Human body burden of Bisphenol A: a case study of lactating mothers in Florianopolis, Brazil

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Research Article

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Abstract

Background:

Exclusive breast milk is the recommended nutrition by the World Health Organization (WHO) until six months of age, followed by introducing foods with continual breastfeeding. Bisphenol A (BPA) is a synthetic chemical used as a monomer in polycarbonate plastics and epoxy resins. Human exposure to BPA can cause numerous adverse health effects such as diabetes, obesity and cardiovascular disease, with children and infants as the most susceptible groups. Thus, this study aimed to determine BPA concentration in the colostrum of 64 mothers hospitalized at the University Hospital Professor Polydoro Ernani de São Thiago through the ELISA technique. We also assessed possible associations between breast milk BPA concentration and lactogenesis II. The results showed that all the breast milk samples contained a high concentration of BPA with a median value of 34.18 ng/mL. In addition, exposure to BPA did not alter the nutritional status of the mother; however, BPA concentration in mothers is influenced by the consumption of food packaged in plastic containers. The total daily intake of BPA in breastfed babies was 19.5 µg/kg/day and 28.5 µg/kg/day was recorded in the 95th percentile of the body weight per day, which is higher than the maximum daily intake by the European Food Safety Authority. This is of public health importance as a high concentration of BPA in the breast milk of the lactating mothers in this study could cause severe health problems in these mothers and much more in the infants breastfeeding on these BPA-contaminated breast milk.

1. Introduction

Exclusive breast milk is the recommended nutrition by the World Health Organization (WHO) until six months of age, followed by introducing foods with continual breastfeeding. Lactogenesis, the process of milk production and secretion can be divided into two stages: lactogenesis I and II. Lactogenesis I begins during gestation and is characterized by the development of the breast, while lactogenesis II starts after birth and signifies the start of milk secretion (PREUSTING *et al.*, 2017). The process of breastfeeding is very important to both the breastfeeding mother and the child. During this process, chemicals, microorganisms, and immunity are transferred from mother to child. This has therefore become a major source of infants' exposure to many chemical agents some of which are of public health importance (BRAUN, 2016).

Bisphenol A (BPA), also called 2,2-bis (4-hydroxyphenyl) propane, is a white crystalline compound with a molecular weight of 228.29 g/mol, a melting point of 156°C, and has low solubility in water. BPA has been widely used as a monomer in plastic polycarbonate and epoxy resin in food packaging, dental sealants, and ducts (HUANG et al., 2012). BPA is a known endocrine disruptor, and its estrogenic and antiandrogenic activities have been described in glucocorticoids and thyroid hormones (SKLEDAR; MAˇ, 2016). The primary source of human exposure to BPA is through the oral route, by eating contaminated food and drinks, although air, dust, and water are other possible sources of exposure. BPA can penetrate food from the internal epoxy resin linings of canned foods and consumer products, such as

polycarbonate tableware, food storage containers, water bottles and baby bottles. The degree to which BPA passes from polycarbonate vials to liquid or food depends on the product's temperature and the container. The greater the temperature change, the greater the release of BPA (DUALDE *et al.*, 2019).

Reports have shown high human exposure to BPA with documentation of the high occurrence of the analyte in biological samples, especially urine samples (AZZOUZ; RASCÓN; BALLESTEROS, 2016). Exposure to BPA can cause numerous adverse health effects such as diabetes, obesity, cardiovascular diseases, reduce basal testosterone secretion, and decrease fertility in males (ROCHESTER, 2013; ELADAK et al., 2015).

It has been shown that a high concentration of urinary BPA during pregnancy increases the possibility of giving birth to children with lower birth weights (HUO *et al.*, 2015). BPA has also been shown to cross the human placenta barrier and present a risk to fetal development (CORBEL et al., 2014). Developmental periods, especially prenatal, birth and childhood, are the most sensitive developmental stages to the toxic effect of BPA, and because it is an endocrine disruptor, it can cause endocrine changes and metabolic disorders (BRAUN, 2016).

Public health concern on infant exposure to BPA is on the increase. According to an expert report by the Food Agriculture Organization (FAO) and WHO, it is estimated that the average exposure of exclusively breastfed babies (0 to 6 months) to BPA is 0.3 µg/kg body weight per day. Exposure estimates are generally higher for babies fed formula in bottles containing polycarbonate compared to bottles without polycarbonate. The most significant exposure occurs in children from 0 to 6 months of age who are formula-fed, suffering an intake of 2.4 µg/kg of body weight per day of BPA. Once solid foods are introduced (at 6–36 months), exposure to BPA decreases proportionally with increasing body weight (WHO, 2010).

In Brazil, Resolution RDC N ° 41, 2011 was enacted to prohibit the use of plastics in infant bottles (MINISTÉRIO DA SAÚDE, 2011), however, lactating mothers may be exposed to BPA due to contact with plastic products and packaging intended for adults thereby exposing their infants to BPA or its metabolites through breastfeeding. Since breastfeeding is a potential source of an infant's exposure to BPA, there is a need to constantly monitor the exposure of lactating mothers to BPA which can invariably transfer such to the lactating infants.

Despite the high rate of the use of plastic containers by women of reproductive age and lactating mothers in many countries, information about the body burden of BPA in lactating mothers is scarce in the literature and not available in Brazil, hence, no data on infant's exposure to BPA through breastfeeding. Therefore, this study aimed at determining the concentration of BPA in the colostrum of mothers hospitalized at University Hospital Professor Polydoro Ernani de São Thiago through the ELISA technique and to establish a possible association(s) between the use of plastics by the mother and lactogenesis II.

2. Materials And Methods

2.1 Participants

This study was approved by the University Hospital Professor Polydoro Ernani de São Thiago (HU – UFSC) and by the Ethical Committee of The Federal University of Santa Catarina (CAAE 68008317.4.0000.0121). Participants from Florianopolis, Brazil were recruited immediately after pregnancy between January and April of 2019. To participate, patients accepted all study procedures and signed the written informed consent. Mothers infected with Human Immunodeficiency Virus (HIV) 1–2, Human T-lymphotropic Virus (HTLV), or any other clinical impairment for breastfeeding were excluded. A total of 80 participants were used for the study.

2.2 Information gathering

A well-designed questionnaire was used to collect the necessary information from the participants while their medical records were used to obtain medical information about them. The mothers were asked about pre-and post-gestational, socio-cultural, and socio-economic information. Also, information about their usage of plastics and plastic materials for food and drink were collected. Clinical data such as Capurro (method for assessing the newborn's gestational age), type of delivery, newborn weight at birth, and duration of labour (the onset of labour was considered when contractions became frequent and regular) were obtained from the patients' medical records. After birth, the participants were followed up monthly by telephone for up to six months and were instructed to attend monthly visits to their paediatrician of choice (private healthcare network or Basic Health Unit) and receive information about breastfeeding importance. Information on their children's growth and/or possible complications were also collected. The breastfeeding status was defined as follows:

- Exclusive breastfeeding;

- Mixed breastfeeding (formula and breast milk);

- Only formula.

2.3 Sample collection and storage

At least 2 mL of breast milk was collected between 24 to 48 hours after birth by manual milking and transferred to clear BPA-free plastic tubes. The samples were kept at -80°C throughout the study.

2.4 Fat extraction and determination of Bisphenol A in breast milk

Only 64 of the 80 breast milk samples collected were centrifuged at 11,200 g for 30 minutes at 4°C, and the liquid intermediate layer was collected using a micropipette. The other 16 were used as a test to standardize the methodology. BPA concentrations were analyzed in the 64 fatless breast milk samples through a sandwich-type immunoenzymatic assay kit (ELISA) manufactured by MyBioSource (San Diego,

California, USA). The analysis was performed according to the protocols provided by the manufacturer. In summary, the samples and the calibration curve were added to corresponding wells, incubated and subsequently the wells were washed. Thereafter, the liquid biotinylated human BPA antibody was added to each well and again incubated and washed. Afterwards, the enzyme-conjugated liquid was added in all wells, except the blank, incubated and washed. Finally, the colour reagent was added to each well, incubated, the stop solution was added, and the absorbance was read in a spectrophotometer at 450nm. Concentrations were determined by interpolation on a calibration curve, and the sensitivity of the assay was 0.23 ng/mL. A comparison was also made between the concentration of BPA in breast milk and the nutritional status of the patient, according to the table developed by Atalah et al. (1997).

2.5 Evaluation of the newborn's exposure to BPA

To obtain an estimated exposure of breastfed children to BPA, information on milk consumption and the total BPA concentrations in the participant's breast milk were combined. Exposure to BPA of breastfed newborns was estimated using the deterministic approach. In this approach, the estimated daily consumption was calculated according to the following equation:

Estimated daily consumption = C x M

Where C is the breast milk's BPA concentration, and M is the average milk consumption rate (amount of human milk consumed per day) (DUALDE *et al.*, 2019), so, the M value was 480 mL/kg/day for girls and 495 mL/kg/day for boys. Breast milk intake of 150 mL/kg of newborn body weight per day was used. Also, exposure to BPA was calculated using the upper percentile (the upper percentile is reported as the mean plus two standard deviations) of breast milk intake as recommended by the United States Environmental Protection Agency (EPA) for children from birth to less than one month of age (220 mL/kg of body weight of the newborn per day), (U.S. EPA., 2011).

2.6 Determination of the maximum permissible BPA concentration in breast milk

The maximum allowable concentration of BPA in breast milk, so that the intake of the newborn does not exceed the tolerable daily intake (TDI) of 4 µg/kg/day established by the European Food Safety Authority (EFSA), (EFSA, 2015) was calculated thus:

C = TDI / M

where C is the maximum allowable BPA concentration in breast milk, TDI is equivalent to 4 µg/kg/day and M is the average rate of milk consumption per day.

We used the average weight of children born at 40 weeks of gestation in Brazil (3.2 kg for girls and 3.3 kg for boys) (PEDREIRA *et al.*, 2011) and 150 mL/kg/day as the average amount of milk ingested by children up to one month of age (U.S. EPA, 2011).

2.7 Statistical Analysis

All analyses were performed using MedCalc v19.0.4 software (MedCalc, Ostend, Belgium). The results were expressed as medians and range or relative frequency. Differences between groups were assessed using the Mann Whitney U tests for numerical variables, and Chi-square for analyses of the association of qualitative variables. Logistic regression was used to test the variables. For this purpose, BPA concentrations were divided into two groups: high and low. The high concentration group were those who presented values above the median and the low ones, values below the median. The odds ratios were calculated (OR), as well as their 95% confidence intervals (95% CI). The differences were considered statistically significant when $P \leq 0.05$.

3. Results

3.1 Clinical data

Table 1 shows the characteristics of the women from HU-UFSC who participated in this study. All 80 women were in their post-gestational period with a median age of 27 years old. Most of the women were white (65%), followed by 35% black and only 2% indigenous. Normal delivery (64%) is the main type of delivery with a median birth weight of 3.18 kg for newborns.

Table 1
Characteristic of lactating women used for the measurement of breast milk's Bisphenol A content.

	Pre gestational	Post gestational
N		80
Age (years)		27 (16–42)
Skin color (%)		White: 65 Black: 35 Indigenous: 2
BMI (kg/m²)	24.2 (17.4–41.3)	28.6 (23.0–43.8)
Type of delivery (%)		Normal: 64 Cesarean: 36
Weight of newborn (kg)		3.18 (2.16–4.64)
Gestational age (weeks)		39 (33–43)
Results expressed in minimum and maximum values of median or percentage.		

The response of the participants to the use of plastic materials for food and drink is shown in Table 2. The majority of the participants have the habit of packing hot food/liquid in plastic containers (51%) and heating food/liquid in plastic containers in the microwave (50%). A total of 14% of the participants get

their hot liquids such as coffee and tea in plastic containers once a day while 21% eat canned food/drink once a day. These answers refer to the use of plastic before and during pregnancy, extending to the lactation period.

Table 2
Data was obtained from lactating mothers on the use of plastics as food or drink containers.

Do you have the habit of packaging hot food/liquids in plastic containers?	Yes, but I wait to cool down to the package	Yes, and I do not wait to cool down to the package	No			
	51%	30%	19%			
Do you have the habit of heating food/liquid in plastic containers in the microwave?	No	Yes	Rarely			
	40%	50%	1%			
How often do you get hot liquids like coffee/tea in plastic containers?	No	Once a day	Once a week	Rarely	Three times a week	More than once a day
	72%	14%	5%	5%	3%	1%
How often do you eat canned food/drink?	Rarely	No	Once a week	Three times a week	Everyday	
	39%	30%	21%	9%	1%	

3.2 Breastfeeding status

After 6 months of telephone follow up with the mothers, the breastfeeding status was determined as 78% of the mothers practised exclusive breastfeeding, 8% practised mixed breastfeeding and 14% used formula only.

3.3 Determination of Bisphenol A

ELISA method used for the detection of BPA in the breast milk of the nursing mothers in this study was sensitive, detecting BPA in all the samples tested as shown in Fig. 3 and more detailed in Supplementary material 1.

Table 3
Bisphenol A concentration in the breast milk of lactating mothers (N = 64).

BPA concentration (ng/mL)		
Median	Range	CI 95%
34.18	25.71–203.26	12.82–41.37

The concentration of BPA in breast milk was also associated with breastfeeding to assess it as a disruptor of lactogenesis II (Fig. 1). In this study, a high concentration of BPA in breast milk did not affect the outcome of breastfeeding. Furthermore, a comparison made between the concentration of BPA in breast milk and the nutritional status of the mothers (Fig. 2) showed no significant association.

The logistic regression of the following variables: gestational age, participants who ate canned food, heated food in a plastic container in the microwave, drank hot liquids in plastic packaged food before or after cooling in plastic containers, type of delivery and birth weight (P = 0.005) showed that mothers who packed food in plastic containers and did not wait to cool down before packaging had 22.05 times (95% CI = 1.69 to 287.64; P = 0.0182) more chances of having high BPA concentrations compared to mothers who did not package food in plastic containers. In addition, women who prepared their food in a plastic container but allowed it to cool down before packaging were 9.81 times (95% CI = 1.05 to 91.06; P = 0.0445) more likely to have high BPA concentrations in breast milk compared to mothers who did not package food in plastic materials. The relationship between BPA concentration and skin colour (white, black or indigenous) was also evaluated, however, there was no statistically significant difference between the groups. In addition, the Mann-Whitney U test was performed to assess the relationship between age and BPA concentration. For this, the median age (26 years) was used and the patients were separated into two groups (up to 26 years and above 26 years). In this case, patients aged up to 26 years had a statistically lower BPA concentration than patients older than 26 years (P = 0.0023).

3.4 Evaluation of new born’s exposure to BPA

In the deterministic approach, the average consumption of BPA by the newborn was calculated. Figure 3 shows the average daily intake of BPA by newborns and the upper percentile of milk consumption.

The median concentration of BPA intake by the newborn up to the first month was 15.4 µg/kg/day and 22.5 µg/kg-day for the upper percentile of milk consumption which is above the maximum acceptable daily intake of 4 µg/kg/day established by European Food Safety Authority (EFSA, 2015).

3.5 Evaluation of the maximum acceptable BPA concentration in breast milk

The maximum permissible BPA concentration in breast milk (C) in the present study was calculated to be 8 ng/mL (Fig. 4). The data showed that all the participants in this study had breast milk BPA concentrations above the calculated upper limit.

4. Discussion

BPA is an industrial chemical that is widely used for the production of polycarbonate plastic used to make materials that come into contact with food, such as baby bottles and food containers; and epoxy resins used as a protective coating for canned food and drinks and coating on metal lids for glass jars and bottles. These result in consumer exposure to BPA through diet (WHO, 2010). Some studies have evaluated the amount of BPA that can be leached from packaging materials, demonstrating human

exposure. Nerin and colleagues analysed microwave-safe plastic food container packaging. BPA was found at a concentration of 30µg/g of plastic and the level of migration to food was 6.5µg/g of food. In addition, heating can further increase the level of BPA leaching (NERÍN *et al.*, 2003). Brotons and colleagues performed one of the first studies that analysed the migration of BPA in the lining of cans, resulting in a BPA leaching range of 4 to 23µg per can (BROTONS et al., 1995). Takao and colleagues also analysed the level of BPA after heating the cans, resulting in an average increase of 18.2x in the concentration of BPA in the water contained within the container (TAKAO *et al.*, 2002). Breastfeeding is fast becoming an important route of infant exposure to BPA, hence, the urgent need for biomonitoring of breastmilk BPA in lactating mothers.

This study reported the presence of a high concentration of BPA in the breast milk of lactating mothers in Florianopolis with a median of 34.18 ng/mL. This concentration is higher than what has been previously reported in other countries. In addition, all newborns were consuming BPA above the maximum permissible limit, thus, they were more exposed to BPA than the safe limit and consequently more susceptible to the consequences of exposure to BPA. In this first moment, the exposure of the newborn to BPA, due to the high rates of exclusive breastfeeding, occurs through breastfeeding. However, even formula-fed babies are ingesting BPA due to the container that stores the milk. The situation becomes even more worrying when we wonder how long these newborns will be exposed, as they will all continue to consume large concentrations of BPA until 6 months, either through breast milk or infant formula, at which time they are highly susceptible. After that, even with the ban on children's plastic packaging, they can continue to consume through breast milk, artificial milk, water, food stored in plastic, extending into adulthood.

To the best of our knowledge, this study is the first in Brazil to analyse the concentration of BPA in the breast milk of lactating mothers. Even though the law that prohibits the use of BPA in baby bottles has been enacted in Brazil, the result of the present study showed that this is not enough to prevent infants' exposure to this xenobiotic. The lack of public policies in Brazil which prevents exposure to BPA is worrisome since newborns are exposed to BPA through breast milk and they are the most sensitive risk group to the toxic effects of BPA exposure. For example, newborns, exposed both during prenatal care, due to the BPA's ability to cross the placental barrier, and after birth, through breast milk, can develop a series of cerebral consequences, such as disturbances in development and interruption of dopaminergic activity (VAN DEN DRIES *et al.*, 2020). Studies on prenatal and perinatal exposure in rodents that have been exposed to relevant human doses of BPA have reported increased growth of epithelial tissue, decreased apoptosis, decreased latency, and increased incidence of pre-neoplastic and neoplastic lesions in the mammary gland. Other studies also in rodents have linked exposure to BPA to neurobehavioral deficits, reproductive disorders, and liver tumours (TUCKER *et al.*, 2018).

The result of the logistic regression showed that women who packaged food in plastic material are more likely to have high concentrations of BPA, an indication of a positive association between the use of plastic materials and breast milk BPA concentration. There is, therefore, a need for the restriction of the use of plastic materials by women of reproductive age, pregnant and lactating mothers. BPA has been

associated with female infertility, as it has been detected more frequently in infertile women. Its deleterious effects are more critical during perinatal exposure, however, both prenatal, perinatal and postnatal exposure can impair several stages of ovarian development. Animal studies have also seen that BPA because it causes hormonal disruption, has been associated with an increased risk of endometriosis, polycystic ovary syndrome and affecting ovarian function (PIVONELLO *et al.*, 2020). Changes in eating habits, such as reduced consumption of canned foods and drinks or food stored in plastic packaging as well as the replacement of plastic bottles and jars with glass, should be encouraged. Although BPA is omnipresent in the environment, however, a decrease in consumption can mitigate the consequences of ingesting high concentrations of BPA.

Furthermore, no association was found between breast milk BPA concentration and lactogenesis II in the present study. Instead, the study showed a high percentage of mothers who continued to breastfeed within the first 6 months of birth. This observation might be due to a breastfeeding incentive program called Central do Incentivo ao Aleitamento Materno (CIAM) at HU-UFSC, where the participants were recruited. CIAM assists all mothers admitted to the HU-UFSC at the time of delivery so that they can breastfeed and continue exclusive breastfeeding after being discharged from the hospital for at least six months.

5. Conclusion

The present study found high concentrations of BPA in the breast milk of mothers in a hospital in Florianopolis, Brazil compared to the reports in the literature from other countries, potentially translating to the high exposure of newborns to BPA. Furthermore, all the participants in this study had BPA concentrations in breast milk above the calculated maximum permissible BPA concentration in breast milk, and all the newborns were ingesting more BPA than the maximum acceptable daily intake. The results further showed that packaging food in plastics increases the chances of having a high concentration of BPA in breast milk. However, exposure to BPA did not alter the mother's nutritional status or lactogenesis II. These data are of public health importance and hence, public policies that reduce both adult and children's exposure to BPA must be enacted in Brazil. Further study is needed to assess the concentration of BPA in lactating mothers in other hospitals in Brazil to gain holistic data on the body burden of BPA in Brazil.

Declarations

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The Federal University of Santa Catarina (CAAE 68008317.4.0000.0121).

Consent to participate

All authors consent to participate in the works of the manuscript.

Consent for publication

All authors consent for publication.

Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Carolina Dumke de Siqueira. The first draft of the manuscript was written by Carolina Dumke de Siqueira and all authors commented on previous versions of the manuscript. Alabi Okunola Adenrele, Ana Carolina Rabello de Moraes and Fabíola Branco Filippin-Monteiro edited the manuscript. Fabíola Branco Filippin-Monteiro also supervised the manuscript. All authors read and approved the final manuscript.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability

Datasets generated during the current study are not publicly available to maintain patient anonymity but are available from the corresponding author upon reasonable request.

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Figures

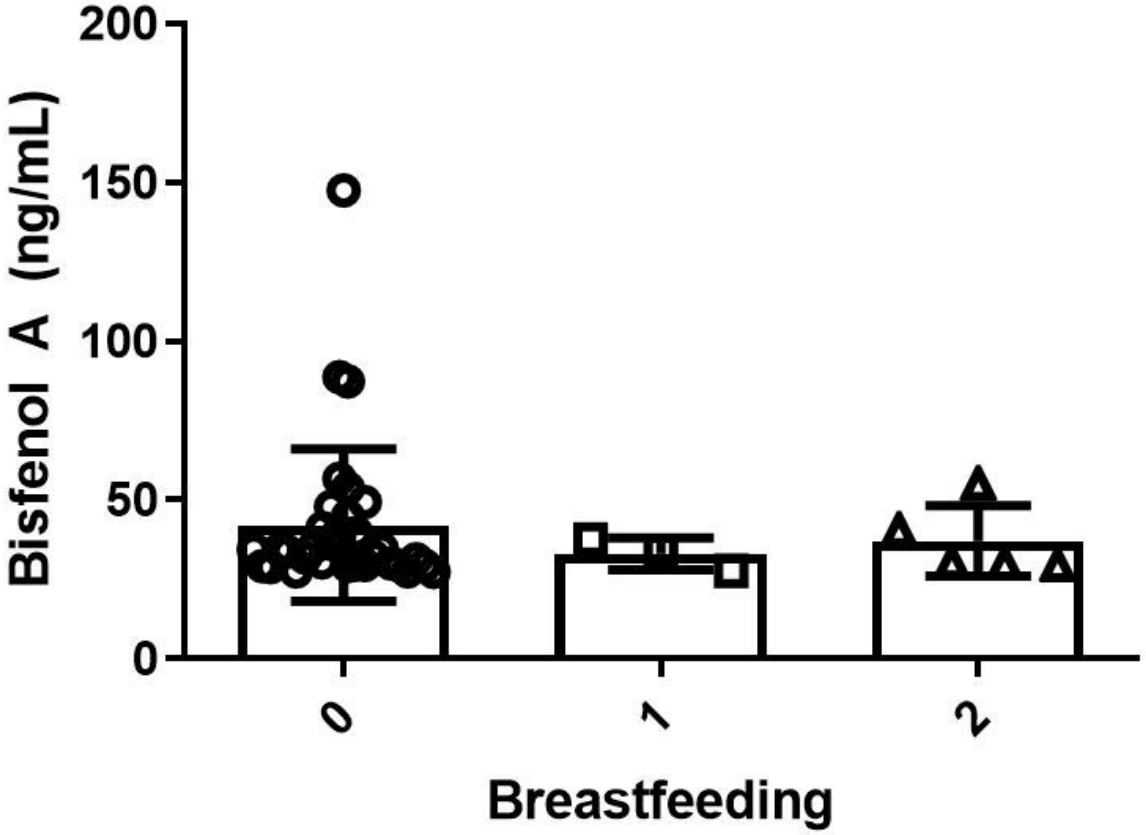

Figure 1

Association between the concentration of bisphenol A and breastfeeding. Legend: 0 - exclusive breast milk; 1 - mixed breastfeeding; 2 - exclusive use of formula. Mann-Whitney-U test between the Exclusive Breast Milk Group and others. N= 64. Samples (colostrum) were collected at least 48 hours after birth

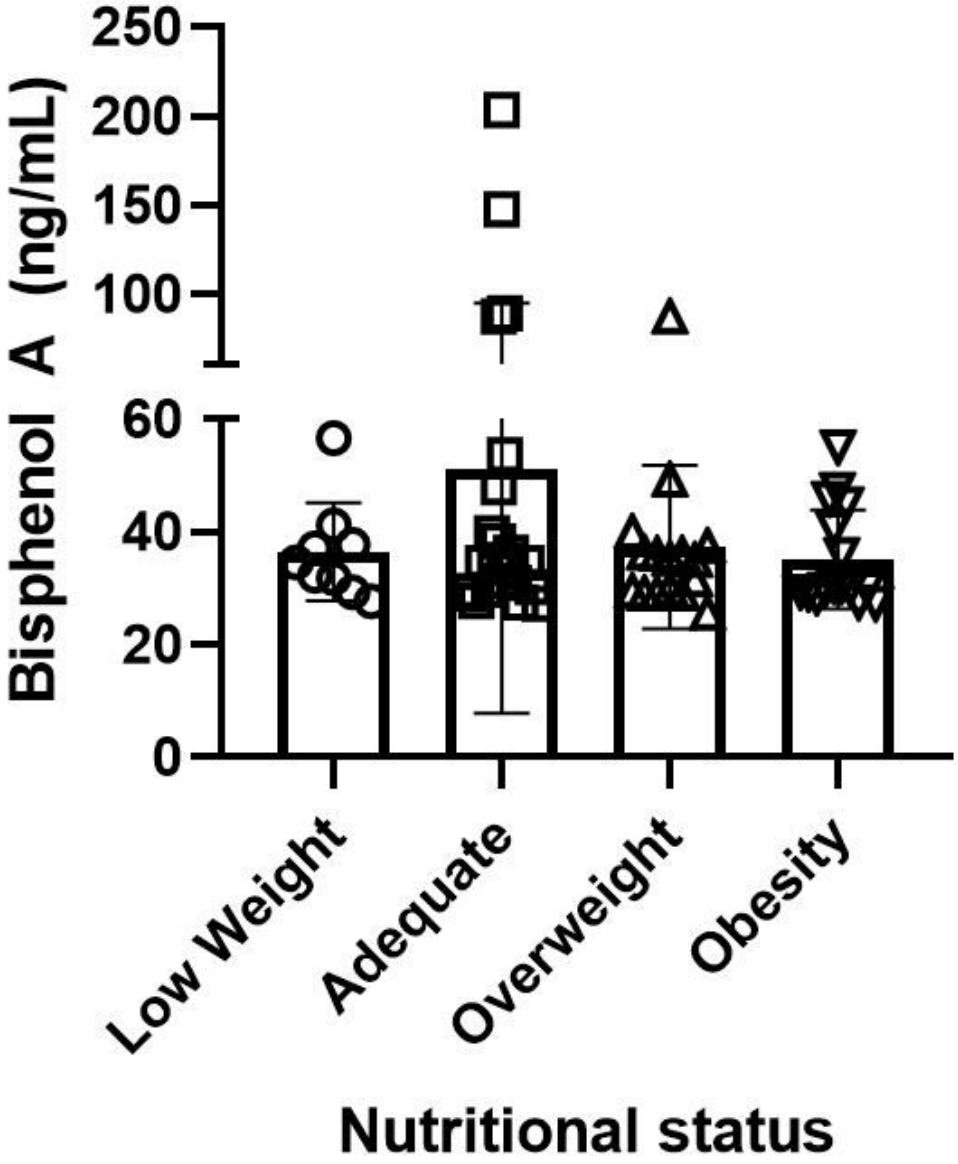

Figure 2

Association between bisphenol A concentration and the nutritional status of the mother. Mann-Whitney-U test between the Adequate Group and others. N=64

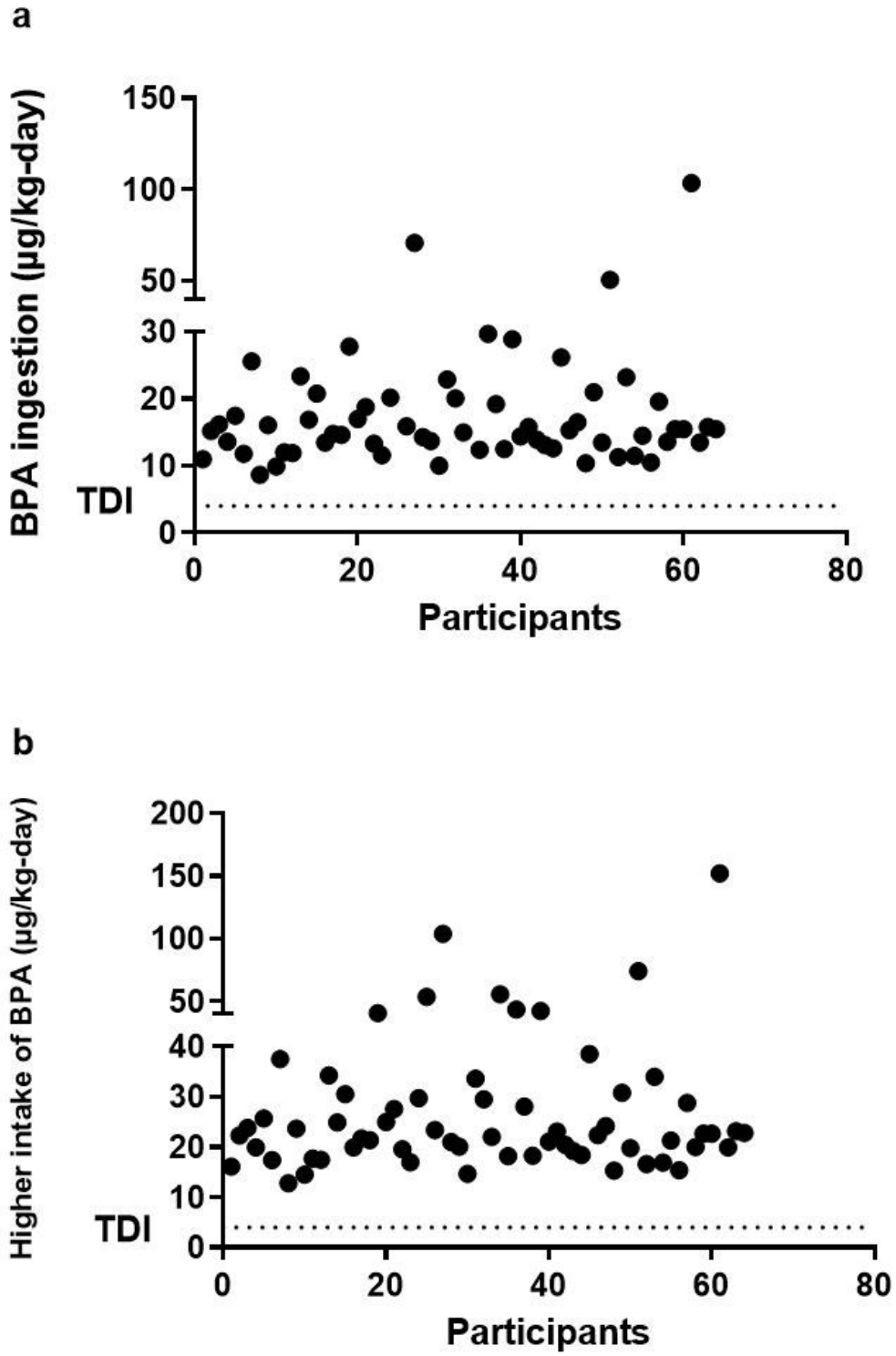

Figure 3

Average daily intake of Bisphenol A by newborns: A - BPA ingestion by the newborn up to the first month; B - Higher intake of BPA ingestion by the newborn up to the first month; TDI - maximum allowable daily intake. N= 64

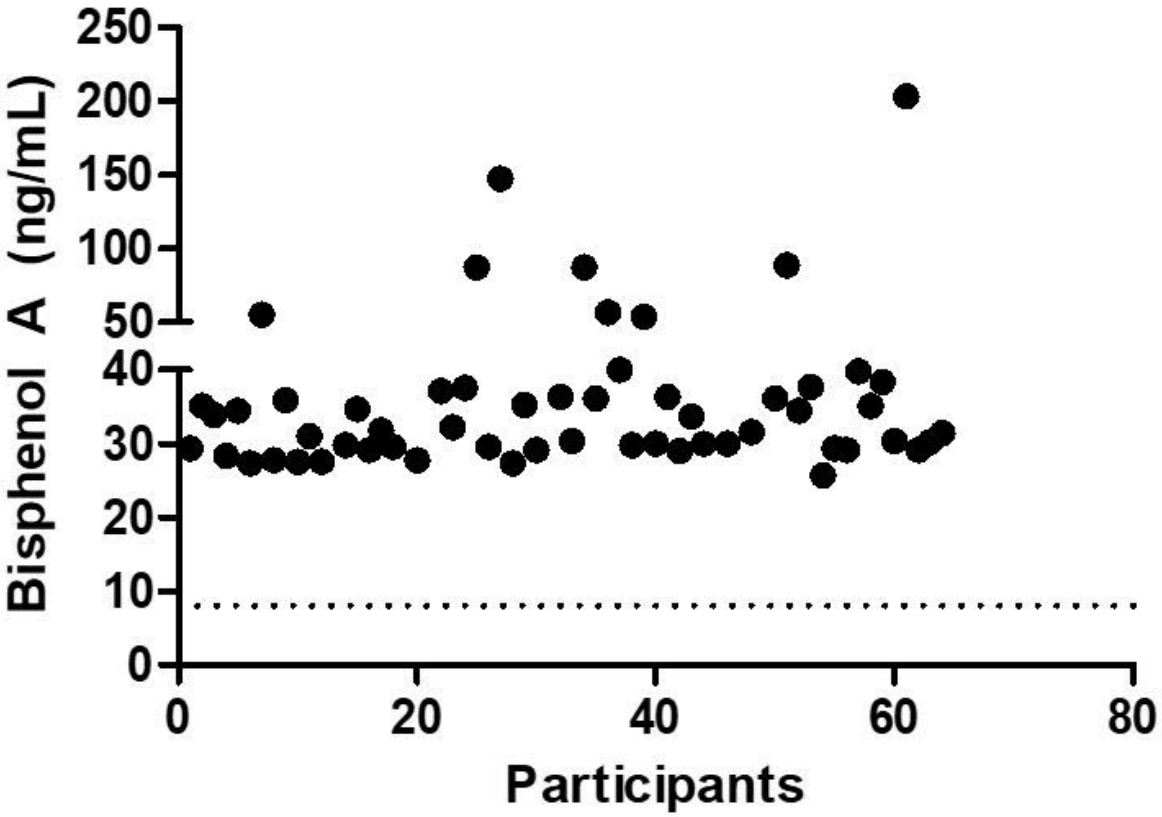

Figure 4

Comparison of Bisphenol A concentrations in the breast milk of Florianopolis women and the maximum acceptable concentration. N=64

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary1TableS1ESPR.docx