Concentrations of bisphenol A and parabens in socks for infants and young children in Spain and their hormone-like activities

Carmen Freire[a,b,c], José-Manuel Molina-Molina[a,b,c], Luz M. Iribarne-Durán[a,d], Inmaculada Jiménez-Díaz[a], Fernando Vela-Soria[a], Vicente Mustieles[a,c,d], Juan Pedro Arrebola[a,e], Mariana F. Fernández[a,b,c,d], Francisco Artacho-Cordón[a,d,*], Nicolás Olea[a,b,c,d,f]

[a] *Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Granada E-18012, Spain*
[b] *CIBER de Epidemiología y Salud Pública (CIBERESP), Granada E-18071, Spain*
[c] *Centro de Investigación Biomédica (CIBM), Universidad de Granada, Granada E-18016, Spain*
[d] *Departamento de Radiología y Medicina Física, Facultad de Medicina, Universidad de Granada, Granada E-18016, Spain*
[e] *Departamento de Medicina Preventiva y Salud Pública, Universidad de Granada, Granada E-18016, Spain*
[f] *Unidad de Gestión Clínica de Medicina Nuclear, Hospital Universitario San Cecilio, Granada E-18016, Spain*

ARTICLE INFO

ABSTRACT

Background: Little information is available on the content of bisphenol A (BPA) and other endocrine-disrupting chemicals (EDCs) such as parabens in infant textiles and clothes.
Objectives: 1) To determine the concentrations of BPA and parabens in socks for infants and young children purchased in Spain, 2) to assess the (anti-)estrogenicity and (anti-)androgenicity of extracts from the socks, and 3) to estimate dermal exposure doses to these chemicals.
Methods: Thirty-two pairs of socks for infants and young children (1–48 months) were purchased from 3 stores in Granada (Spain). Textile material was cut from the foot, toe, and leg of each sock ($n = 96$ samples) for chemical analysis. Hormone-like activities were determined in foot sections ($n = 32$ samples) by using the E-Screen assay for (anti-)estrogenicity and PALM luciferase assay for (anti-)androgenicity.
Results: BPA was present in 90.6% of samples at concentrations ranging from < 0.70 to 3736 ng/g. BPA levels were around 25-fold higher in socks from store 1, which had a higher cotton content compared to stores 2 and 3. Ethyl-paraben was found in 100% of samples, followed by methyl-paraben (81.0%), and propyl-paraben (43.7%). No butyl-paraben was detected in any sample. Estrogenic activity was detected in 83.3% of socks from store 1 (range = 48.2–6051 pM E_2eq/g) but in only three socks from stores 2 and 3. Anti-androgenic activity was detected in six of the 32 socks studied (range = 94.4–2989 μM Proceq/g), all from store 1. Estimated dermal exposure to BPA was higher from socks for children aged 36–48 months (median = 17.6 pg/kg/day), and dermal exposure to parabens was higher from socks for children aged 24–36 months (median = 0.60 pg/kg/day).
Discussion: This is the first report in Europe on the wide presence of BPA and parabens in socks marketed for infants and children. BPA appears to contribute to the hormone-like activity observed in sock extracts.

1. Introduction

Bisphenol A (BPA, 4,4′-isopropylidenediphenol) is a high-production-volume chemical mostly employed in the manufacture of polycarbonate plastics and in epoxy resins used for the inner coatings of food and beverage cans. BPA is a well-known endocrine-disrupting chemical (EDC) that has the ability to bind to the nuclear estrogen receptor (ER) (ANSES, 2018; Wetherill et al., 2007), to modify gene expression under the control of estrogens (Chianese et al., 2018), to bind to other membrane ER families (Alonso-Magdalena et al., 2012), and to induce anti-androgenic activity *in vitro* (Molina-Molina et al., 2013). Various human studies have reported that prenatal and postnatal/childhood urinary levels of BPA are associated with adverse health outcomes in children, including obesity (Valvi et al., 2013), asthma (Gascon et al., 2015), behavioral problems (Braun et al., 2017; Mustieles et al., 2015), and alterations in puberty timing (Berger et al., 2018a; Leonardi et al., 2017), blood pressure (Sanders et al., 2018), and serum hormones (Aker et al., 2016; Scinicariello and Buser, 2016).

Parabens are alkyl esters of p-hydroxybenzoic acid and mainly used as preservatives in personal care products, cosmetics, and pharmaceuticals (Ashrap et al., 2018; Haman et al., 2015). Parabens are also classified as EDCs and have been found to exert weak estrogenic activity (Karpuzoglu et al., 2013; Lange et al., 2014) and to stimulate the proliferation of breast cancer cells *in vitro* (Pan et al., 2016). Although the number of human studies has been limited, there is an increasing body of epidemiological evidence associating early-life exposure to parabens with adverse health outcomes. Thus, maternal urinary levels of parabens have been linked to adverse pregnancy outcomes (Aker et al., 2018), reduced neonatal thyroid hormones (Berger et al., 2018b), altered puberty timing (Harley et al., 2019), behavioral problems (Philippat et al., 2017), and respiratory and allergic disorders (Berger et al., 2018c). Childhood exposure to methyl-paraben (MPB) and propyl-paraben (PPB) has also been associated with puberty timing (Harley et al., 2019).

Diet is considered the main pathway for BPA exposure in humans, but other sources are now known to make a substantial contribution, especially in infants and children (Healy et al., 2015; Xue et al., 2017). For instance, BPA is commonly present as a plasticizer in food-packaging materials, baby bottles, electronics, and other household plastics (Healy et al., 2015). It can be found in automobiles, sports equipment and bicycle helmets, dental composites and sealants and is also widely used as an additive in thermal paper products, including receipts and magazines (Healy et al., 2015; Geens et al., 2012b; Molina-Molina et al., 2019; Pulgar et al., 2000; Vandenberg et al., 2010). For their part, parabens are used as food additives to inhibit microbial growth and have also been detected in paper products, baby teethers, and other consumer products (Ashrap et al., 2018; Asimakopoulos et al., 2016; Berger et al., 2015; Liao and Kannan, 2014). Since the seminal article by R.H. Barker (Baker, 1975), increasing concerns have been raised about EDCs such as BPA and parabens in textiles and clothing, especially when these contain synthetic fibers (*e.g.*, nylon, polyester, polypropylene, and spandex), and about the potential for human exposure through dermal absorption (Li and Kannan, 2018; Liu et al., 2017; Xue et al., 2017).

A large number of chemicals (~1900) are used in industrial textile production, and many of these (~165) are classified as potentially toxic to humans and/or the environment, including antioxidants, plasticizers, dyes, flame retardants, surfactants, and pesticides (Lacasse and Baumann, 2004; Swedish Chemicals Agency, 2013). These chemicals are used in several processes (*e.g.*, fiber and tissue preparation, washing, dyeing, and finishing) to achieve a variety of effects, including softening, stiffening, wrinkling, shrinking, UV resistance, antifading, repellence (against water, oil, stains, *etc.*), non-slip finishing, anti-microbiotic finishing, and antistatic protection (Baker, 1975; Papaspyrides et al., 2009; Swedish Chemicals Agency, 2013). Some of these chemicals may remain within the final textile product, either intentionally or unintentionally, and wearers of the product, including children, can be directly or indirectly exposed to them. In fact, several recent studies have demonstrated the presence of BPA and other bisphenols, parabens, benzophenones, benzothiazoles, benzotriazoles, antimicrobial compounds (triclocarban), phthalates, and flame retardants in textiles and clothing from various countries (Avagyan et al., 2013, 2015; Li and Kannan, 2018; Liu et al., 2017; Negev et al., 2018; Xue et al., 2017). Among these, Xue et al. (2017) detected the presence of BPA in 82% of infant sock samples at a mean concentration of 366 ng/g, finding the highest BPA concentrations (up to 13,300 ng/g) in socks made of polyester and spandex. Likewise, Liu et al. (2017) studied different items of infant clothing and found that socks were responsible for the highest proportion of dermal exposure to benzotriazoles and benzothiazoles. In another study, BPA and the parabens MPB and PPB were detected in pantyhose samples at concentrations of 100–600 ng/g, finding the greatest concentrations of bisphenols and EPB in the samples with highest spandex content (Li and Kannan, 2018).

Epidemiological studies on determinants of BPA exposure in pregnant women and children have reported that the consumption of canned food/beverages and packaged and processed food is associated with urinary BPA levels (Casas et al., 2013; Covaci et al., 2015; Quirós-Alcalá et al., 2013; Snoj Tratnik et al., 2019). For instance, the intake of canned tuna was a major predictor of urinary BPA in 4-year-old children and their mothers from the Spanish Environment and Childhood (INMA) birth cohort (Casas et al., 2013). In general, exposure to BPA from dietary sources is thought to represent > 90% of overall exposure, with exposure from non-food sources being considered at least one order of magnitude lower than that from food sources (Geens et al., 2012a). However, no epidemiologic evidence has yet been published on the relationship between non-dietary exposure and urinary BPA levels. With regard to parabens, the utilization of cosmetics and personal care products may be major determinants of urinary biomarkers in children (Larsson et al., 2014; Sakhi et al., 2018).

Early-life exposure to BPA and other EDCs is associated with a number of health risks, and little information is available on potentially toxic chemicals in textiles and clothes, particularly in those intended for infants and children. Therefore, this study was designed to determine concentrations of BPA and four paraben compounds (MPB, EPB, PPB, and butyl-paraben [BPB]) in socks for infants and young children purchased in Spain and to estimate the resulting dermal exposure to these chemicals. Children may be simultaneously exposed to multiple EDCs from textiles and clothing, but most available toxicity data derive from single-exposure studies, and their combined effects are poorly understood. For this reason, a further study objective was to assess the (anti-)estrogenic and (anti-)androgenic activities of extracts from the socks in order to determine the combined effect of the hormonally active compounds present.

2. Material and methods

2.1. Sample collection

In May 2018, we purchased 32 pairs of socks for infants aged 1–12 months and young children aged 12–48 months from three stores in Granada, Southern Spain: a local low-cost retailer (store 1), a low-cost, fast-fashion clothing international retailer (store 2), and a higher-quality international retailer clothing brand (store 3). We purchased 10 packs containing three pairs of socks each and one pack containing two pairs of socks (four packs in stores 1 and 2, respectively, and three packs in store 3). The price per pack ranged between 1.50€ and 1.80€ for store 1, 3.00€ and 4.50€ for store 2, and 6.95€ and 7.95€ for store 3. The socks varied in composition (% cotton, % polyamide, % polyester, % elastane or spandex), color (black, white, grey, navy blue, dark blue, light blue, red, multi-color, and patterned), and size. All pack labels gave information on the "country of origin" (66% of socks from Spain, 25% from Turkey, and 9% from Italy) but did not specify whether the country of origin of the fiber was the same or different. Socks were stored in sealed polyethylene bags at 4 °C in the dark until their analysis. Textile samples were cut from three sections of each sock (foot, toe, and leg), yielding a total of 96 samples for chemical analyses. Hormone-like activities were determined in samples from the foot section of each sock. A detailed description of the sock samples is displayed in Tables S1–S3 (Supplementary material).

2.2. Chemicals and reagents

All reagents were analytical grade unless otherwise specified. BPA, parabens (MPB, EPB, PPB, and BPB), labelled deuterium BPA (BPA-d_{16}), and labelled EPB ring $^{13}C_6$ (EP-$^{13}C_6$) were purchased from Sigma-Aldrich (Madrid, Spain). High-performance liquid chromatography (HPLC)-grade acetone and dichloromethane used for the extraction step were supplied by Merck (Darmstadt, Germany). Liquid chromatography-mass spectrometry (LC-MS) grade methanol, water, and ammonia (25%) were purchased from Sigma-Aldrich. Water (18.2 MΩ cm)

was purified using an in-house Milli-Q system (Millipore, Bedford, MA, USA). For chemical analyses, stock standard solutions (100 mg/L) of each compound were prepared in acetonitrile and stored at 4 °C in the dark. The solutions remained stable for at least two months. Working standards were prepared immediately before use by dilution with pure acetonitrile.

For in vitro cell assays, reference standards 17β-estradiol (E_2), methyltrienolone (R1881), ICI 182780 (henceforth, ICI), puromycin, geneticin (G418), luciferin (sodium salt), sulforhodamine B (SRB), and trichloroacetic acid (TCA) were obtained from Sigma-Aldrich Inc. (St Louis, MO). Stock solutions (10 mM) of E_2, R1881, procymidone, and ICI were prepared in ethanol, and successive dilutions were performed in culture medium. Stock solutions were kept at −20 °C and dilution series were freshly prepared before each experiment. Finally, culture medium and fetal bovine serum (FBS) were supplied by Gibco (Invitrogen, Barcelona, Spain) and all cell culture plastics by Falcon (VWR International Eurolab, Barcelona, Spain).

2.3. Instrumentation

Ultra performance liquid chromatography - tandem mass spectrometry (UPLC-MS/MS) analyses were performed using an ACQUITY UPLC™ H-Class (Waters, Manchester, UK), consisting of ACQUITY UPLC™ binary solvent manager and ACQUITY UPLC™ sample manager. A Xevo TQS tandem quadrupole mass spectrometer (Waters) equipped with an orthogonal Z-spray™ electrospray ionization (ESI) source was used for BPA and parabens detection. Chromatographic separation of compounds was performed using an ACQUITY UPLC BEH™ C18 (50 mm × 2.1 mm I.D., 1.7 μm particle size) from Waters. The gradient mobile phase consisted of 0.025% (v/v) ammonia aqueous solution (solvent A) and 0.025% (v/v) ammonia in methanol (solvent B). Gradient conditions were as follows: 0.0–3.5 min, 60% B; 3.5–4.0 min, 60–100% B; 4.0–6.5 min, 100% B, and back to 60% in 0.1 min. Flow rate was 0.25 mL/min. The injection volume was 5 μL. The column temperature was maintained at 40 °C. The mass spectrometer was operated in both positive and negative ESI mode, using optimized MS/MS parameters as defined in a previous study (Vela-Soria et al., 2014).

For cell proliferation assays, the absorbance was measured in a Titertek Multiscan plate reader (Flow, Irvine, CA, USA) at 492 nm, and an infinite M200 luminometer (Tecan, Barcelona, Spain) was used to detect luciferase activity in intact cells.

2.4. Sample extraction, treatment, and LC-MS conditions

Extraction of BPA and parabens from the textile samples was performed following the methodology used by Xue et al. (2017) with some modifications. Briefly, approximately 0.5 g of each textile sample were accurately weighed, cut, placed in 15 mL glass centrifuge tubes, and spiked with 0.25 mL of the isotope-labelled surrogate mixture solution (250 μg/L of BPA-d_{16} and 62.5 μg/L of EP-$^{13}C_6$ in acetonitrile). Extraction was done with 7.5 mL of a mixture of acetone and dichloromethane (1:4, v/v). After sonication for 20 min and centrifugation at 5000g for 5 min, the solvent was collected, filtered through 0.2 μm nylon filter, and transferred to another glass tube. The solvent was evaporated to dryness under a gentle stream of nitrogen and the residue dissolved with 250 μL of acetonitrile, injecting 5 μL into the LC system. For the E-Screen and PALM assays, samples were analyzed in duplicate using the aforementioned extraction procedure but without adding the isotope-labelled surrogate solution.

2.5. Quality assurance and quality control in chemical analyses

Textile samples used as blanks for matrix-matched calibration, method validation, and quality control assessment were previously analyzed to confirm that compounds of interest were not present or were below the limit of detection (LD). Two different textile samples

were used, because all of them contained at least one of the studied compounds. LDs and limits of quantification (LQs) were based on the lowest point of the calibration standard with a signal-to-noise (S/N) ratio of > 3 and > 10, respectively. LDs were 0.7 ng/g for BPA, 0.5 ng/g for MPB and BPB, and 0.4 ng/g for EPB and PPB; LQs were 2.2 ng/g for BPA, 1.8 ng/g for MPB and BPB, and 1.4 ng/g for EPB and PPB.

Textile samples were analyzed in duplicate. Extraction was carried out in batches of 15 (12 samples and 3 quality control samples). Quality-control samples were a procedural blank (no textile sample) to check for interferences or laboratory contamination and two spiked blank samples (5 ng/g of BPA and 2.5 ng/g of parabens). Samples were frozen after extraction and injected into the LC-MS/MS in a single batch in the same order as that of their preparation. No BPA or parabens was detected in any procedural blank. Recoveries for all target compounds in the quality-control spiked samples ranged between 82 and 107%, and the coefficient of variation (CV) was under 20% in all cases.

2.6. E-Screen bioassay

The E-Screen bioassay and data analysis were performed as previously described (Molina-Molina et al., 2013, 2014) with some modifications. Briefly, MCF-7 cells were trypsinized and plated in 96-well culture plates at initial concentrations of 4×10^3 cells per well. One day later, the seeding medium was removed and replaced with 150 μL test culture medium. For agonistic assays, dry extracts of the textile samples were resuspended in 1.25 mL of experimental medium, vigorously shaken, left at rest for 30 min, and then filtered through a 0.22 μm filter and tested (50 μL added per well) on MCF-7 cells at 1:1 to 1:10 dilutions. A dose-response curve (0.1–1000 pM) for estradiol (E_2) and a negative control (cell treated only with hormone-free medium) and solvent controls (blank and solvent) was included in each experiment. The bioassay was ended on day 6 (late exponential phase) by removing the media from wells, fixing the cells, and staining them with SRB. Finally, bound dye was solubilized and the absorbance read at 492 nm. Next, the ratio between the cell yield obtained and the proliferation of hormone-free control cells (negative control) was calculated for each concentration. Tests were done in triplicate and results were expressed as proliferative effect (PE) [MCF-7 cell proliferation (-fold over control)]. The antagonistic activities of sample extracts were determined by co-incubation with the agonist E_2 at 100 pM. Because the PE only provides information on the effect of the extract in the E-Screen bioassay, this was transformed into E_2 equivalent (E_2eq) or anti-estrogen (ICI 182780) equivalent (ICIeq) units related to 1 g of textile sample by reading from dose-response curves of E_2 or ICI. In this manner, the PE of each extract was referred to the maximal PE obtained with E_2 or ICI and transformed into E_2eq or ICIeq. E_2eq and ICIeq values for each sample extract were calculated by using the concentration that obtained the greatest induction or inhibition of cell proliferation, respectively. E_2eq and ICIeq values were corrected for the dilution factor and reported as E_2eq/g or ICIeq/g of the original textile sample.

2.7. PALM cell luciferase assay

PALM cells were seeded at a density of 5×10^4 cells per well in 96-well white opaque tissue culture plates in 150 μL test culture medium, following a protocol reported elsewhere (Molina-Molina et al., 2013, 2014). Dry extracts of the textile samples were serially diluted (as described above for the E-Screen bioassay), and 50 μL per well were added at 8 h after seeding. Serial dilutions of the agonist methyltrienolone-R1881 (1–10,000 pM) and the test culture medium alone were included on each plate with the test samples as positive and negative controls, respectively. PALM cells were incubated for 40 h at 37 °C, and the medium was then removed and replaced by test culture medium containing 0.3 mM luciferin. Next, the 96-well plate was introduced into a luminometer for 2 s to measure luminescence from intact living cells.

Human androgen receptor (hAR)-agonistic activities were tested at

1:1 to 1:10 dilutions of the textile samples, performing tests in quadruplicate for each dilution. Maximal luciferase activity (100%) was obtained in the presence of 10 nM R1881. The antagonistic activity of extracts was determined by co-incubation with R1881 agonist (0.3 nM). Results were expressed as percentage of maximal luciferase activity. Finally, the luciferase activity in each sample extract was expressed as percentage of the maximal luciferase activity obtained with R1881 or procymidone (Proc) and transformed into R1881 or procymidone equivalent units (R1881eq or Proceq, respectively) by reading from dose-response curves of R1881 or procymidone (standard serial dilutions) included on each plate. R1881Eq and Proceq were calculated from the concentration that obtained the greatest induction or inhibition of luciferase activity, respectively. R1881eq and Proceq values obtained were corrected for the dilution factor and reported as R1881eq/g and Proceq/g of the original textile sample.

2.8. Estimation of dermal exposure

Dermal exposure of feet to BPA and parabens (individual compounds and sum of parabens) from wearing the socks was estimated for infants aged 1–6, 6–12, 12–24, 24–36, and 36–48 months. Exposure doses were calculated according to exposure assessment guidelines of the USA EPA (US EPA Exposure Factors Handbook, 2011) and based on previous studies on hazardous chemicals in clothing (Li and Kannan, 2018; Liu et al., 2017; Rovira et al., 2015; Xue et al., 2017), using the following formula:

$$Exp_{derm} = C \times D \times SA \times F_{mig} \times F_{contact} \times F_{pen} \times T \times N/BW$$

where Exp_{derm} is the estimated daily dermal exposure dose (pg/kg body weight/day), C is the concentration of chemicals in the sock (ng per g), D is the density of sock fiber (mg per cm^2), SA is the skin contact surface area, F_{mig} is the migration rate of chemicals to the skin (recommended default value as worst-case exposure scenario: 0.5% per day; Federal Institute for Risk Assessment, 2012), $F_{contact}$ is the fraction of the skin contact area (recommended default value as worst-case assumption: 100%; Federal Institute for Risk Assessment, 2012), F_{pen} is the penetration rate of chemicals into the body (recommended default value as worst-case assumption: 1%; Federal Institute for Risk Assessment, 2012), T is the contact time between sock and skin (assumed to be 1 day), N is the number of events per day (assumed to be 1), and BW is the average body weight of infants/children by age (US EPA Exposure Factors Handbook, 2011). The skin surface covered by socks was assumed to be the total foot surface area of the infants/children for each age group (230, 290, 330, 380, and 490 cm^2, respectively; EPA Exposure Factors Handbook, 2011). The body weight of the infants/children in the five age groups was considered to be 6.6, 9.2, 11.4, 13.8, and 16.0 kg, respectively (EPA Exposure Factors Handbook, 2011).

2.9. Statistical data analysis

The frequency of samples with detected concentrations of BPA and/or parabens was analyzed, calculating the median value and range of their concentrations in the sock samples and the total concentration of paraben compounds (ΣPBs). Given the absence of standards for the maximum content of EDCs in clothing, we calculated the frequency of samples with BPA concentrations that exceeded the EU migration standard for toys (0.1 ppm or μg/g) (Commission Directive 2014/81/EU). Estrogenic and anti-androgenic activities were reported as the frequency of positive samples and the range of activity. Spearman correlation analysis was applied to examine the relationship between concentrations of BPA and parabens. We used box plots to display the distribution of chemicals by sock characteristics with log-transformed BPA data and non-transformed parabens levels. Non-parametric Kruskal-Wallis and Mann-Whitney tests were used to analyze differences in chemical concentrations by store, cotton content (grouped

Table 1
BPA and parabens concentrations (ng/g) and estrogenic and anti-androgenic activities in the total sample of socks and by store.

Chemicals and hormone-like activities	Total	Store 1	Store 2	Store 3
n (%)	96 (100)	36 (37.5)	36 (37.5)	24 (25.0)
BPA				
% detection	90.6	100	77.7	100
Median	20.5	255	8.17	7.60
Range	< 0.70–3736	75.6–3739	< 0.70–27.6	4.44–49.6
% > EU standard for toys[a]	35.4	94.4	0	0
MPB				
% detection	81.2	75.0	100	62.5
Median	3.09	1.31	7.12	3.26
Range	< 0.50–23.8	< 0.50–3.56	1.94–23.8	< 0.50–16.9
EPB				
% detection	100	100	100	100
Median	2.44	2.40	2.44	2.43
Range	1.01–9.21	1.01–3.92	1.12–4.23	1.13–9.21
PPB				
% detection	43.7	50.0	0.0	100
Median	< 0.40	0.27	< 0.40	0.97
Range	< 0.40–2.45	< 0.40–2.45	< 0.40	0.74–1.69
ΣPBs				
Median	5.75	4.13	9.53	5.65
Range	2.56–27.6	2.56–7.48	4.07–26.2	3.17–27.6
Estrogenic activity				
% positive	40.6	83.3	8.3	25.0
Range[b] (pM E$_2$eq/g)[c]	48.2–6051	48.2–6051	62.5	151–230
Anti-androgenic activity				
% positive	18.7	50.0	0.0	0.0
Range[b] (μM Proceq/g)[d]	94.4–2989	94.4–2989	–	–

BPA: bisphenol A; MPB: methyl-paraben; EPB: ethyl-paraben; PPB: propyl-paraben; ΣPBs: total concentrations of parabens.
[a] Percent of samples exceeding the EU migration standard of 0.1 ppm for toys.
[b] Range of positive values.
[c] Concentrations equivalent to E$_2$ per gram.
[d] Concentrations equivalent to procymidone per gram.

as < 80%, 85%, or > 90%), polyester content (grouped as 0%, 10–20%, or > 20%), color, sock section, and country of origin. Finally, mean, median, and 95th percentile values were calculated for estimated dermal absorption doses. Statistical significance was set at $p < 0.05$. SPSS v.23.0 (IBM, Chicago, IL, USA) was used for statistical analyses.

3. Results

BPA was detected in 90.6% of samples, of which 35.4% exceeded the EU standard of 0.1 ppm for toys, and was undetectable in only three socks for infants aged 1–6 months purchased from store 2 (Tables 1 and S2). BPA concentrations ranged between 75.6 and 3736 ng/g in socks from store 1, including 15 socks with concentration > 1000 ng/g; between undetected and 27.6 ng/g in store 2; and between 4.44 and 49.6 in store 3 (Table 1). The median BPA concentration was around 25-fold higher in socks from store 1 than in those from stores 2 and 3 (p-value < 0.001). With regard to parabens, EPB was found in all samples at concentrations ranging between 1.01 and 9.21 ng/g, with no significant differences between the stores (p-value = 0.77); MPB was detected in 81% of samples at concentrations ranging between undetected and 23.8 ng/g, observing a higher median concentration in socks from store 2 (p-value < 0.001); and PPB was detected in 43.7% of samples at concentrations ranging between undetected and 2.45 ng/g, observing a higher median concentration in socks from store 3 (p < 0.001) (Table 1). BPB was not detected in any sample.
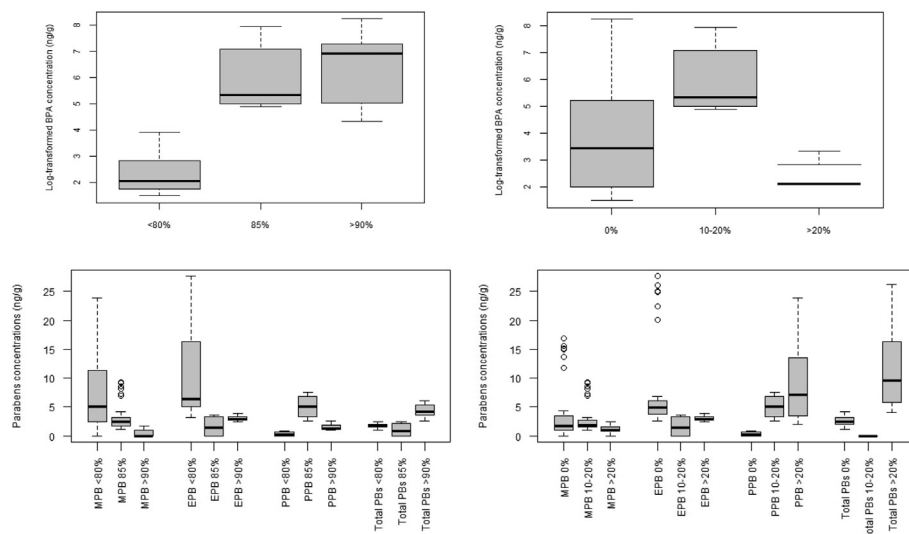
Fig. 1. Concentrations of BPA and parabens according to percent composition of cotton (left) and polyester (right) (BPA: bisphenol A; MPB: methyl-paraben; EPB: ethyl-paraben; PPB: propyl-paraben; PBs: parabens).

The E-Screen test demonstrated estrogenic activity in almost all of the socks from store 1 (10 out of 12 samples), with values ranging from 48.2 to 6051 pM E$_2$eq/g, but in only one sample from store 2 and two samples from store 3 (Tables 1 and S1–S3). The PALM luciferase assay revealed anti-androgenic activity in only 6 out of the 12 samples from store 1, ranging between 94.4 and 2989 μM Proceq/g (Tables 1 and S1–S3). No anti-estrogenic or androgenic activity was observed in any sample.

BPA concentrations were inversely and significantly correlated with MPB concentrations (Spearman rho, $r = -0.24$, p-value = 0.02) and EPB ($r = -0.20$, p-value = 0.05) but not with PPB or ΣPBs concentrations. Higher median concentrations of BPA were observed in socks composed of 85% and > 90% cotton (store 1) than in those with lower percentages of cotton (p-value < 0.001) (Fig. 1), in socks with 0% or 10–20% *vs.* > 20% polyester (p-value < 0.001) (Fig. 1), in socks without polyamide (p-value < 0.001), and in those with 0% or 5% elastane (p-value < 0.001). In relation to the fabric color, higher BPA concentrations were found in grey and black, grey and white, and grey and navy-blue socks (p-value < 0.001) (Fig. 2). With regard to parabens, MPB and EPB concentrations were higher in samples with lower cotton content (p-value < 0.001) and 0% polyester (p-value = 0.003) (Fig. 1), and in those with < 20% polyamide (p-value < 0.001). By contrast, PPB and ΣPBs concentrations were higher in socks composed of 85% and > 90% cotton than in those with < 80% cotton (p-value = 0.10 and < 0.001, respectively) and were higher in socks with greater polyester content (p-value < 0.001) (Fig. 1). We observed no significant differences in parabens levels by sock color (data not shown). Among the countries of origin, BPA concentrations were higher in socks made in Spain (p-value < 0.001), and parabens concentrations were higher in those from Turkey (p-value < 0.001) (Fig. 3). No significant differences in BPA or parabens concentrations were found among the three different sock sections studied.

Table 2 exhibits the estimated daily mean dermal exposure doses to BPA and parabens by age. Median and 95th percentile values for dermal exposure doses from socks were, respectively, 0.93 and 129 pg/kg/day for BPA, 0.14 and 0.95 pg/kg/day for MPB, 0.12 and 0.38 pg/kg/day for EPB, 0.00 and 0.10 pg/kg/day for PPB, and 0.27 and 1.19 pg/kg/day for ΣPBs. The median BPA dermal exposure dose was highest for children aged 36–48 months (17.6 pg/kg/day), followed by those aged 24–36 months (0.75 pg/kg/day), 6–12 months (0.46 pg/kg/day), 12–24 months (0.22 pg/kg/day), and 1–6 months (BPA not detected). The median dose of dermal exposure to the sum of parabens was highest for children aged 24–36 months (0.60 pg/kg/day), followed by those aged 6–12 months (0.39 pg/kg/day), 1–6 months (0.33 pg/kg/day), 12–24 months (0.23 pg/kg/day), and 36–48 months (0.22 pg/kg/day).
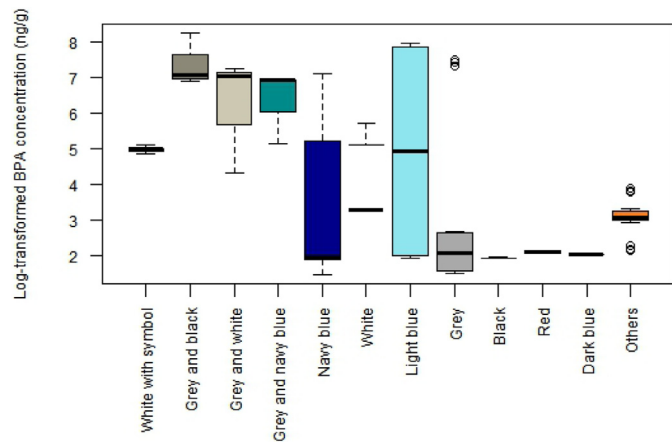
4. Discussion

The present study evidenced for first time in Europe the wide presence of BPA in textile samples from socks marketed for infants and young children in Spain. It is noteworthy that 15 out of 96 samples (16%) had BPA concentrations above 1000 ng/g (or 1 μg/g) and more than one-third had a concentration above 0.1 μg/g. Among parabens, EPB was detected in all samples, followed by MPB and PPB, at several-fold lower concentrations in comparison to BPA. The estimated dermal exposure doses to BPA and parabens were relatively low (of the order of pg/kg/day) but may be relevant, as discussed below. This is also the first study to determine the combined hormonal activity of extracts from consumer textile products. Interestingly, estrogenic and anti-androgenic activities were found in the sock samples with highest concentrations of BPA.
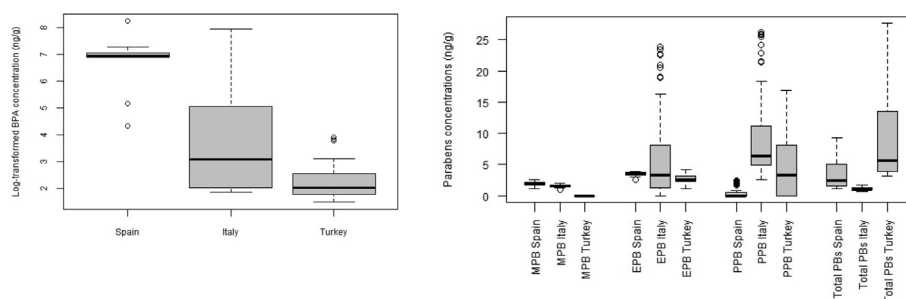

Fig. 2. BPA concentrations according to color of sock.(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. Concentrations of BPA and parabens according to country of sock (BPA: bisphenol A; MPB: methyl-paraben; EPB: ethyl-paraben; PPB: propyl-paraben; PBs: parabens).

Table 2
Estimated dermal exposure doses (pg/kg/day) to BPA and parabens.

Chemicals	Mean	Median	95th percentile	Maximum
All samples (N = 96)				
BPA	19.6	0.93	129	206
MPB	0.26	0.14	0.95	1.03
EPB	0.14	0.12	0.38	0.45
PPB	0.03	0.00	0.10	0.16
ΣPBs	0.43	0.27	1.19	1.34
Age 1–6 months (N = 9)				
BPA	0.00	0.00	0.00	0.00
MPB	0.27	0.26	–	0.35
EPB	0.08	0.07	–	0.12
PPB	0.00	0.00	–	0.00
ΣPBs	0.35	0.33	–	0.45
Age 6–12 months (N = 33)				
BPA	12.1	0.46	118	125
MPB	0.27	0.08	0.81	0.82
EPB	0.19	0.16	0.44	0.44
PPB	0.06	0.05	0.16	0.16
ΣPBs	0.51	0.39	1.32	1.34
Age 12–24 months (N = 9)				
BPA	0.23	0.22	–	0.33
MPB	0.14	0.14	–	0.17
EPB	0.06	0.06	–	0.07
PPB	0.04	0.04	–	0.06
ΣPBs	0.24	0.23	–	0.28
Age 24–36 months (N = 18)				
BPA	0.72	0.75	–	1.19
MPB	0.52	0.47	–	1.03
EPB	0.11	0.11	–	0.15
PPB	0.00	0.00	–	0.00
ΣPBs	0.63	0.60	–	1.15
Age 36–48 months (N = 27)				
BPA	54.4	17.6	199	206
MPB	0.11	0.10	0.24	0.24
EPB	0.15	0.16	0.24	0.25
PPB	0.01	0.00	0.05	0.05
ΣPBs	0.27	0.22	0.49	0.50

BPA: bisphenol A; MPB: methyl-paraben; EPB: ethyl-paraben; PPB: propyl-paraben; ΣPBs: total concentrations of parabens.

4.1. Bisphenol A

In general, our data are in agreement with previous reports on BPA in clothing. Xue et al. (2017) detected BPA in all 14 infant socks from China purchased in Albany, USA, at higher concentrations than observed in our study (range: 186–13,300 *vs.* < 0.70–3736 ng/g), although the median BPA concentration (396 ng/g) was of the same order as in socks from store 1, the low-cost retailer (255 ng/g). The same authors found BPA in other infant textiles at similar concentrations to the present findings (< 2.21–1830 ng/g), reporting that BPA concentrations were much higher in socks than in other items of clothing or in raw textiles (Xue et al., 2017). In a study of pantyhose, Li and Kannan (2018) detected BPA in 96% of samples from China, Japan, Korea, Portugal, Chile, and the USA at concentrations ranging from < 1.3 to

504 ng/g, reporting a similar median BPA concentration (14.3 ng/g) to that in the present socks (20.5 ng/g). Another recent study found that BPA was present, at concentrations below 0.5 ppm (500 ng/g), in two out of seven baby textile items purchased in Israel (Negev et al., 2018).

Unlike in the present study, Xue et al. (2017) found higher mean BPA concentrations in clothing made of 97–98% polyester *vs.* 100% cotton and in colored *vs.* white clothing. They also reported that BPA concentrations were up to 72-fold higher in clothing made of synthetic fibers *vs.* 100% or 60% cotton. In the same line, Li and Kannan (2018) found higher concentrations of several bisphenols in black pantyhose *vs.* tan or khaki and in those made of 21–50% *vs.* 0–20% spandex. The authors of both studies proposed that the high concentrations of bisphenols in socks and pantyhose were related to their high content of spandex (or elastane). The elasticity and strength of this synthetic fiber has led to its utilization in socks, active wear, hosiery, elastic waistbands, gloves, underwear, and other skin-tight clothing.

The source of BPA in the present textile samples cannot be readily identified, given that the highest concentrations of BPA were observed in socks with no or scant polyester content and high % cotton. It is possible that BPA was introduced to improve the performance and durability of the socks. BPA ethoxylate diacrylate has been used in the hydrophilization of synthetic polyester fabric (https://www.lookchem.com/cas-644/64401-02-1.html?countryid=0). Moreover, BPA derivatives are employed as an intermediate chemical in the manufacture of antioxidants and dyes (Xue et al., 2017) that are added to fibers to prevent photo-degradation and to color the original raw material, respectively. In this context, Česen et al. (2018) reported higher concentrations of BPA and other bisphenol residues in wastewater samples from two textile cleaning companies than in those from other industrial activities. They suggested that BPA may originate from textile packaging and that bisphenols are washed during textile cleaning into the sewerage system. Furthermore, recycled plastic bottles made of polyethylene and polycarbonate are increasingly used by the textile industry to produce polyester fibers (Al-Salem et al., 2009; Rochman et al., 2013). Hence, the source of BPA in socks containing polyester may be recycled plastic bottles used as raw materials in its production.

BPA and bisphenol B are known to be employed as "proton donors" in color developers. However, there was no clear association of BPA concentrations with the color of the socks, suggesting that the presence of BPA in these items was not related to fiber dyeing. Regarding the country of origin, it is very likely that the fiber in the socks from store 1 derived from an Asian country (*e.g.*, China), which may have contributed to the high BPA concentrations observed. In this regard, Li and Kannan (2018) reported that the highest concentrations of all studied EDCs were in pantyhose samples from Asian countries. In addition, our findings indicate that BPA is not yet being replaced by BPA analogues (*e.g.*, bisphenol S) in socks made in Spain, Italy, or Turkey. In Japan, where the use of BPA has been restricted in many consumer products since 2001, elevated concentrations of BPS and other BPA analogues have been found in pantyhose (Li and Kannan, 2018), as well as in thermal paper receipts (Liao and Kannan, 2011).

4.2. Parabens

To our knowledge, the presence of parabens in clothing has only been examined in one study (Li and Kannan, 2018), which found higher concentrations of MPB, EPB, PPB, and BPB in pantyhose than those observed in the present socks. In comparison to findings in the socks, the frequency of their detection in pantyhose samples was higher for EPB (100 *vs.* 63%) but lower for MPB (81 *vs.* 94%), PPB (44 *vs.* 85%), and BPB (0 *vs.* 32%). As in our study, parabens concentrations in the pantyhose were several-fold lower than BPA concentrations. The same authors found that parabens concentrations were 100-fold higher in pantyhose samples purchased from China than in those from other countries (Li and Kannan, 2018). Because the country in which the fiber was produced was not specified on the labels of the socks, we were unable to determine the influence of this variable. We found no clear pattern in parabens concentrations according to the composition and color of the socks. The presence of parabens in socks is most likely attributable to their utilization as antimicrobials in textile production (Goldade and Vinidiktova, 2017).

4.3. Hormone-like activity

BPA is known to interfere with steroid signaling *via* human estrogen (hER) and human androgen (hAR) receptors (Molina-Molina et al., 2013; Wetherill et al., 2007), whereas parabens have been shown to exert weak estrogenic activity (Karpuzoglu et al., 2013). We previously demonstrated that BPA is a potent hER agonist and hAR antagonist using E-Screen and PALM cell assays (Molina-Molina et al., 2013), supporting the present finding of a relationship between hormone-like activity and high BPA concentrations in the sock extracts. This observation is also consistent with the recent report by our group of significant positive correlations between BPA concentrations in thermal paper receipts and their estrogenic and anti-androgenic activity (Molina-Molina et al., 2019). In the same line, our group previously reported that the estrogenic activity of vegetables packed in lacquer-coated cans (ranging from 5.44 to 720 nM E_2eq/L) was related to the amount of BPA in the liquid these contained (Brotons et al., 1995). Hence, BPA appears to have made a major contribution to the estrogenic and anti-androgenic activity of the socks. However, we cannot rule out the presence of other EDCs in the socks, which may also have played a role in their hormone-like effects. In comparison to findings previously published by our group, the estrogenic activity measured in the socks is comparable to the activity observed in paper and cardboard used as food containers (geometric mean [GM] = 11.9 pM E_2eq/g) (Lopez-Espinosa et al., 2007) but much lower than recently detected in thermal paper receipts (GM = 0.12 μM E_2eq/g) (Molina-Molina et al., 2019). Likewise, anti-androgenic activity of the sock extracts was much lower than found in thermal paper receipts (GM = 213 mM Proceq/g) (Molina-Molina et al., 2019) but markedly higher than recorded in commercial bottled waters (GM = 1.61 nM Proceq/L) (Real et al., 2015).

4.4. Dermal exposure doses and risk assessment

The mean dermal exposure dose to BPA from the socks in our study was 19.6 pg/kg/day and was higher in those marketed for older children. The mean dose estimated by Xue et al. (2017) from textile products and clothing for infants was several-fold higher (222 pg/kg/day), being highest in products for newborns aged < 1 month (248 pg/kg/day). The dermal exposure dose from socks was several-fold lower for parabens than for BPA. Although the estimated dermal exposure doses were relatively low in our study, various factors should be taken into account. For instance, socks produce direct dermal exposure because they are worn in contact with the skin, and absorption may be increased by high temperatures and body moisture from the feet. In addition, infants and small children may be directly exposed to the chemicals in socks by putting them (or their feet) in their mouth. In addition, toxic chemicals can transfer from contaminated to uncontaminated clothes during washing and can disperse from textile fibers into indoor air, where they can bind to dust particles and cause indirect exposure though the inhalation and ingestion of dust. In this respect, indoor dust is believed to be the main route for the exposure of young children to brominated flame retardants and perfluorinated compounds (Björklund, 2011), EDCs commonly present in household textiles.

In 2015, the European Food Safety Authority (EFSA) reduced the tolerable daily intake (TDI) of BPA from 50 to 4 μg/kg/day and concluded that BPA poses no health risk to consumers of any age group (including fetuses, infants, and children) at current exposure concentrations (EFSA, 2015). Subsequently, in 2018, the EU Commission Regulation 2018/213 established that "no migration of BPA shall be permitted from varnishes or coatings applied to food contact materials and articles and similar products specifically intended for young children". Moreover, BPA may not be used in toys or in components of toys, except if inaccessible to children (Commission Directive 2014/81/EU). It remains unclear whether there is a no-effect concentration of BPA for its most sensitive endpoints (Vandenberg et al., 2012). There is consistent evidence that BPA affects the reproductive function, neurodevelopment, and metabolism (ANSES, 2018). Hence, given that young children often suck their feet and put parts of their clothing in their mouth, it appears appropriate to propose a complete ban on BPA in clothing and textile products sold for children on public health grounds. In fact, the endocrine-disrupting properties of BPA led to its inclusion by the EU in the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) list as a Substance of Very High Concern (SVHC) in January 2017. Moreover, the ecological criteria for awarding the EU Ecolabel to textile products include the absence from the manufacturing process of any substance on the REACH SVHC list (Regulation 2014/350/EU).

Overall, the estimated dermal exposure doses to BPA and parabens from these socks were not high. However, infants and young children are particularly susceptible to EDCs, and they are usually exposed to multiple chemicals; therefore, the potential cumulative health risk from their daily use of socks and other clothing items might not be negligible. There is need for epidemiological and risk assessment studies to quantify early-life exposure to chemicals from clothing. In the meantime, the precautionary principle should prevail in order to protect this vulnerable population.

4.5. Strengths and limitations

One study limitation was that the socks were purchased in one country and from a small number of stores, although different fabric qualities, colors, and compositions were represented, and samples were taken from three different sections of each sock. In addition, all socks were new and had not been washed, a process that is likely to remove some of the chemical residues. Furthermore, the measurement of other hormonally active bisphenols (*e.g.*, bisphenol S and bisphenol F) would have provided additional relevant information. However, there has been scant research on the potential for BPA exposure from non-dietary exposure sources in early childhood, and only toys, baby bottles, teethers, and teats have been analyzed to date (Healy et al., 2015). Besides being one of the few investigations into the presence of EDCs in consumer textile products, this is only the second study on the concentrations of BPA and parabens in clothing for infants and young children. Furthermore, the hormone-like activity of extracts from textile products has not been assessed in previous studies.

4.6. Conclusions

This study provides the first evidence of the utilization of BPA and parabens in European textile manufacturing and suggests that socks may be a relevant source of exposure to these EDCs for infants and

young children. The findings also indicate that BPA contributes to the estrogenic and anti-androgenic activity of these socks. There is an urgent need for epidemiological research into the potential routes of exposure to chemicals used in textile products and clothing for newborns, infants, and children. Importantly, there are currently no environmental and health requirements for textiles in European regulations with the exception of Regulation 2014/350/EU on the EU Ecolabel for textile products. The present findings and previous data on the presence of hazardous chemicals in clothing and textiles, especially in those made of synthetic fibers, underscore the need for legal regulations that include the mandatory labeling of consumer textile products with their chemical content.

Acknowledgments

Competing financial interests' declaration

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.04.013.

References

Aker, A.M., Watkins, D.J., Johns, L.E., Ferguson, K.K., Soldin, O.P., Anzalota Del Toro, L.V., Alshawabkeh, A.N., Cordero, J.F., Meeker, J.D., 2016. Phenols and parabens in relation to reproductive and thyroid hormones in pregnant women. Environ. Res. 151, 30–37. PMID: 27448730. https://doi.org/10.1016/j.envres.2016.07.002.

Aker, A.M., Ferguson, K.K., Rosario, Z.Y., Mukherjee, B., Alshawabkeh, A.N., Cordero, J.F., Meeker, J.D., 2018. The associations between prenatal exposure to triclocarban, phenols and parabens with gestational age and birth weight in northern Puerto Rico. Environ. Res. 169, 41–51. PMID: 30412856. https://doi.org/10.1016/j.envres.2018.10.030.

Alonso-Magdalena, P., Ropero, A.B., Soriano, S., García-Arévalo, M., Ripoll, C., Fuentes, E., Quesada, I., Nadal, A., 2012. Bisphenol-A acts as a potent estrogen via non-classical estrogen triggered pathways. Mol. Cell. Endocrinol. 355 (2), 201–207. PMID: 22227557. https://doi.org/10.1016/j.mce.2011.12.012.

Al-Salem, S.M., Lettieri, P., Baeyens, J., 2009. Recycling and recovery routes of plastic solid waste (PSW): a review. Waste Manag. 29 (10), 2625–2643. PMID: 19577459. https://doi.org/10.1016/j.wasman.2009.06.004.

ANSES's Working Group on "Endocrine disruptors", ANSES's Expert Committee on "Chemicals covered by the REACh and CLP Regulations", Pouzaud, F., Thierry-Mieg, M., Burga, K., Vérines-Jouin, L., Fiore, K., Beausoleil, C., Michel, C., Rousselle, C., Pasquier, E., 2018. Concerns related to ED-mediated effects of Bisphenol A and their regulatory consideration. Mol. Cell. Endocrinol. 475, 92–106. PMID: 29428396. https://doi.org/10.1016/j.mce.2018.02.002.

Ashrap, P., Watkins, D.J., Calafat, A.M., Ye, X., Rosario, Z., Brown, P., Vélez-Vega, C.M., Alshawabkeh, A., Cordero, J.F., Meeker, J.D., 2018. Elevated concentrations of urinary triclocarban, phenol and paraben among pregnant women in Northern Puerto

Rico: predictors and trends. Environ. Int. 121 (Pt 1), 990–1002. PMID: 30316544. https://doi.org/10.1016/j.envint.2018.08.020.

Asimakopoulos, A.G., Elangovan, M., Kannan, K., 2016. Migration of parabens, bisphenols, benzophenone-type UV filters, triclosan, and triclocarban from teethers and its implications for infant exposure. Environ. Sci. Technol. 50 (24), 13539–13547. PMID: 27993041. https://doi.org/10.1021/acs.est.6b04128.

Avagyan, R., Sadiktsis, I., Thorsen, G., Ostman, C., Westerholm, R., 2013. Determination of benzothiazole and benzotriazole derivates in tire and clothing textile samples by high performance liquid chromatography-electrospray ionization tandem mass spectrometry. J. Chromatogr. A 1307, 119–125. PMID: 23928413. https://doi.org/10.1016/j.chroma.2013.07.087.

Avagyan, R., Luongo, G., Thorsén, G., Östman, C., 2015. Benzothiazole, benzotriazole, and their derivates in clothing textiles-a potential source of environmental pollutants and human exposure. Environ. Sci. Pollut. Res. 22, 5842–5849. PMID: 25342452. https://doi.org/10.1007/s11356-014-3691-0.

Baker, R.H., 1975. Additives in fibers and fabrics. Environ. Health Perspect. 11, 41–45. PMID: 1242130. https://doi.org/10.1289/ehp.751141.

Berger, E., Potouridis, T., Haeger, A., Püttmann, W., Wagner, M., 2015. Effect-directed identification of endocrine disruptors in plastic baby teethers. J. Appl. Toxicol. 35 (11), 1254–1261. PMID: 25988240. https://doi.org/10.1002/jat.3159.

Berger, K., Eskenazi, B., Kogut, K., Parra, K., Lustig, R.H., Greenspan, L.C., Holland, N., Calafat, A.M., Ye, X., Harley, K.G., 2018a. Association of prenatal urinary concentrations of phthalates and bisphenol A and pubertal timing in boys and girls. Environ. Health Perspect. 126 (9), 97004. PMID: 30203993. https://doi.org/10.1289/EHP3424.

Berger, K., Gunier, R.B., Chevrier, J., Calafat, A.M., Ye, X., Eskenazi, B., Harley, K.G., 2018b. Associations of maternal exposure to triclosan, parabens, and other phenols with prenatal maternal and neonatal thyroid hormone levels. Environ. Res. 165, 379–386. PMID: 29803919. https://doi.org/10.1016/j.envres.2018.05.005.

Berger, K., Eskenazi, B., Balmes, J., Holland, N., Calafat, A.M., Harley, K.G., 2018c. Associations between prenatal maternal urinary concentrations of personal care product chemical biomarkers and childhood respiratory and allergic outcomes in the CHAMACOS study. Environ. Int. 121 (Pt 1), 538–549. PMID: 30293015. https://doi.org/10.1016/j.envint.2018.09.027.

Björklund, J., 2011. Brominated Flame Retardants and Perfluoroalkyl Acids in Swedish Indoor Microenvironments. Implication for Human Exposure. Doctorial thesis in Applied Environmental Science. Stockholm University.

Braun, J.M., Yolton, K., Stacy, S.L., Erar, B., Papandonatos, G.D., Bellinger, D.C., Lanphear, B.P., Chen, A., 2017. Prenatal environmental chemical exposures and longitudinal patterns of child neurobehavior. Neurotoxicology 62, 192–199. PMID: 28736150. https://doi.org/10.1016/j.neuro.2017.07.027.

Brotons, J.A., Olea-Serrano, M.F., Villalobos, M., Pedraza, V., Olea, N., 1995. Xenoestrogens released from lacquer coatings in food cans. Environ. Health Perspect. 103 (6), 608–612. PMID: 7556016. https://doi.org/10.1289/ehp.95103608.

Casas, M., Valvi, D., Luque, N., Ballesteros-Gomez, A., Carsin, A.E., Fernandez, M.F., Koch, H.M., Mendez, M.A., Sunyer, J., Rubio, S., Vrijheid, M., 2013. Dietary and sociodemographic determinants of bisphenol A urine concentrations in pregnant women and children. Environ. Int. 56, 10–18. PMID: 23542682. https://doi.org/10.1016/j.envint.2013.02.014.

Česen, M., Lenarčič, K., Mislej, V., Levstek, M., Kovačič, A., Cimrmančič, B., Uranjek, N., Kosjek, T., Heath, D., Dolenc, M.S., Heath, E., 2018. The occurrence and source identification of bisphenol compounds in wastewaters. Sci. Total Environ. 616–617, 744–752. PMID: 29096955. https://doi.org/10.1016/j.scitotenv.2017.10.252.

Chianese, R., Troisi, J., Richards, S., Scafuro, M., Fasano, S., Guida, M., Pierantoni, R., Meccariello, R., 2018. Bisphenol A in reproduction: epigenetic effects. Curr. Med. Chem. 25 (6), 748–770. PMID: 28990514. https://doi.org/10.2174/0929867324666171009121001.

Commission Directive 2014/81/EU of 23 June 2014 amending Appendix C of Annex II to Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys, as regards bisphenol A, n.d.

Covaci, A., Den Hond, E., Geens, T., Govarts, E., Koppen, G., Frederiksen, H., Knudsen, L.E., Mørck, T.A., Gutleb, A.C., Guignard, C., Cocco, E., Horvat, M., Heath, E., Kosjek, T., Mazej, D., Tratnik, J.S., Castaño, A., Esteban, M., Cutanda, F., Ramos, J.J., Berglund, M., Larsson, K., Jönsson, B.A., Biot, P., Casteleyn, L., Joas, R., Joas, A., Bloemen, L., Sepai, O., Exley, K., Schoeters, G., Angerer, J., Kolossa-Gehring, M., Fiddicke, U., Aerts, D., Koch, H.M., 2015. Urinary BPA measurements in children and mothers from six European member states: overall results and determinants of exposure. Environ. Res. 141, 77–85. PMID: 25440295. https://doi.org/10.1016/j.envres.2014.08.008.

EFSA explains the Safety of Bisphenol A, 2015. Scientific opinion on bisphenol A. http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/factsheetbpa150121.pdf, Accessed date: 5 January 2019.

Gascon, M., Casas, M., Morales, E., Valvi, D., Ballesteros-Gómez, A., Luque, N., Rubio, S., Monfort, N., Ventura, R., Martínez, D., Sunyer, J., Vrijheid, M., 2015. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J. Allergy Clin. Immunol. 135 (2), 370–378. 25445825. https://doi.org/10.1016/j.jaci.2014.09.030.

Geens, T., Aerts, D., Berthot, C., Bourguignon, J.P., Goeyens, L., Lecomte, P., Maghuin-Rogister, G., Pironnet, A.M., Pussemier, L., Scippo, M.L., Van Loco, J., Covaci, A., 2012a. A review of dietary and non-dietary exposure to bisphenol-A. Food Chem. Toxicol. 50 (10), 3725–3740. PMID: 22889897. https://doi.org/10.1016/j.fct.2012.07.059.

Geens, T., Goeyens, L., Kannan, K., Neels, H., Covaci, A., 2012b. Levels of bisphenol A in thermal paper receipts from Belgium and estimation of human exposure. Sci. Total Environ. 435 (436), 30–33. PMID: 22846760. https://doi.org/10.1016/j.scitotenv.2012.07.001.

Goldade, V., Vinidiktova, N., 2017. Antimicrobial fibers for textile clothing and medicine: current state. ISJ Theoretical & Applied Science 3 (47), 178–194.

Haman, C., Dauchy, X., Rosin, C., Munoz, J.F., 2015. Occurrence, fate and behavior of parabens in aquatic environments: a review. Water Res. 68, 1–11. PMID: 25462712. https://doi.org/10.1016/j.watres.2014.09.030.

Harley, K.G., Berger, K.P., Kogut, K., Parra, K., Lustig, R.H., Greenspan, L.C., Calafat, A.M., Ye, X., Eskenazi, B., 2019. Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys. Hum. Reprod. 34 (1), 109–117. PMID: 3051766. https://doi.org/10.1093/humrep/dey337.

Healy, B.F., English, K.R., Jagals, P., Sly, P.D., 2015. Bisphenol A exposure pathways in early childhood: reviewing the need for improved risk assessment models. J. Expo. Sci. Environ. Epidemiol. 25 (6), 544–556. PMID: 26350983. https://doi.org/10.1038/jes.2015.49.

Karpuzoglu, E., Holladay, S.D., Gogal Jr., R.M., 2013. Parabens: potential impact of low-affinity estrogen receptor binding chemicals on human health. J. Toxicol. Environ. Health B Crit. Rev. 16 (5), 321–335. PMID: 23909435. https://doi.org/10.1080/10937404.2013.809252.

Lacasse, K., Baumann, W., 2004. Textile Chemicals: Environmental Data and Facts. Springer Berlin Heidelberg, New York, pp. 609.

Lange, C., Kuch, B., Metzger, J.W., 2014. Estrogenic activity of constituents of underarm deodorants determined by E-Screen assay. Chemosphere 108, 101–106. PMID: 24875918. https://doi.org/10.1016/j.chemosphere.2014.02.082.

Larsson, K., Ljung Björklund, K., Palm, B., Wennberg, M., Kaj, L., Lindh, C.H., Jönsson, B.A., Berglund, M., 2014. Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children. Environ. Int. 73, 323–333. PMID: 25216151. https://doi.org/10.1016/j.envint.2014.08.014.

Leonardi, A., Cofini, M., Rigante, D., Lucchetti, L., Cipolla, C., Penta, L., Esposito, S., 2017. The effect of bisphenol A on puberty: a critical review of the medical literature. Int. J. Environ. Res. Public Health 14 (9). https://doi.org/10.3390/ijerph14091044. PMID: 28891963.

Li, A.J., Kannan, K., 2018. Elevated concentrations of bisphenols, benzophenones, and antimicrobials in pantyhose collected from six countries. Environ. Sci. Technol. 52, 10812–10819. PMID: 30137966. https://doi.org/10.1021/acs.est.8b03129.

Liao, C., Kannan, K., 2011. Widespread occurrence of bisphenol A in paper and paper products: implications for human exposure. Environ. Sci. Tech. 45 (21), 9372–9379. https://doi.org/10.1021/es202507f. PMID: 21939283.

Liao, C., Kannan, K., 2014. Concentrations and composition profiles of parabens in currency bills and paper products including sanitary wipes. Sci. Total Environ. 475, 8–15. PMID: 24419282. https://doi.org/10.1016/j.scitotenv.2013.12.097.

Liu, W., Xue, J., Kannan, K., 2017. Occurrence of and exposure to benzothiazoles and benzotriazoles from textiles and infant clothing. Sci. Total Environ. 592, 91–96. PMID: 28319723. https://doi.org/10.1016/j.scitotenv.2017.03.090.

Lopez-Espinosa, M.J., Granada, A., Araque, P., Molina-Molina, J.M., Puertollano, M.C., Rivas, A., Fernández, M., Cerrillo, I., Olea-Serrano, M.F., López, C., Olea, N., 2007. Oestrogenicity of paper and cardboard extracts used as food containers. Food Addit. Contam. 24 (1), 95–102. PMID: 17164220. https://doi.org/10.1080/02652030600936375.

Molina-Molina, J.M., Amaya, E., Grimaldi, M., Sáenz, J.M., Real, M., Fernández, M.F., Balaguer, P., Olea, N., 2013. *In vitro* study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. Toxicol. Appl. Pharmacol. 272, 127–136. PMID: 23714657. https://doi.org/10.1016/j.taap.2013.05.015.

Molina-Molina, J.M., Real, M., Jiménez-Díaz, I., Belhassen, H., Hedhili, A., Torné, P., Fernández, M.F., Olea, N., 2014. Assessment of estrogenic and anti-androgenic activities of the mycotoxin zearalenone and its metabolites using in vitro receptor-specific bioassays. Food Chem. Toxicol. 74, 233–239. PMID: 25455890. https://doi.org/10.1016/j.fct.2014.10.008.

Molina-Molina, J.M., Jiménez-Díaz, I., Fernández, M.F., Rodriguez-Carrillo, A., Peinado, F.M., Mustieles, V., Barouki, R., Piccoli, C., Olea, N., Freire, C., 2019. Determination of bisphenol A and bisphenol S concentrations and assessment of estrogen- and anti-androgen-like activities in thermal paper receipts from Brazil, France, and Spain. Environ. Res. 170, 406–415. PMID: 30623888. https://doi.org/10.1016/j.envres.2018.12.046.

Mustieles, V., Pérez-Lobato, R., Olea, N., Fernández, M.F., 2015. Bisphenol A: human exposure and neurobehavior. Neurotoxicology 49, 174–184. PMID: 26121921. https://doi.org/10.1016/j.neuro.2015.06.002.

Negev, M., Berman, T., Reicher, S., Sadeh, M., Ardi, R., Shammai, Y., 2018. Concentrations of trace metals, phthalates, bisphenol A and flame-retardants in toys and other children's products in Israel. Chemosphere 192, 217–224. PMID: 29102866. https://doi.org/10.1016/j.chemosphere.2017.10.132.

Pan, S., Yuan, C., Tagmount, A., Rudel, R.A., Ackerman, J.M., Yaswen, P., Vulpe, C.D., Leitman, D.C., 2016. Parabens and human epidermal growth factor receptor ligand cross-talk in breast cancer cells. Environ. Health Perspect. 124 (5), 563–569. PMID: 26502914. https://doi.org/10.1289/ehp.1409200.

Papaspyrides, C.D., Pavlidou, S., Vouyiouka, S.N., 2009. Development of advanced textile materials: natural fibre composites, antimicrobial, and flame-retardant fabrics. Proc.

Inst. Mech. Eng. L 223 (2), 91–102. https://doi.org/10.1243/14644207JMDA200.

Philippat, C., Nakiwala, D., Calafat, A.M., Botton, J., De Agostini, M., Heude, B., Slama, R., EDEN Mother–Child Study Group, 2017. Prenatal exposure to nonpersistent endocrine disruptors and behavior in boys at 3 and 5 years. Environ. Health Perspect. 125 (9), 097014 PMID: 28937960. https://doi.org/10.1289/EHP1314.

Pulgar, R., Olea-Serrano, M.F., Novillo-Fertrell, A., Rivas, A., Pazos, P., Pedraza, V., Navajas, J.M., Olea, N., 2000. Determination of bisphenol A and related aromatic compounds released from bis-GMA-based composites and sealants by high performance liquid chromatography. Environ. Health Perspect. 108 (1), 21–27. PMID: 10620520. https://doi.org/10.1289/ehp.0010821.

Quirós-Alcalá, L., Eskenazi, B., Bradman, A., Ye, X., Calafat, A.M., Harley, K., 2013. Determinants of urinary bisphenol A concentrations in Mexican/Mexican-American pregnant women. Environ. Int. 59, 152–160. PMID: 23816546. https://doi.org/10.1016/j.envint.2013.05.016.

Real, M., Molina-Molina, J.M., Jiménez-Díaz, I., Arrebola, J.P., Sáenz, J.M., Fernández, M.F., Olea, N., 2015. Screening of hormone-like activities in bottled waters available in Southern Spain using receptor-specific bioassays. Environ. Int. 74, 125–135. PMID: 25454229. https://doi.org/10.1016/j.envint.2014.10.006.

Rochman, C.M., Browne, M.A., Halpern, B.S., Hentschel, B.T., Hoh, E., Karapanagioti, H.K., Rios-Mendoza, L.M., Takada, H., Teh, S., Thompson, R.C., 2013. Classify plastic waste as hazardous. Nature 494, 169–171. PMID: 23407523. https://doi.org/10.1038/494169a.

Rovira, J., Nadal, M., Schuhmacher, Domingo, J.L., 2015. Human exposure to trace elements through the skin by direct contact with clothing: risk assessment. Environ. Res. 140, 308–316. PMID: 25889781. https://doi.org/10.1016/j.envres.2015.03.032.

Sakhi, A.K., Sabaredzovic, A., Papadopoulou, E., Cequier, E., Thomsen, C., 2018. Levels, variability and determinants of environmental phenols in pairs of Norwegian mothers and children. Environ. Int. 114, 242–251. PMID: 29524920. https://doi.org/10.1016/j.envint.2018.02.037.

Sanders, A.P., Saland, J.M., Wright, R.O., Satlin, L., 2018. Perinatal and childhood exposure to environmental chemicals and blood pressure in children: a review of literature 2007–2017. Pediatr. Res. 84 (2), 165–180. PMID: 29884847. https://doi.org/10.1038/s41390-018-0055-3.

Scinicariello, F., Buser, M.C., 2016. Serum testosterone concentrations and urinary bisphenol A, benzophenone-3, triclosan, and paraben levels in male and female children and adolescents: NHANES 2011–2012. Environ. Health Perspect. 124 (12), 1898–1904. PMID: 27383665. https://doi.org/10.1289/EHP150.

Snoj Tratnik, J., Kosjek, T., Heath, E., Mazej, D., Ćehić, S., Karakitsios, S.P., Sarigiannis, D.A., Horvat, M., 2019. Urinary bisphenol A in children, mothers and fathers from Slovenia: overall results and determinants of exposure. Environ. Res. 168, 32–40. PMID: 30253314. https://doi.org/10.1016/j.envres.2018.09.004.

Swedish Chemicals Agency, 2013. Hazardous chemicals in textiles – report of a government assignment. http://www.kemikalieinspektionen.se, Accessed date: 31 October 2018.

The Federal Institute for Risk Assessment, 2012. Introduction to the problems surrounding garment textiles. https://www.bfr.bund.de/cm/349/introduction-to-the-problems-surroundinggarment-textiles.pdf, Accessed date: 15 November 2018.

United States Environmental Protection Agency, 2011. Exposure Factors Handbook: 2011 Edition. https://www.epa.gov/sites/production/files/2015-09/documents/techoverview_efh-complete.pdf, Accessed date: 15 November 2018.

Valvi, D., Casas, M., Mendez, M.A., Ballesteros-Gómez, A., Luque, N., Rubio, S., Sunyer, J., Vrijheid, M., 2013. Prenatal bisphenol A urine concentrations and early rapid growth and overweight risk in the offspring. Epidemiology 24, 791–799. PMID: 24036610. https://doi.org/10.1097/EDE.0b013e3182a67822.

Vandenberg, L., Chahoud, I., Heindel, J., Padmanabhan, V., Paumgartten, F.J.R., Schoenfelder, G., 2010. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environ. Health Perspect. 118, 1055–1070. PMID: 20338858. https://doi.org/10.1289/ehp.0901716.

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, D.R., Lee, D.H., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T., Myers, J.P., 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr. Rev. 33 (3), 378–455. PMID: 22419778. https://doi.org/10.1210/er.2011-1050.

Vela-Soria, F., Ballesteros, O., Zafra-Gómez, A., Ballesteros, L., Navalón, A., 2014. UHPLC-MS/MS method for the determination of bisphenol A and its chlorinated derivatives, bisphenol S, parabens, and benzophenones in human urine samples. Anal. Bioanal. Chem. 406 (15), 3773–3785. PMID: 24710638. https://doi.org/10.1007/s00216-014-7785-9.

Wetherill, Y.B., Akingbemi, B.T., Kanno, J., McLachlan, J.A., Nadal, A., Sonnenschein, C., Watson, C.S., Zoeller, R.T., Belcher, S.M., 2007. In vitro molecular mechanisms of bisphenol A action. Reprod. Toxicol. 24, 178–198. PMID: 17628395. https://doi.org/10.1016/j.reprotox.2007.05.010.

Xue, J., Liu, W., Kannan, K., 2017. Bisphenols, benzophenones, and bisphenol A diglycidyl ethers in textiles and infant clothing. Environ. Sci. Technol. 51 (9), 5279–5286. PMID: 28368574. https://doi.org/10.1021/acs.est.7b00701.