] or infant formulas, UHT milk and mineral water in Brazil. Therefore, this study aimed to determine BPA in several milk and powdered milk brands sold in Rio de Janeiro, Brazil, and also estimated daily BPA intake for children.

2. Material and Methods

2.1. Chemicals and Reagents

A BPA standard (purity > 99%) was purchased from Sigma-Aldrich (Pennsylvania, USA). Acetonitrile (HPLC-grade), sodium chloride (purity > 99%), anhydrous magnesium sulfate (purity > 98%) and ammonium hydroxide 25% (for analysis) were purchased from Merck (Darmstadt, Germany). Methanol (HPLC-grade) was purchased from Tedia (Darmstadt, Germany). Hexane (purity > 96%) was obtained from J. T. Baker (Pennsylvania, USA). Ultrapure water was obtained from a Milli-Q Gradient water system (Millipore, Bedford, MA, USA).

2.2. Standard Solutions

A BPA standard stock solution (1000 $\mu g \cdot mL^{-1}$) was prepared by dissolving 10 mg

(±0.1 mg) of the BPA standard with methanol (MeOH) and making up the volume to 10 mL in a volumetric flask. This stock solution was stored in screw capped glass tubes at −18˚C in the dark. Working solutions were prepared weekly by serially diluting the stock solution with MeOH to the concentration range of 5 to 2 ng·mL^{-1}, stored at 5˚C and used to prepare both calibration and spiked samples.

2.3. Sample Collection

A total of 51 whole fluid milk and whole milk powder samples from twenty-seven different brands were purchased randomly in local supermarkets in the Rio de Janeiro Metropolitan Region, RJ, Brazil from April 2019 to July 2019, totaling 19 milk powder, 27 UHT fluid milk and five pasteurized fluid milk samples.

In addition to a categorization of fluid (UHT and pasteurized) and powdered milk, the investigated samples were also divided into packaging categories, as follows: whole fluid milk: glass, poly(ethylene terephthalate—PET), polyethylene (PE), poly(vinylidene chloride—PVDC) and Tetra Pak® packaging; powdered milk: metal cans and metallized polyester-polyethylene (laminated film) (**Figure 1**).

2.4. Sample Preparation Procedure Employing a QuEChERS Treatment

The method reported by Souza *et al.* [29] was employed to treat all samples. Briefly, fluid milk samples (3.0 g) were weighed in 15 mL centrifuge tubes, mixed with 3 mL of acetonitrile and 2 mL of hexane and thoroughly vortex-mixed for 30 s (Marconi, MA 162). Anhydrous magnesium sulfate (1.2 g) and sodium chloride (0.3 g) were then added followed by another thorough vortex-mixin for 2 min and centrifugation at 3000 rpm for 7 min in an Eppendorf 5804R centrifuge. A 1 mL acetonitrile extract aliquot was evaporated to dryness under a gentle nitrogen flow at room temperature using a Reacti-Therm III, 18935/Reacti-Vap III, 18785 equipment. The residues were then dissolved with 1 mL of a methanol/water (80:20, v/v) solution containing 0.1% ammonium hydroxide. The final solutions were then filtered through 0.22 µm hydrophobic PTFE filters before analyses. For powdered milk samples, 0.3 g of each sample were weighed in polypropylene (PP) centrifuge tube, mixed with 3 mL of ultrapure water and thoroughly vortex-mixed for 30 s. The subsequent procedure steps followed the steps previously described for the fluid samples.

2.5. UHPLC-MS/MS Analysis

Liquid chromatography analyses were performed employing an ACQUITY UPLC™ system (Waters). A BEH C_{18} column (100 mm × 2.1 mm i.d., 1.7 µm particle size) was used as the stationary phase. The column temperature was maintained at 35˚C. Methanol and water (70:30, v/v) were used the mobile

Figure 1. Different milk packaging materials. (a) Tetra Pak®; (b) poly(ethylene terephthalate—PET) packaging; (c) metal can; (d) polyethylene (PE) and poly(vinylidene chloride—PVDC); (e) metallized polyester-polyethylene (laminated film); (f) glass.

phase. An isocratic elution at a 0.3 mL·min^{-1} flow rate was applied. The system was washed with acetonitrile:methanol:isopropyl alcohol:water (1:1:1:1, v/v/v/v) at the end of each run for five minutes and re-equilibrated for five minutes in the initial mobile phase composition. A 5 μL injection volume was applied to all samples.

Detections were performed using a tandem quadrupole mass spectrometer (Waters, Xevo® TQ-S) equipped with an electrospray ionization (ESI) source. Source parameters were optimized as follows: ion spray voltage, 2 kV for ESI (-), capillary temperature of 400˚C, source temperature of 150˚C. Nitrogen was used as the cone and desolvation gas at 150 L·h^{-1} and 750 L·h^{-1} flows, respectively. Argon was used as the collision gas at a 0.15 mL·min^{-1} flow. Collision energies of 15 and 20 V were used for the quantification (m/z 227 > 212) and qualification (m/z 227 > 133) transitions, respectively.

2.6. Method Validation

The analytical methods employed herein have been previously validated and shown to be suitable for use in the direct determination of BPA in milk [29] and for use in the direct determination of free fumonisins and the indirect determination of total fumonisins after alkaline hydrolysis in corn and corn products which are also in low concentrations in food [30]. Linearity, selectivity, matrix effect, precision (repeatability and intermediate precision), recovery, LOD and LOQ were evaluated. The linearity of all matrix-matched calibration used in routine was confirmed [31].

2.7. Internal Quality Control

Several quality controls were applied to ensure method accuracy. Blanks were analyzed at the end of each sample batch (10 samples) which, prepared with reagent blank (without the presence of the sample) to verify the absence of reagent/solvent interferences and possible BPA contamination. A reconstituted powdered milk sample fortified with 0.5 ng·mL^{-1} BPA was also analyzed after each batch, confirming the absence of contamination and verifying method recovery during the analyses.

To avoid any BPA system contamination, all exogenous BPA contamination sources were measured and glassware was used whenever possible, cleaned with methanol using an ultrasonic bath. Both $MgSO_4$ and NaCl, used in the QuEChERS treatment were heated at 400˚C overnight in a muffle furnace and stored in sealed glass vials after cooling. Hexane was filtered through an ENVI^{TM}– 18 DSK 47 MM membrane (Sigma-Aldrich) using a vacuum filtration system.

2.8. Estimated Dietary Intake (EDI) Calculations

Daily intakes were estimated considering children aged one week, one month, six months and 12 months, based on daily milk consumptions of 590, 642, 560 and 452 mL, respectively, based on the Food Guide for Children under 2 years old, which calculates the amount of breast milk (in grams) ingested in 24 hours, per age group [32]. The average weights for boys and girls were applied as 3.3 and 3.2 kg for infant aged one week, 4.5 and 4.2 kg for one month, 7.9 and 7.3 kg for six months, and 9.6 and 8.9 kg for twelve months, respectively [33].

3. Results and Discussion

The 51 samples from 27 different brands were purchased as six different packages, namely glass, poly(ethylene terephthalate) (PET), polyethylene (PE) and poly(vinylidene chloride) (PVDC) and Tetra Pak® cartons for whole fluid milk, while whole powdered milk was packaged in metal cans and packages lined with metallized polyester-polyethylene (laminated film).

Figure 2 indicates the packaging categories for the analyzed milk samples.

Of the total analyzed samples, only two (3.9%) contained BPA levels above the LOQ (0.36 ng·mL^{-1}), quantified as 0.53 ng·mL^{-1} and 0.50 ng·mL^{-1} in reconstituted whole milk powder (1:10) and total fluid milk, respectively. All other samples (44) contained levels below the method LOD (0.12 ng·mL^{-1}), with five samples (9.8%) above the LOD but below the LOQ.

Concerning the 19 powdered milk samples, BPA was detected in two samples marketed in metallized polyester-polyethylene packaging (laminated film) and one in a metal can packaging. Regarding the laminated film packaging (metallized polyester-polyethylene), one sample contained 0.53 ng·mL^{-1} BPA (above the LOQ).

With regard to the 32 whole fluid milk samples BPA below the LOQ was detected in two milk samples subjected to UHT heat treatment, packed in PET and

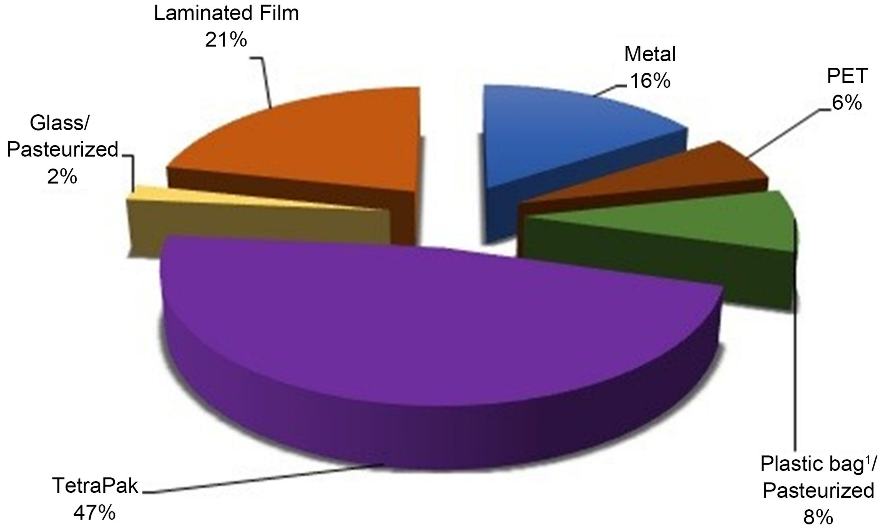

Figure 2. Milk sample packagings analyzed herein. [1]polyethylene (PE) and poly(vinylidene chloride—PVDC) packaging.

Tetra Pak® packaging. One sample submitted to pasteurized heat treatment, packed in polyethylene and poly(vinylidene chloride—PVDC) packaging, contained 0.50 ng·mL^{-1} BPA (above LOQ).

Studies in several countries have been carried out to evaluate milk BPA contamination, with levels reported as very variable, with several not detecting any BPA levels in milk [34] [35] [36]. In another study, [37] when evaluating different foods, including milk, detected an average value of 1.47 ng·g^{-1} BPA in milk, while [38], when assessing milk BPA contamination detected levels ranging from 1.6 to 2.6 ng·mL^{-1}. Finally, [27] investigated at least one bisphenol analogue in infant formulas, reporting concentrations between 10.9 and 198.9 μg·kg^{-1}.

The BPA levels determined in reconstituted whole milk powder (1:10) (0.53 ng·mL^{-1}, or 0.53 ng·g^{-1} considering a density equal to 1) and pasteurized whole fluid milk (0.50 ng·mL^{-1}) were close to the values of 0.49 ng·g^{-1} and 0.22 ng·g^{-1} reported by [39] in China and [40] in France, respectively.

In a study by [41], UHT and sterilized milk samples contained different mean BPA values, ranging from 0.99 to 2.64 ng·mL^{-1} for UHT milk and 1.17 a 1.29 ng·mL^{-1} for sterilized milk. Herein, pasteurized whole fluid milk was contaminated by BPA at 0.50 ng·mL^{-1}.

Of the 68 commercial milk samples analyzed by [42], free BPA was detected in four samples, ranging from 15 ng·g^{-1} to 481 ng·g^{-1}. Another assessment conducted by [23] evaluated BPA milk chain contamination, reporting that the highest BPA contamination levels were detected in raw milk at an average value of 0.265 μg·L^{-1} (0.265 ng·mL^{-1}).

The time milk is in contact with the packaging during heat treatment may account for the different BPA levels reported in different milk samples. For example, [37] also analyzed whole fluid milk packed in different types of packaging, detecting BPA values of 2.6 ng·mL^{-1} and 1.6 ng·mL^{-1} in polyethylene and high density polyethylene packagings, respectively. However, the authors report no BPA detected in samples packaged in Tetra Pak® cartons. This may be attributed to BPA migration, which increases with increasing temperatures and product exposure times to the packaging, as sterilization leads to product exposure from 20 to 40 minutes at temperatures between 110˚C and 130˚C, while UHT treatment decreases exposure times to 2 to 4 seconds at temperatures between 130˚C and 150˚C.

In another study, [43] evaluated 14 canned food samples, reporting differential BPA levels between the solid and aqueous portions of the same food items. As for metal packaging, [44] point to BPA migration from plastic packaging to food when samples are subjected to heating. In fact, BPA contamination is frequently reported in dairy products, powdered milk and infant formulas packed in metal cans, due to BPA migration from epoxy resins [25] [45] [46] [47].

Milk BPA contamination does not occur only from BPA migration via packaging, as BPA can enter the milk chain via multiple paths, such as animal feed, farm environments, and various milk production stages (*i.e.*, milk processing tubes, milk transfer to storage locations, filling equipment, among others), in addition to final stage technological processing duration. For example, [23] reported higher BPA levels in raw milk from storage tanks compared to both pasteurized and packaged milk.

Bisphenol A Exposure Assessment

The total dietary BPA milk exposures for children are depicted in **Table 1**, calculated based on the average volume of milk consumed by children under 2 years old based on the Brazilian Food Guide for Children [32]. This guide calculates the amount of breast milk in grams ingested in 24 hours, per age group, considering the exclusive used of fluid or powdered milk. A concentration of 0.53 $ng \cdot mL^{-1}$ BPA was used to calculate the EDI for reconstituted powder milk (1:10).

Table 1. Estimated daily intake values (ng/kg body weight/day) for children up to 12 months olf considering the exclusive use of reconstituted whole milk powder naturally contaminated with BPA (0.53 $ng \cdot mL^{-1}$).

Age	Daily milk consumption[1] (mL)	Average weight[2] (kg)		Estimated daily intake (ng/kg body weight/day)	
	Daily milk consumption[1] (mL)	Boys	Girls	Boys	Girls
1 week	590	3.3	3.2	94.76	97.72
1 month	642	4.5	4.2	75.61	81.01
6 months	560	7.9	5.6	37.57	40.66
12 months	452	9.6	8.9	24.95	26.92

[1]Values obtained from [32]; [2]Values obtained from [33].

The age groups mentioned herein require greater care, due to restricted diets and low body weights combined with physiological immaturity. Boys 1 week old ingesting only the contaminated milk analyzed herein would display an EDI of 95 ng/kg body weight/day, decreasing to 38 ng/kg body weight/day at 6 months old. Girls, on the other hand, at 1 week old would display an EDI of 98 ng/kg body weight/day decreasing to 41 ng/kg body weight/day at 6 months old.

The European Food Safety Authority (EFSA) estimated a daily intake of between 30 and 80 ng/kg body weight/day for babies (0 to 6 months) fed infant formula in 2015 [16]. A study by [48], considering the worst case scenario for babies (0 to 4 months) fed infant formula, estimated EDI between 0.99 to 1.27 μg/kg body weight/day (990 to 1270 ng/kg body weight/day). The values calculated herein are close to that estimated by EFSA and lower than that estimated by [48]. Considering the worst case scenario, the estimated exposure obtained per age group and sex in this study is below the current tolerable daily BPA intake of 4000 ng/kg body weight/day [16].

BPA can bind to extranuclear estrogen receptors and estrogen-related receptors and induce nuclear responses the independent of estrogen response elements, all of which can occur within specific cell types at environmentally relevant exposure levels. Thus, studies have indicate potential health effects with chronic BPA exposures, even at low levels, reporting positive correlations between BPA exposure and decreased glucose tolerance and increased risks of developing obesity, cancer, increased insulin resistance, increase the susceptibility at gastric inflammation, damage to the colonic epithelium, abdominal fat, adipose tissue and metabolic syndrome [8] [9] [10] [49] [50] [51] [52] [53].

4. Conclusion

Bisphenol A is a ubiquitous substance used in polycarbonate plastics and one of the most employed chemicals in volume. The findings reported herein are consistent with previous studies indicating the presence of BPA in milk, albeit at lower levels than those established by the EU. However, in view of new discoveries concerning BPA effects even at low doses, new measures to reduce exposure risks are paramount, as children are also exposed to other contamination sources (oral, inhalation and dermal), contributing to increased daily exposure which may result in potential health risks. Thus, monitoring programs involving each milk processing stage should be implemented, representing a useful strategy to ensure food safety throughout the milk chain. Risk assessments should also be established for BPA in both fluid milk and milk powder, especially considering the most vulnerable exposure period, including newborns and young children.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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