



Article

Exposure to New Emerging Bisphenols Among Young Children in Switzerland

Fiorella Lucarini ¹, Tropoja Krasniqi ¹, Gaëlle Bailat Rosset ², Nicolas Roth ³ , Nancy B Hopf ^{3,4} , Marie-Christine Broillet ¹ and Davide Staedler ^{1,2,*} 

¹ Department of Biomedical Sciences, University of Lausanne, 1011 Lausanne, Switzerland; fiorella.lucarini@unil.ch (F.L.); tropoja.krasniqi@unil.ch (T.K.); marie-christine.broillet@unil.ch (M.-C.B.)

² Scitec Research SA, Av. De Provence 18, 1007 Lausanne, Switzerland; gbailat@scitec-research.com

³ Swiss Centre for Applied Human Toxicology (SCAHT), University of Basel, 4055 Basel, Switzerland; nicolas.roth@unibas.ch (N.R.); nancy.hopf@unisante.ch (N.B.H.)

⁴ Center for Primary Care and Public Health (Unisanté), University of Lausanne, 1007 Lausanne, Switzerland

* Correspondence: davide.staedler@unil.ch; Tel.: +41-079-702-14-23

Received: 5 June 2020; Accepted: 1 July 2020; Published: 3 July 2020



Abstract: Restrictions on the use of bisphenol A (BPA) in consumer products led to its replacement by various bisphenol (BP) analogues, yet young children's exposure to these analogues has been poorly characterized so far. This study aimed to characterize infants' and toddlers' exposure to BPA and 14 emerging BP analogues (i.e., bisphenol AF, bisphenol AP, bisphenol B, bisphenol BP, bisphenol C (BPC), bisphenol E, bisphenol F (BPF), bisphenol G, bisphenol M (BPM), bisphenol P, bisphenol PH, bisphenol S (BPS), bisphenol TMC, and bisphenol Z). We extracted infants' and toddlers' urine from diapers ($n = 109$) collected in Swiss daycare centers as a practical and noninvasive alternative approach to urinary biomonitoring. Bisphenols were present in 47% of the samples, with BPC and BPM being the most frequently detected (23% and 25% of all samples, respectively). The mean concentrations of urinary BPS and BPF were greater than that of BPA. This contrasts with data reported previously. Furthermore, statistical analysis revealed a significant and negative correlation between urinary BPM concentration and the population's age. Our results provide a first characterization of infants' and toddlers' exposure to bisphenols in Switzerland. This knowledge can be used to support ongoing biomonitoring studies and to prioritize exposure reduction and prevention strategies.

Keywords: bisphenol analogues; biomonitoring; endocrine disruptors; urine; children's health

1. Introduction

Bisphenols (BPs) are a wide group of chemicals extensively utilized in polycarbonate plastics and epoxy resins, especially for the production of plastic packages for foods and beverages, dental sealants, thermal papers, medical devices, and toys. Among BP analogues, bisphenol A (BPA) is the most commonly used, with an annual production that reaches over 7.7 million tons, and is present in several consumer products [1]. Biomonitoring measurements of BPA in human serum, urine, hair, and breast milk have revealed widespread low-dose exposure to BPA in the EU and U.S. population [2–8]. A large body of experimental and epidemiological literature is available that links BPA exposure to a wide range of adverse health outcomes, and the evidence has been (or is currently being) reviewed by several governmental organizations [9–16].

BPA is a presumed human reproductive toxicant and is classified as Repro. Cat 1B, H360f [*May damage the fertility or the unborn child*] under EU Classification, Labelling and Packaging (CLP) Regulation (EC/1272/2008) (EC 2008).

In 2017, the European Chemical Agency (ECHA) added BPA to the Candidate List of Substances of Very High Concern (SVHC), based on evidence for endocrine-disruption-mediated effects on various reproductive, cognitive, and metabolic endpoints [17]. There is some concern that fetuses, infants, toddlers, and children may be particularly vulnerable to adverse effects of BPA due to the vulnerability of developing organs to endocrine disrupting chemicals, particularly the brain, following pre- and/or postnatal exposure to BPA [16]. Indeed, early exposure to BPA has been associated with an increased risk of altered cognitive function (e.g., learning, memory) and behavior (e.g., hyperactivity), metabolic disorders (e.g., obesity), and breast or prostate cancer developed in later life [18–21]. In order to reduce the exposure to BPA in young children, BPA was banned in baby bottles in Canada, Europe, and USA [15,22]. Restrictions on the use of BPA in consumer products have led to its replacement by a number of BP analogues. Recently, more than 200 BPs have been identified as BPA analogues in consumer goods [23–25]. However, only a few have been considered relevant to human exposure even though they have widespread use (Table 1) and their presence has been documented in the environment.

Table 1. Structures and physicochemical properties of the bisphenols (BPs) investigated.

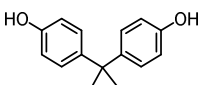
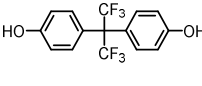
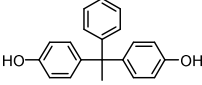
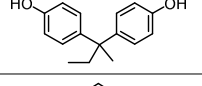
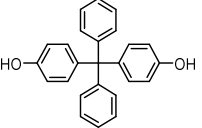
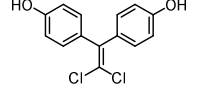
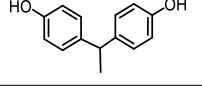
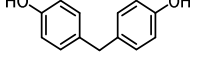
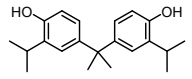
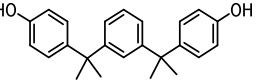
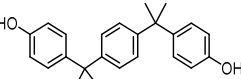
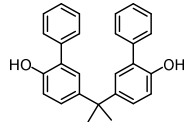
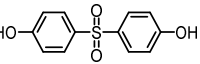
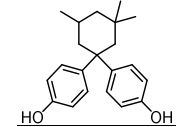
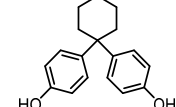
BP CAS n°	Structural Formula	Log k_{ow}	Applications	Potential Exposure Sources	Ref.
BISPHENOL A (BPA) 80-05-7		3.43	Polycarbonate plastics, epoxy resins	Thermal papers, food, beverages, dust, personal care products, textile products	[26] [23] [9] [5]
BISPHENOL AF (BPAF) 1478-61-1		4.47	Coating products, epoxy resins	Food, beverages, dust, dental materials, personal care products, textile products	[23] [26] [9]
BISPHENOL AP (BPAP) 1571-75-1		4.86	Coating products, epoxy resins	Food, beverages, thermal papers, dust, textile products	[23] [26] [9]
BISPHENOL B (BPB) 77-40-7		4.13	Coating products, epoxy resins	Food, beverages, dust, textile products	[23] [26] [27]
BISPHENOL BP (BPBP) 1844-01-5		6.08	Flame retardants, polycarbonate plastics	Plastic products, furniture	[26]
BISPHENOL C (BPC) 14868-03-2		3.74	Flame retardants, polycarbonate plastics	Thermal papers, textile products	[26] [23]
BISPHENOL E (BPE) 2081-08-5		3.19	Coating products, polycarbonate plastics	Food, beverages, textile products	[26] [23]
BISPHENOL F (BPF) 620-92-8		3.06	Coating products, lacquers	Food, adhesives, varnishes, textile products, dust	[23] [26] [27]

Table 1. Cont.

BP CAS n°	Structural Formula	Log k_{ow}	Applications	Potential Exposure Sources	Ref.
BISPHENOL G (BPG) 127-54-8		6.55	Polycarbonate plastics, epoxy resins	Dental materials	[26]
BISPHENOL M (BPM) 13595-25-0		6.25	Thermoplastics, polycarbonate plastics	Plastic products, dental materials	[28]
BISPHENOL P (BPP) 2167-51-3		6.25	Polycarbonate plastics, epoxy resins	Food, dust	[23]
BISPHENOL PH (BPPH) 24038-68-4		7.17	Polycarbonate plastics, epoxy resins	Food, beverages	[28]
BISPHENOL S (BPS) 80-09-1		1.65	Coating products, dyes, leather tanning agents	Food, beverages, thermal papers, dust, textile products	[23] [26] [27]
BISPHENOL TMC (BPTMC) 129188-99-4		6.29	Polycarbonate plastics, epoxy resins, polyesters	Dental materials, dust	[29] [28]
BISPHENOL Z (BPZ) 843-55-0		5.00	Coating products, polycarbonate plastics	Food, personal care products, textile products	[23] [26]

Log K_{ow} = octanol-water partition coefficient [28].

Our work focused on the most significant BPA analogues selected on the basis of previous studies and includes bisphenol AF (BPAF), bisphenol AP (BPAP), bisphenol B (BPB), bisphenol BP (BPBP), bisphenol C (BPC), bisphenol E (BPE), bisphenol F (BPF), bisphenol G (BPG), bisphenol M (BPM), bisphenol P (BPP), bisphenol PH (BPPH), bisphenol S (BPS), bisphenol TMC (BPTMC), and bisphenol Z (BPZ) [26,28] (Table 1). The selected compounds are structurally similar to BPA with analogous physicochemical properties (Table 1), but their effects on animals and humans have been poorly studied [30,31]. Little is known about the toxicity of alternative BPs, and most of the toxicological information is limited to their endocrine disrupting potential [23]. Some studies suggested that these BPs have biological activities comparable to those of BPA due to their structural similarity [32–34]; other studies suggested that they have endocrine and toxicological activities even greater than BPA [35–37]. A systematic review by Rochester et al. showed that BPF and BPS exhibit hormonal activity with similar estrogenic, androgenic, and antiestrogenic potencies across different in vitro assays, and of the same order of magnitude as BPA [38]. Other studies have shown that BPB, BPC, and BPE exhibit estrogenic and antiandrogenic activities [24,32,39–41]. In vitro studies on zebrafish showed that BPS exposure (>0.5 µg/L) led to reproductive disruption decreasing egg production and gonadosomatic index [30,31]. Furthermore, it was observed that BPAF, BPB, and BPC exhibit estrogenic potencies similar to or greater than that of BPA. Antiandrogenic activity has been reported for BPAF, BPE, BPF, and BPB [28]. Moreover, in vitro and in vivo studies suggested other effects mediated by BPs, such as genotoxicity, oxidative stress, serum protein binding, and metabolic disorders [23,35,36,42–44].

Previous works suggested that infants and toddlers may have substantial exposure to BPs because of frequent contact with plastic objects such as baby bottles, teething rings, and toys, leading to hand-to-mouth transfers [45–47]. Available data on exposure to BP analogues, however, are very limited, and only a few studies have focused on the detection of urinary levels of these bisphenols in infants and toddlers [8,28,38]. Indeed, only nine (i.e., BPA, BPAF, BPAP, BPB, BPF, BPM, BPP, BPS, and BPZ) of the most common BPs have previously been analyzed in urine obtained from adults and children [8,28,48–53]. The analysis of human urine is a preferred approach in monitoring total BP concentrations, as urinary excretion is the main route of BP elimination, independently of the exposure route [49,51].

There is a need to characterize human exposure to BPs from various consumer products and to conduct more epidemiological research on the association between exposure to these emerging BPs and potential adverse health outcomes. In this regard, biomonitoring is a useful tool to quantify human exposure to BPs, and this approach can help in human health risk assessments [54].

As a first step in understanding BP exposure among children, we analyzed 15 bisphenols (bisphenol A, bisphenol AF, bisphenol AP, bisphenol B, bisphenol BP, bisphenol C, bisphenol E, bisphenol F, bisphenol G, bisphenol M, bisphenol P, bisphenol PH, bisphenol S, bisphenol TMC, and bisphenol Z) in urine extracted from diapers of infants and toddlers [55,56] attending Swiss daycare centers. Urine extracted from used diapers is a reliable sampling procedure, and sufficient quantities of urine can be obtained for the chemical analytical methods [57–59]. This sampling approach allowed us to investigate internal BP dose distributions in this young population at risk.

To the best of our knowledge, this is the first study focusing on the analysis of such a large number of BPA analogues in human urine; in addition, it also included BPPB, BPC, BPG, BPE, BPPH, and BPTMC, which have never before been assessed in infants' and toddlers' urine.

2. Materials and Methods

2.1. Chemicals

Bisphenol A ($\geq 99\%$), bisphenol AF ($\geq 99\%$), bisphenol AP ($\geq 99\%$), bisphenol B ($\geq 98\%$), bisphenol BP ($\geq 98\%$), bisphenol C ($\geq 98\%$), bisphenol E ($\geq 98\%$), bisphenol F ($\geq 98\%$), bisphenol G ($\geq 98\%$), bisphenol M ($\geq 99\%$), bisphenol P ($\geq 99\%$), bisphenol PH ($\geq 99\%$), bisphenol S ($\geq 98\%$), bisphenol TMC ($\geq 97\%$), and bisphenol Z ($\geq 99\%$) were purchased from Sigma-Aldrich. Stock standard solutions (100 mg/L) were individually prepared by dissolving standard compounds in acetonitrile. A stock standard mixture containing all the individual standards (100 mg/L) was also prepared and stored at $-20\text{ }^{\circ}\text{C}$. Working solutions for calibrations were prepared by serial dilution of the stock standard mixture with acetonitrile (Sigma-Aldrich). Beta-glucuronidase from *E. coli* (200 units/mL) was purchased from La Roche AG group. Bis(trimethylsilyl)trifluoroacetamide (BSTFA) with 1% of trimethylchlorosilane (TMCS) solution was used for BPs derivatization and was purchased from Sigma-Aldrich. Ammonium acetate (98%), calcium chloride (CaCl_2) ($\geq 99\%$), creatinine hydrochloride ($\geq 97\%$), ammonium phosphate dibasic ($\geq 99\%$), magnesium chloride hexahydrate ($\geq 99\%$), potassium chloride ($\geq 99\%$), sodium sulphate ($\geq 99\%$), urea ($\geq 98\%$), acetone (99.9%), formic acid ($\geq 95\%$), and methanol (99.9%) were purchased from Sigma-Aldrich. Nanopure water was provided by an ultrapure water system (ariumPro, Sartorius, Germany).

2.2. Artificial Urine

A solution of artificial urine was prepared for calibration and blank controls to have a uniform matrix effect. The solution was adapted from Hu et al. [58] and from CSN EN 1616 (DIN EN 1616) and is composed of 1.2 g of creatinine hydrochloride, 3.4 g of ammonium phosphate dibasic, 0.5 g of magnesium chloride

hexahydrate, 4.5 g of potassium chloride, 21 g of sodium sulphate, 1.5 g of urea, and 0.32 g of calcium chloride dehydrate. All compounds were dissolved in nanopure water, then stored at 4 °C [60].

2.3. Urine Sample Extraction

Urine samples were extracted from used disposable diapers ($n = 109$) with small modifications of a method reported by Hu et al. [58]. Briefly, the absorbent pad (i.e., polyacrylate) was removed from the diaper and placed into a flask containing 150 mL of CaCl_2 at 150 g/L in nanopure water. The mixture was stirred 30 min in a shaker at 180 rpm at room temperature and filtered using a paper filter (Whatman, GE Healthcare Life Sciences; Chicago, Illinois, USA). The filtrate containing the expressed urine was placed in a graduate cylinder to quantify the total volume obtained, which was stored at -20 °C before analysis of BPs.

2.4. Chemical Analysis of BPs

The amount of BPs quantified in urine samples included unconjugated BPs and glucuronide conjugate metabolites. Glucuronidation of BPs in the intestine and liver is considered the main metabolic pathway for most bisphenols. These metabolites are mainly excreted through urine, and other metabolites only result when the glucuronidation pathway is saturated [41,57]. The total amount of free and glucuronide-conjugate BPs was extracted from samples by enzymatic deconjugation followed by Solid Phase Extraction (SPE) according to Hu et al. [58]. For each sample, the solution extracted from the diapers was buffered at pH 5.5–6 with ammonium acetate, then treated with 80 μL of β -glucuronidase to hydrolyze the glucuronide conjugates, and kept overnight at 37 °C [57,59]. BPs were extracted and purified using a SPE-offline protocol based on Chromabond Easy column (3 mL, 200 mg, Macherey-Nagel) [61]. Samples were loaded on a Solid Phase Extraction (SPE) cartridge preconditioned with 6 mL of methanol and 6 mL of water. The cartridge was washed with 3 mL of water (pH = 2 with HCl), and the compounds were eluted with 9 mL of acetone and formic acid (in ratio 99:1). After solvent evaporation, BPs were derivatized using BSTFA with 1% TMCS for 30 min at 75 °C and analyzed by gas chromatography-mass spectrometry (GC-MS, model GCMS-QP2010 Ultra, Shimadzu Corporation, Japan) equipped with an amine column (Rtx-5, length = 30 m, column diameter = 0.25 mm and thickness = 0.25 μm) and operated by the LabSolutions GC-MS Shimadzu software. Helium was used as carrier gas with a flow rate at initial temperature of 5 mL/min. The injection occurred at 280 °C in a splitless mode, the temperature ramp started at 45 °C, increased to 300 °C at 10 °C/min, and then was kept at 300 °C for 5 min.

The ion source temperature was adjusted to 250 °C, and the mass spectrometer detector was set in the full scan acquisition mode to first identify the BPs. A selected ion monitoring (SIM) mode was then used to quantify the analytes in the samples and the standard mixture (Table 2). Creatinine analyses were performed by the company Unilabs Ticino (Breganzona, Switzerland), a certified bio-medical laboratory (ISO 15189 and ISO 17025), using the kinetic alkaline picrate method. BP urinary concentrations were adjusted to the concentration of creatinine and expressed in micrograms of BPs per gram of urinary creatinine ($\mu\text{g/g}$) and in micrograms per liter of urine ($\mu\text{g/L}$).

2.5. Calibration and Blank Assessment

Fifty mL of artificial urine were spiked with the standard mixture of BPA, BPAF, BPAP, BPB, BPBP, BPC, BPE, BPF, BPG, BPM, BPP, BPPH, BPS, BPTMC, and BPZ at 1, 2, 20, 60, 120, and 300 $\mu\text{g/L}$ and added to unused disposable diapers. After incubation at room temperature (5 min), diapers were processed with the same procedure described for the analysis of the samples and used for calibration. Background analyte concentrations in disposable diapers were evaluated by pouring 50 mL of (i) nanopure water and (ii) artificial urine in unused disposable diapers. Different diaper brands ($n = 23$) among the most used in

Switzerland were tested. The analysis of artificial urine extracted from diapers of different brands did not show the presence of the investigated BPs at concentrations higher than the limits of detection (LODs). The blanks were subjected to the same extraction protocol of the samples. Concentrations of the target analytes measured in blank controls were below the limits of detection. To assess the efficiency of the extraction from diapers, we calculated the recoveries of unconjugated BPA spiked in artificial urine at three concentrations: 1, 60, and 200 µg/L. Unused diapers were wetted with 50 mL of spiked artificial urine which was extracted as previously described. The recoveries of BPA were near quantitative (96%), and the same value was assumed for the other BPs. The limits of quantification (LOQs) and LODs (in parenthesis) were between 0.3–0.5 (0.09–0.15) µg/L.

Table 2. List of target analytes with gas chromatography-mass spectrometry (GC-MS) parameters used for identification.

Derivatized Bisphenols	Retention Time (min)	Monitored Ions (<i>m/z</i>)
BPAF	18.85	480, 411, 225
BPF	20.26	344, 179, 157
BPE	20.52	358, 372
BPA	20.84	372, 357, 207
BPB	21.53	371, 357, 191
BPG	21.78	456, 441, 249
BPC	22.95	424, 354
BPZ	23.93	412, 369
BTMC	24.20	454, 397, 383
BPS	24.55	394, 379, 229
BPAP	24.83	434, 419, 269
BPM	26.12	490, 475, 207
BPP	27.40	490, 475, 207
BPBF	28.23	496, 419, 331
BPPH	28.40	509, 267, 247

2.6. Study Population

This study was based on infants and toddlers aged between 6 and 36 months, living in Switzerland. The mean age of the population was 20.2 months, and there were more boys than girls (63% vs. 37%). We obtained the samples ($n = 109$) from daycare centers, from 9 am to 12 o'clock, between June and July (2019). The samples were stored at $-20\text{ }^{\circ}\text{C}$ immediately after collection. This study was approved by the local ethics committee (CER-VD). Written consent was obtained from all parents/guardians of infants and toddlers that participated in this study before enrolment. To maintain anonymity, only age and sex of infants and toddlers were associated with the samples, and one diaper per child was collected to avoid unknown duplicates.

2.7. Statistical Analysis

Data were summarized using Microsoft Excel 2013 (Microsoft 365, Microsoft Corporation, USA), mean concentrations were calculated on volume-based and creatinine-adjusted basis for positive samples. Statistical analyses were performed using the R3.4.3 statistical package (R Foundation for Statistical Computing, Vienna, Austria). The influence of age and sex on the results obtained for each BP was analyzed using a generalized linear model (GLM) corrected for the binomial family based on the presence ($\geq\text{LOQ} = 1$) and absence ($<\text{LOQ} = 0$) of BPs. The plot of BPM concentration (µg/g) vs. age (in months) of infants and toddlers (Figure 1) was obtained from the average concentrations of BPM per months of

life. In the case of infants or toddlers with same months of life and detectable concentrations of BPM, an average concentration between the values was used on the y-axis.

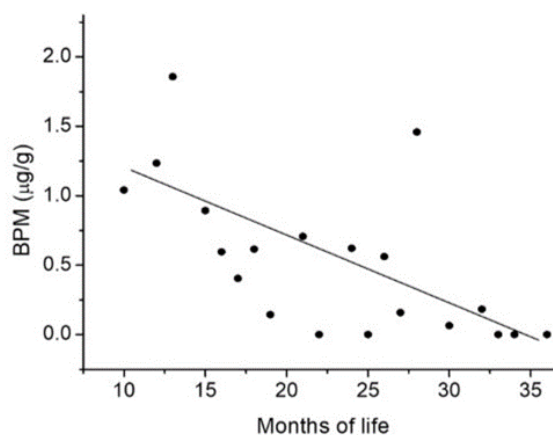


Figure 1. Graph showing the decline in average bisphenol M(BPM) concentrations (µg/g) (y-axis) by age (months of life) of infants and toddlers (x-axis).

3. Results

In our study, 47% of the samples were found to test positive for BPs, and 7 of the 15 BPs analyzed were detected. The concentrations of BPs correspond to the total amount of BPs in urine, resulting from unconjugated BPs and glucuronide-conjugate metabolites. Average mean concentrations and detection frequency for each BP were calculated and are reported in Table 3.

Table 3. Summary of BPs detection frequency (%), mean concentrations (average calculated for positive samples), and concentration ranges (micrograms bisphenol per gram of urinary creatinine (µg/g) and µg/L in parenthesis).

Bisphenols Derivatized	Detection Frequency % (Case Numbers)	Mean µg/g Creatinine (µg/L)	Range (µg/g Creatinine (µg/L))
BPF	2 (2)	0.07 (2.7)	0.06–0.08 (1.80–3.61)
BPE	2 (2)	0.12 (5.85)	0.07–0.17 (2.7–9.00)
BPA	7 (8)	0.06 (2.40)	0.01–0.11 (1.22–3.30)
BPC	23 (25)	0.25 (11.22)	0.03–1.03 (1.84–52.34)
BPS	3 (3)	0.15 (6.41)	0.11–0.19 (2.60–12.02)
BPM	25 (27)	1.31 (53.07)	0.13–8.56 (6.18–273.48)
BPP	4 (4)	0.58 (20.54)	0.04–1.85 (4.38–49.36)
BPAF	<LOD	n.a.	n.a.
BPB	<LOD	n.a.	n.a.
BPG	<LOD	n.a.	n.a.
BPZ	<LOD	n.a.	n.a.
BPTMC	<LOD	n.a.	n.a.
BPAP	<LOD	n.a.	n.a.
BPBF	<LOD	n.a.	n.a.
BPPH	<LOD	n.a.	n.a.

n.a. = not available.

The highest detection frequency was observed for BPM and BPC, which were found in 25% and 23% of all samples, respectively. The BPs with the highest urinary concentrations were BPM (8.56 µg/g), BPP (1.85 µg/g), and BPC (1.03 µg/g); meanwhile, lower concentrations were detected for BPF (0.06 µg/g)

and BPA (0.01 µg/g). Among the positive samples, 60% showed the presence of BPM. The concentrations of BPAF, BPB, BPG, BPZ, BPTMC, BPAP, BPBF, and BPPH were below the LOD. Correlations between the presence of BPs and the sex and age of the infants and toddlers were analyzed. We found that the presence of BPM significantly decreased with the age of infants and toddlers (p -value < 0.05) (Figure 1) but was not influenced by sex (p -value > 0.1). Other BPs tested were not significantly influenced by age or sex (p -value > 0.1).

4. Discussion

BPM and BPC were detected in about 1 in 4 samples, while BPAF, BPB, BPG, BPZ, BPTMC, BPAP, BPBF, and BPPH were not detected.

BPM is used as an ingredient to synthesize a blend of diphthalonitrile ether resins [62]. This BP has been rarely analyzed in human biomonitoring studies. Rocha et al. found no detectable concentrations of BPM in 300 urinary samples from Brazilian school children aged 6 to 14 years collected in 2012–2013 [50].

Data on urinary concentrations of BPC, BPPH, BPG, and BPE in human populations have never before been published. To date, the presence of these BPs have only been detected in human breast milk at concentrations lower than the limit of quantification [26,63]. Among the BPs analyzed, BPA, BPF, and BPS have been the most frequently detected and investigated in the literature [23]. In our study, BPA was detected in 7% of the samples, with a mean concentration of 2.4 µg/L (0.06 µg/g creatinine). BPA concentrations were similar to the concentration of BPF (2.7 µg/L, 0.07 µg/g, mean values), while a higher concentration was detected for BPS (6.41 µg/L, 0.15 µg/g, mean values). Compared to our results, BPA was more frequently detected (range from 74 to 100%) in urine samples of children collected from 2006 to 2014 in different countries such as USA, Greece, Germany, and Spain [8,64–66]. In the present study, we observed a decreased detection frequency of BPA with respect to other BPs, which can be explained on the basis of the restrictions on the use of BPA that several countries have adopted over the past few years.

Internal dose values for BPA were greater than for the other BPs. The BPA concentrations that we detected in this study were slightly higher than those found in urine samples collected in 2014 in the National Health And Nutrition Examination Survey (NHANES) study in the USA (1.3 µg/L, median value, $n = 409$) for children aged between 6 and 11 years [8]. In contrast, urinary BPA levels (2 µg/L, geometric mean (GM)) reported for Greek young children (aged 2–3 years) sampled in 2009–2011 were comparable to our BPA concentrations (2.4 µg/L) [64]. Others have reported urinary BPA concentrations of 4, 3.5, and 3.1 µg/L (as GM) obtained from toddlers (age <5 years) from China, Germany, and Spain, respectively. These were higher compared to our BPA values [57,65,66]. The similarities and differences observed might be due to geographical locations, age groups included in the study, and governing regulations. Nevertheless, the current tolerable daily intake (TDI) determined by the European Food Safety Authority for BPA in 2015 is 4 µg/kg-day, which is lower than the estimated median BPA exposures calculated from international studies (0.02–0.12 µg/kg-day for children) [67]. TDIs for the other BPs do not yet exist.

Only limited data regarding the detection and quantification of BPF and BPS are available in both adult and children exposure studies. Reliable chemical analytical methods including LODs and LOQs need to be established to be able to compare data across biomonitoring studies. A study conducted with USA children (aged 6–11 years) in 2014 reported lower median levels of BPF (0.27 µg/L) and BPS (0.27 µg/L) compared to our findings and a lower detection frequency with respect to BPA [8]. Other BPs have been sporadically detected in environmental and human samples [26,28]. In our study, the urinary BPAF concentrations were lower than the LOD. Other studies have reported detectable BPAF concentrations [68–71], with the highest concentrations (0.018 µg/L) reported in a Chinese cohort in 2013 [72].

Exposure data for BPs other than BPA are scarce. The findings of our study showed that average BPM concentrations are higher in infants than in toddlers. We can only hypothesize that these results are related to different sources of exposure for infants and toddlers. Infants may ingest contaminated food and beverage, while toddlers could potentially be exposed from eating dust (hand to mouth) generated from the building materials, as BPM has been reported used in coating, adhesives, electronics, and structural applications as well as in automobiles. Urinary presence of BPM could also be an indicator of the presence of this BP in childcare products leading to skin absorption. However, it is difficult to identify the contribution of various exposure routes and sources to the overall internal dose, as no comprehensive BPM exposure characterization has been conducted among the investigated population. The advantage of biomonitoring is that it incorporates all routes of exposure and provides a total internal dose. The limitation of the biomonitoring approach is that the source of this body-burden cannot be assessed.

There is a need to characterize the various exposure sources of BP analogues in consumer and childcare products as well as in the indoor environment. Furthermore, as a consequence of restrictions on the use of BPA in consumer products, urinary BPA levels have decreased steadily over time in USA and EU populations [73], while urinary BP analogues levels are now on the rise. Despite the extensive amount of experimental data generated for BPA, our ability to link chronic low-dose environmental exposure to BPA with adverse human health effects remains so far limited. Controversies over low-dose effects of BPA exist as well as knowledge gaps and shortcomings in BPA basic biology data and dose-response analysis, and in the integration of academic research findings into regulatory risk assessment [74]. This situation has prompted several consortium-based initiatives to address the remaining areas of uncertainty [75–77]. Closing all the gaps will require massive research efforts.

Adverse outcome pathways (AOP)-based thinking has been proposed as a driver for generating new experimental data for BPA [74]. AOPs have been proposed recently for BPS [78] and BPF [79]. Similarly, applying exposure-based, pathway-oriented approaches (e.g., aggregate exposure pathways, AEPs) [80,81] can support a better characterization of the source-to-outcome continuum by exploring the linkages between exposure sources and pathways with internal exposure information (i.e., biomonitoring data), which can be then linked to AOPs. The value of integrating biomonitoring data to better support human health risk assessment and regulatory decision-making regarding chemicals has been widely acknowledged, yet the use of biomonitoring data and the level of implementation across sectorial chemical regulatory frameworks and regions vary [6,82]. Knowledge assembly tools like AOPs and AEPs can facilitate this integration and help focus and prioritize experimental and epidemiological research efforts on BPs to meet critical regulatory risk assessment needs.

This study represents a first snapshot of young children's exposure to BP analogues; however, it has a number of limitations, both from an epidemiological and a methodological point of view. The number of samples investigated is too limited to provide results representative of a whole population. The extraction efficiency was investigated only for BPA, assuming the same behavior for the other BPs. A 24-h urine collection was not possible because of the setup of the study (i.e., protocol for sample anonymization). Despite these limitations, our results provide a first landmark characterization of infants' and toddlers' exposure to BPs in Switzerland, even though the single spot urine samples utilized in the study mainly reflect the exposure occurring shortly before urine collection [83]. However, further studies on a larger population scale could enable the single spot approach to accurately reflect the average exposure to BPs [83]. Furthermore, our study highlights the feasibility of using commercial diapers to monitor infants' and toddlers' exposure to new emerging bisphenols. In particular, these preliminary results can inform the ongoing debate of whether to establish a national program to monitor the environmental chemical exposure of the Swiss population [84,85].

5. Conclusions

Results from our study show that toddlers and infants are extensively exposed to BP derivatives; however, in comparison with the existing literature, the exposure to this class of compounds has changed over time, as demonstrated by the decreased BPA detection frequency and the increasing concentrations of other BPs. In this context, the mean urinary levels of BPS and BPF were higher than those measured for BPA, which is in contrast with data reported in the literature until now [8,28]. Information on emerging BPs is still scarce, and it is warranted to include these compounds in extended prospective studies with greater samples sizes to prevent the potential harmful human exposure to BPs and health consequences. Finally, these studies should be coupled with the analysis of BPs in products and cosmetics for childcare to assess BPM and BPC presence and migration from such products.

Author Contributions: Conceptualization, N.R., N.B.H., and D.S.; Formal analysis, T.K. and G.B.R.; Funding acquisition, D.S.; Investigation, T.K. and G.B.R.; Methodology, F.L., T.K., M.-C.B., and D.S.; Project administration, D.S.; Resources, G.B.R. and D.S.; Supervision, M.-C.B. and D.S.; Validation, F.L.; Visualization, F.L.; Writing—original draft, F.L.; Writing—review & editing, F.L., N.R., N.B.H., M.-C.B., and D.S. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Department of Biomedical Sciences, in collaboration with SCAHT and Unisanté.

Acknowledgments: We thank Federico Tettamanti for the help with statistical analysis and Julien Brechbühl for scientific advice. We also thank the staff of the daycare centers and parents for their support and contribution to our study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Expert Industry. Bisphenol-A A Global Market Overview. Available online: <https://industry-experts.com/verticals/files/articles/cp021-bisphenol-a-a-global-market-overview.pdf> (accessed on 18 February 2020).
2. Huang, R.-P.; Liu, Z.-H.; Yuan, S.-F.; Yin, H.; Dang, Z.; Wu, P.-X. Worldwide human daily intakes of bisphenol A (BPA) estimated from global urinary concentration data (2000–2016) and its risk analysis. *Environ. Pollut.* **2017**, *230*, 143–152. [CrossRef] [PubMed]
3. Calafat, A.M.; Kuklennyik, Z.; Reidy, J.A.; Caudill, S.P.; Ekong, J.; Needham, L.L. Urinary Concentrations of Bisphenol A and 4-Nonylphenol in a Human Reference Population. *Environ. Health Perspect.* **2005**, *113*, 391–395. [CrossRef] [PubMed]
4. Wang, L.; Zhang, Y.; Liu, Y.; Gong, X.; Zhang, T.; Sun, H. Widespread Occurrence of Bisphenol A in Daily Clothes and Its High Exposure Risk in Humans. *Environ. Sci. Technol.* **2019**, *53*, 7095–7102. [CrossRef] [PubMed]
5. Covaci, A.; Den Hond, E.; Geens, T.; Govarts, E.; Koppen, G.; Frederiksen, H.; Knudsen, L.E.; Morck, T.A.; Gutleb, A.C.; Guignard, C.; et al. Urinary BPA measurements in children and mothers from six European member states: Overall results and determinants of exposure. *Environ. Res.* **2015**, *141*, 77–85. [CrossRef]
6. Louro, H.; Heinala, M.; Bessems, J.; Buekers, J.; Vermeire, T.; Woutersen, M.; van Engelen, J.; Borges, T.; Rousselle, C.; Ougier, E.; et al. Human biomonitoring in health risk assessment in Europe: Current practices and recommendations for the future. *Int. J. Hyg. Environ. Health* **2019**, *222*, 727–737. [CrossRef] [PubMed]
7. Vandenberg, L.N.; Chahoud, I.; Heindel, J.J.; Padmanabhan, V.; Paumgartten, F.J.; Schoenfelder, G. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. *Environ. Health Perspect.* **2010**, *118*, 1055–1070. [CrossRef]
8. Lehmler, H.J.; Liu, B.; Gadogbe, M.; Bao, W. Exposure to Bisphenol A, Bisphenol F, and Bisphenol S in U.S. Adults and Children: The National Health and Nutrition Examination Survey 2013–2014. *ACS Omega* **2018**, *3*, 6523–6532. [CrossRef]

9. French Agency for Food, Environmental and Occupational Health and Safety (ANSES). Reprotoxic Substances and Endocrine Disruptors. Compounds of the Bisphenol Family: Bisphenols M, S, B, AP, AF, F and BADGE. Expert Committee Report. 2013. Available online: <https://www.anses.fr/fr/system/files/CHIM2009sa0331Ra-1.pdf> (accessed on 18 February 2020).
10. ANSES. Annex XV report. Proposal for identification of a substance of very high concern on the basis of the criteria set out in REACH Article 57. Substance Name(s): 4,4'-isopropylidenediphenol (Bisphenol A). EC Number: 201-245-8. CAS Number: 80-05-7. Available online: <https://echa.europa.eu/documents/10162/93bf4be3-9af6-d7ca-8b07-4e8fb42bad11> (accessed on 18 February 2020).
11. Environment Canada, Health Canada (ECHC). Screening Assessment for the Challenge Phenol, 4,4' -(1-Methylethylidene)bis-(Bisphenol A), Chemical Abstracts Service Registry Number 80-05-7. 2008. Available online: http://www.ec.gc.ca/ese-ees/3C756383-BEB3-45D5-B8D3-E8C800F35243/batch2_80-05-7_en.pdf (accessed on 18 February 2020).
12. European Chemicals Agency (ECHA). Opinion on an Annex XV Dossier Proposing Restrictions on Bisphenol, A. Compiled Version Prepared by the ECHA Secretariat of RAC's Opinion (Adopted 5 June 2015) and SEAC's Opinion (Adopted 4 December 2015). Available online: <https://echa.europa.eu/documents/10162/9ce0977b-3540-4de0-af6d-16ad6e78ff20> (accessed on 18 February 2020).
13. European Food Safety Authority (EFSA). Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. *EFSA J.* **2015**, *13*, 3978. [CrossRef]
14. EFSA; Croera, C.; Batke, M.; Corsini, E.; FitzGerald, R.E.; Gott, D.; Ntzani, E.; Gundert-Remy, U.; Halldorsson, T.; Schroeder, H.; et al. Testing the study appraisal methodology from the 2017 Bisphenol A (BPA) hazard assessment protocol. *EFSA Supporting Publ.* **2019**, *16*, 2397–8325. [CrossRef]
15. U.S. Food & Drug Administration (USFDA). Bisphenol A (BPA): Use in Food Contact Application. 2018. Available online: <https://www.fda.gov/food/food-additives-petitions/bisphenol-bpa-use-food-contact-application> (accessed on 18 February 2020).
16. U.S. National Toxicology Program (NTP). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. CERHR, Ed.; National Toxicology Program: Raleigh, NC, USA, 2020. Available online: <https://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf> (accessed on 18 February 2020).
17. Beausoleil, C.; Emond, C.; Cravedi, J.P.; Antignac, J.P.; Applanat, M.; Appenzeller, B.R.; Beaudouin, R.; Belzunces, L.P.; Canivenc-Lavier, M.C.; Chevalier, N.; et al. Regulatory identification of BPA as an endocrine disruptor: Context and methodology. *Mol. Cell. Endocrinol.* **2018**, *475*, 4–9. [CrossRef]
18. Seachrist, D.D.; Bonk, K.W.; Ho, S.M.; Prins, G.S.; Soto, A.M.; Keri, R.A. A review of the carcinogenic potential of bisphenol A. *Reprod. Toxicol.* **2016**, *59*, 167–182. [CrossRef]
19. Ejaredar, M.; Lee, Y.; Roberts, D.J.; Sauve, R.; Dewey, D. Bisphenol A exposure and children's behavior: A systematic review. *J. Expo. Sci. Environ. Epidemiol.* **2017**, *27*, 175–183. [CrossRef] [PubMed]
20. Rochester, J.R.; Bolden, A.L.; Kwiatkowski, C.F. Prenatal exposure to bisphenol A and hyperactivity in children: A systematic review and meta-analysis. *Environ. Int.* **2018**, *114*, 343–356. [CrossRef] [PubMed]
21. Kim, K.Y.; Lee, E.; Kim, Y. The Association between Bisphenol A Exposure and Obesity in Children—A Systematic Review with Meta-Analysis. *Int. J. Environ. Res. Public Health* **2019**, *16*, 2521. [CrossRef] [PubMed]
22. European Commission (EU). Bisphenol A: EU Ban on Baby Bottles to Enter into Force Tomorrow. 2011. Available online: https://ec.europa.eu/commission/presscorner/detail/en/IP_11_664 (accessed on 18 February 2020).
23. Pelch, K.; Wignall, J.A.; Goldstone, A.E.; Ross, P.K.; Blain, R.B.; Shapiro, A.J.; Holmgren, S.D.; Hsieh, J.H.; Svoboda, D.; Auerbach, S.S.; et al. A scoping review of the health and toxicological activity of bisphenol A (BPA) structural analogues and functional alternatives. *Toxicology* **2019**, *424*, 152235. [CrossRef]
24. Serra, H.; Beausoleil, C.; Habert, R.; Minier, C.; Picard-Hagen, N.; Michel, C. Evidence for Bisphenol B Endocrine Properties: Scientific and Regulatory Perspectives. *Environ. Health Perspect.* **2019**, *127*, 106001. [CrossRef]
25. Swedish Chemical Agency (KEMI). Bisfenoleren Kartläggning och Analys Rapport Från Ett Deluppdrag Inom Handlingsplanen för En Giftfri Vardag. 2017. Available online: <https://www.kemi.se/en/global/rapporter/2017/rapport-5-17-bisfenoler-en-kartlaggning-och-analys.pdf> (accessed on 18 February 2020).

26. Cesen, M.; Lenarcic, K.; Mislej, V.; Levstek, M.; Kovacic, A.; Cimrmancic, B.; Uranjek, N.; Kosjek, T.; Heath, D.; Dolenc, M.S.; et al. The occurrence and source identification of bisphenol compounds in wastewaters. *Sci. Total Environ.* **2018**, *616*, 744–752. [[CrossRef](#)]
27. Ijaz, S.; Ullah, A.; Shaheen, G.; Jahan, S. Exposure of BPA and its alternatives like BPB, BPF, and BPS impair subsequent reproductive potentials in adult female Sprague Dawley rats. *Toxicol. Mech. Methods* **2020**, *30*, 60–72. [[CrossRef](#)]
28. Chen, D.; Kannan, K.; Tan, H.; Zheng, Z.; Feng, Y.L.; Wu, Y.; Widelka, M. Bisphenol Analogues Other Than BPA: Environmental Occurrence, Human Exposure, and Toxicity—A Review. *Environ. Sci. Technol.* **2016**, *50*, 5438–5453. [[CrossRef](#)]
29. Bal'tser, A.E.; Zaitsev, D.A.; Zubritskaya, N.G.; Ivanova, T.V.; Babenko, T.G.; Barskova, E.N. Optimization of technological parameters of the process for obtaining bisphenols on cation-exchange catalyst in the presence of hydrogen sulfide. *Russ. J. App. Chem.* **2017**, *89*, 1421–1426. [[CrossRef](#)]
30. Naderi, M.; Wong, M.Y.; Gholami, F. Developmental exposure of zebrafish (*Danio rerio*) to bisphenol-S impairs subsequent reproduction potential and hormonal balance in adults. *Aquat. Toxicol.* **2014**, *148*, 195–203. [[CrossRef](#)] [[PubMed](#)]
31. Ji, K.; Hong, S.; Kho, Y.; Choi, K. Effects of bisphenol S exposure on endocrine functions and reproduction of zebrafish. *Environ. Sci. Technol.* **2013**, *47*, 8793–8800. [[CrossRef](#)] [[PubMed](#)]
32. Rosenmai, A.K.; Dybdahl, M.; Pedersen, M.; van Vugt-Lussenburg, B.M.A.; Wedebye, E.B.; Taxvig, C.; Vinggaard, A.M. Are structural analogues to bisphenol a safe alternatives? *Toxicol. Sci.* **2014**, *139*, 35–47. [[CrossRef](#)] [[PubMed](#)]
33. Usman, A.; Ahmad, M. From BPA to its analogues: Is it a safe journey? *Chemosphere* **2016**, *158*, 131–142. [[CrossRef](#)]
34. Andra, S.S.; Charisiadis, P.; Arora, M.; van Vliet-Ostaptchouk, J.V.; Makris, K.C. Biomonitoring of human exposures to chlorinated derivatives and structural analogs of bisphenol A. *Environ. Int.* **2015**, *85*, 352–379. [[CrossRef](#)]
35. Macczak, A.; Cyrkler, M.; Bukowska, B.; Michalowicz, J. Bisphenol A, bisphenol S, bisphenol F and bisphenol AF induce different oxidative stress and damage in human red blood cells (in vitro study). *Toxicol. In Vitro* **2017**, *41*, 143–149. [[CrossRef](#)]
36. Ding, Z.M.; Jiao, X.F.; Wu, D.; Zhang, J.Y.; Chen, F.; Wang, Y.S.; Huang, C.J.; Zhang, S.X.; Li, X.; Huo, L.J. Bisphenol AF negatively affects oocyte maturation of mouse in vitro through increasing oxidative stress and DNA damage. *Chem. Biol. Interact.* **2017**, *278*, 222–229. [[CrossRef](#)]
37. DeFoor, W.; Asplin, J.; Jackson, E.; Jackson, C.; Reddy, P.; Sheldon, C.; Erhard, M.; Minevich, E. Urinary metabolic evaluations in normal and stone forming children. *J. Urol.* **2006**, *176*, 1793–1796. [[CrossRef](#)]
38. Rochester, J.R.; Bolden, A.L. Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. *Environ. Health Perspect.* **2015**, *123*, 643–650. [[CrossRef](#)]
39. Kitamura, S.; Suzuki, T.; Sanoh, S.; Kohta, R.; Jinno, N.; Sugihara, K.; Yoshihara, S.; Fujimoto, N.; Watanabe, H.; Ohta, S. Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds. *Toxicol. Sci.* **2005**, *84*, 249–259. [[CrossRef](#)]
40. Molina-Molina, J.M.; Amaya, E.; Grimaldi, M.; Saenz, J.M.; Real, M.; Fernandez, M.F.; Balaguer, P.; Olea, N. 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.* **2013**, *272*, 127–136. [[CrossRef](#)] [[PubMed](#)]
41. Kang, J.S.; Choi, J.S.; Kim, W.K.; Lee, Y.J.; Park, J.W. Estrogenic potency of bisphenol S, polyethersulfone and their metabolites generated by the rat liver S9 fractions on a MVLN cell using a luciferase reporter gene assay. *Reprod. Biol. Endocrinol.* **2014**, *12*, 102. [[CrossRef](#)] [[PubMed](#)]
42. Wang, Y.Q.; Zhang, H.M.; Cao, J.; Tang, B.P. Binding of a new bisphenol analogue, bisphenol S to bovine serum albumin and calf thymus DNA. *J. Photochem. Photobiol. B* **2014**, *138*, 182–190. [[CrossRef](#)] [[PubMed](#)]
43. Audebert, M.; Dolo, L.; Perdu, E.; Cravedi, J.P.; Zalko, D. Use of the gammaH2AX assay for assessing the genotoxicity of bisphenol A and bisphenol F in human cell lines. *Arch. Toxicol.* **2011**, *85*, 1463–1473. [[CrossRef](#)] [[PubMed](#)]

44. Ma, Y.; Liu, H.; Wu, J.; Yuan, L.; Wang, Y.; Du, X.; Wang, R.; Marwa, P.W.; Petlulu, P.; Chen, X.; et al. The adverse health effects of bisphenol A and related toxicity mechanisms. *Environ. Res.* **2019**, *176*, 108575. [[CrossRef](#)] [[PubMed](#)]
45. Wong, K.H.; Durrani, T.S. Exposures to Endocrine Disrupting Chemicals in Consumer Products—A Guide for Pediatricians. *Curr. Probl. Pediatr. Adolesc. Health Care* **2017**, *47*, 107–118. [[CrossRef](#)]
46. Wang, H.; Liu, L.; Wang, J.; Tong, Z.; Yan, J.; Zhang, T.; Qin, Y.; Jiang, T.; She, J.; Shen, H. Urinary sexual steroids associated with bisphenol A (BPA) exposure in the early infant stage: Preliminary results from a Daishan birth cohort. *Sci. Total Environ.* **2017**, *601*, 1733–1742. [[CrossRef](#)]
47. Andaluri, G.; Manickavachagam, M.; Suri, R. Plastic toys as a source of exposure to bisphenol-A and phthalates at childcare facilities. *Environ. Monit. Assess.* **2018**, *190*, 65. [[CrossRef](#)]
48. Gonzalez, N.; Cunha, S.C.; Monteiro, C.; Fernandes, J.O.; Marques, M.; Domingo, J.L.; Nadal, M. Quantification of eight bisphenol analogues in blood and urine samples of workers in a hazardous waste incinerator. *Environ. Res.* **2019**, *176*, 108576. [[CrossRef](#)]
49. Owczarek, K.; Kubica, P.; Kudlak, B.; Rutkowska, A.; Konieczna, A.; Rachon, D.; Namiesnik, J.; Wasik, A. Determination of trace levels of eleven bisphenol A analogues in human blood serum by high performance liquid chromatography-tandem mass spectrometry. *Sci. Total Environ.* **2018**, *628*, 1362–1368. [[CrossRef](#)]
50. Rocha, B.A.; Asimakopoulos, A.G.; Honda, M.; da Costa, N.L.; Barbosa, R.M.; Barbosa, F., Jr.; Kannan, K. Advanced data mining approaches in the assessment of urinary concentrations of bisphenols, chlorophenols, parabens and benzophenones in Brazilian children and their association to DNA damage. *Environ. Int.* **2018**, *116*, 269–277. [[CrossRef](#)] [[PubMed](#)]
51. Asimakopoulos, A.G.; Xue, J.; De Carvalho, B.P.; Iyer, A.; Abualnaja, K.O.; Yaghmoor, S.S.; Kumosani, T.A.; Kannan, K. Urinary biomarkers of exposure to 57 xenobiotics and its association with oxidative stress in a population in Jeddah, Saudi Arabia. *Environ. Res.* **2016**, *150*, 573–581. [[CrossRef](#)] [[PubMed](#)]
52. Calafat, A.M.; Ye, X.; Valentin-Blasini, L.; Li, Z.; Mortensen, M.E.; Wong, L.Y. Co-exposure to non-persistent organic chemicals among American pre-school aged children: A pilot study. *Int. J. Hyg. Environ. Health* **2017**, *220*, 55–63. [[CrossRef](#)]
53. Xue, J.; Wu, Q.; Sakthivel, S.; Pavithran, P.V.; Vasukutty, J.R.; Kannan, K. Urinary levels of endocrine-disrupting chemicals, including bisphenols, bisphenol A diglycidyl ethers, benzophenones, parabens, and triclosan in obese and non-obese Indian children. *Environ. Res.* **2015**, *137*, 120–128. [[CrossRef](#)] [[PubMed](#)]
54. Calafat, A.M.; Ye, X.; Silva, M.J.; Kuklenyik, Z.; Needham, L.L. Human exposure assessment to environmental chemicals using biomonitoring. *Int. J. Androl.* **2006**, *29*, 166–171, discussion 181–165. [[CrossRef](#)]
55. Environmental Protection Agency (EPA). Exposure Factors Handbook 2011 Edition (Final Report). National Center for Environmental Assessment, Washington, DC.; EPA/600/R-09/052F. 2011. Available online: <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252> (accessed on 22 June 2020).
56. Cohen Hubal, E.A.; de Wet, T.; Du Toit, L.; Firestone, M.P.; Ruchirawat, M.; van Engelen, J.; Vickers, C. Identifying important life stages for monitoring and assessing risks from exposures to environmental contaminants: Results of a World Health Organization review. *Regul. Toxicol. Pharmacol.* **2014**, *69*, 113–124. [[CrossRef](#)]
57. Liu, L.; Xia, T.; Zhang, X.; Barr, D.B.; Alamdar, A.; Zhang, J.; Tian, M.; Huang, Q.; Shen, H. Biomonitoring of infant exposure to phenolic endocrine disruptors using urine expressed from disposable gel diapers. *Anal. Bioanal. Chem.* **2014**, *406*, 5049–5054. [[CrossRef](#)]
58. Hu, Y.; Beach, J.; Raymer, J.; Gardner, M. Disposable diaper to collect urine samples from young children for pyrethroid pesticide studies. *J. Expo. Anal. Environ. Epidemiol.* **2004**, *14*, 378–384. [[CrossRef](#)]
59. Liu, L.; Xia, T.; Guo, L.; Cao, L.; Zhao, B.; Zhang, J.; Dong, S.; Shen, H. Expressing urine from a gel disposable diaper for biomonitoring using phthalates as an example. *J. Expo. Sci. Environ. Epidemiol.* **2012**, *22*, 625–631. [[CrossRef](#)]
60. Lock, J.Y.; Wyatt, E.; Upadhyayula, S.; Whall, A.; Nuñez, V.; Vullev, V.I.; Liu, H. Degradation and antibacterial properties of magnesium alloys in artificial urine for potential resorbable ureteral stent applications. *J. Biomed. Mater. Res. A* **2014**, *102*, 781–792. [[CrossRef](#)]

61. Volkel, W.; Colnot, T.; Csanady, G.A.; Filser, J.G.; Dekant, W. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. *Chem. Res. Toxicol.* **2002**, *15*, 1281–1287. [CrossRef] [PubMed]
62. Yao, J.; Gao, M.; Guo, X.; Ai, F.; Wang, Z. Enhanced degradation performance of bisphenol M using peroxymonosulfate activated by zero-valent iron in aqueous solution: Kinetic study and product identification. *Chemosphere* **2019**, *221*, 314–323. [CrossRef] [PubMed]
63. Deceuninck, Y.; Bichon, E.; Marchand, P.; Boquien, C.Y.; Legrand, A.; Boscher, C.; Antignac, J.P.; Le Bizec, B. Determination of bisphenol A and related substitutes/analogues in human breast milk using gas chromatography-tandem mass spectrometry. *Anal. Bioanal. Chem.* **2015**, *407*, 2485–2497. [CrossRef] [PubMed]
64. Myridakis, A.; Fthenou, E.; Balaska, E.; Vakinti, M.; Kogevinas, M.; Stephanou, E.G. Phthalate esters, parabens and bisphenol-A exposure among mothers and their children in Greece (Rhea cohort). *Environ. Int.* **2015**, *83*, 1–10. [CrossRef]
65. 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.; et al. Dietary and sociodemographic determinants of bisphenol A urine concentrations in pregnant women and children. *Environ. Int.* **2013**, *56*, 10–18. [CrossRef]
66. Becker, K.; Goen, T.; Seiwert, M.; Conrad, A.; Pick-Fuss, H.; Muller, J.; Wittassek, M.; Schulz, C.; Kolossa-Gehring, M. GerES IV: Phthalate metabolites and bisphenol A in urine of German children. *Int. J. Hyg. Environ. Health* **2009**, *212*, 685–692. [CrossRef] [PubMed]
67. Geens, T.; Aerts, D.; Berthot, C.; Bourguignon, J.P.; Goeyens, L.; Lecomte, P.; Maghuin-Rogister, G.; Pironnet, A.M.; Pussemier, L.; Scippo, M.L.; et al. A review of dietary and non-dietary exposure to bisphenol-A. *Food Chem. Toxicol.* **2012**, *50*, 3725–3740. [CrossRef]
68. National Toxicology Program (NTP). Research Concept: Bisphenol AF. 2008. Available online: https://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/bisphenolaf_093008_508.pdf (accessed on 18 February 2020).
69. Song, S.; Ruan, T.; Wang, T.; Liu, R.; Jiang, G. Distribution and preliminary exposure assessment of bisphenol AF (BPAF) in various environmental matrices around a manufacturing plant in China. *Environ. Sci. Technol.* **2012**, *46*, 13136–13143. [CrossRef]
70. Yang, Y.; Lu, L.; Zhang, J.; Yang, Y.; Wu, Y.; Shao, B. Simultaneous determination of seven bisphenols in environmental water and solid samples by liquid chromatography-electrospray tandem mass spectrometry. *J. Chromatogr. A* **2014**, *1328*, 26–34. [CrossRef]
71. Song, S.; Song, M.; Zeng, L.; Wang, T.; Liu, R.; Ruan, T.; Jiang, G. Occurrence and profiles of bisphenol analogues in municipal sewage sludge in China. *Environ. Pollut.* **2014**, *186*, 14–19. [CrossRef]
72. Yang, Y.; Guan, J.; Yin, J.; Shao, B.; Li, H. Urinary levels of bisphenol analogues in residents living near a manufacturing plant in south China. *Chemosphere* **2014**, *112*, 481–486. [CrossRef] [PubMed]
73. Hendryx, M.; Luo, J. Children’s environmental chemical exposures in the USA, NHANES 2003–2012. *Environ. Sci. Pollut. Res. Int.* **2018**, *25*, 5336–5343. [CrossRef]
74. FitzGerald, R.E.; Wilks, M.F. Bisphenol A-Why an adverse outcome pathway framework needs to be applied. *Toxicol. Lett.* **2014**, *230*, 368–374. [CrossRef] [PubMed]
75. Birnbaum, L.S.; Bucher, J.R.; Collman, G.W.; Zeldin, D.C.; Johnson, A.F.; Schug, T.T.; Heindel, J.J. Consortium-based science: The NIEHS’s multipronged, collaborative approach to assessing the health effects of bisphenol A. *Environ. Health Perspect.* **2012**, *120*, 1640–1644. [CrossRef]
76. Schug, T.T.; Heindel, J.J.; Camacho, L.; Delclos, K.B.; Howard, P.; Johnson, A.F.; Aungst, J.; Keefe, D.; Newbold, R.; Walker, N.J.; et al. A new approach to synergize academic and guideline-compliant research: The CLARITY-BPA research program. *Reprod. Toxicol.* **2013**, *40*, 35–40. [CrossRef] [PubMed]
77. NTP. Draft NTP Research Report on the CLARITY-BPA Core Study: A Perinatal and Chronic Extended-Dose-Range Study of Bisphenol A in Rats. NTP Research Report 9, 1–249. 2018. Available online: https://ntp.niehs.nih.gov/ntp/about_ntp/rrprp/2018/april/rr09peerdraft.pdf (accessed on 20 February 2020).
78. Carvaille, J.C.; Barouki, R.; Coumoul, X.; Audouze, K. Linking Bisphenol S to Adverse Outcome Pathways Using a Combined Text Mining and Systems Biology Approach. *Environ. Health Perspect.* **2019**, *127*, 47005. [CrossRef] [PubMed]

79. Rugard, M.; Coumoul, X.; Carvaillo, J.C.; Barouki, R.; Audouze, K. Deciphering Adverse Outcome Pathway Network Linked to Bisphenol F Using Text Mining and Systems Toxicology Approaches. *Toxicol. Sci.* **2020**, *173*, 32–40. [[CrossRef](#)]
80. Teeguarden, J.G.; Tan, Y.M.; Edwards, S.W.; Leonard, J.A.; Anderson, K.A.; Corley, R.A.; Kile, M.L.; Simonich, S.M.; Stone, D.; Tanguay, R.L.; et al. Completing the Link between Exposure Science and Toxicology for Improved Environmental Health Decision Making: The Aggregate Exposure Pathway Framework. *Environ. Sci. Technol.* **2016**, *50*, 4579–4586. [[CrossRef](#)]
81. Tan, Y.M.; Leonard, J.A.; Edwards, S.; Teeguarden, J.; Paini, A.; Egeghy, P. Aggregate Exposure Pathways in Support of Risk Assessment. *Curr. Opin. Toxicol.* **2018**, *9*, 8–13. [[CrossRef](#)]
82. Aylward, L.L. Integration of biomonitoring data into risk assessment. *Curr. Opin. Toxicol.* **2018**, *9*, 14–20. [[CrossRef](#)]
83. Ye, X.; Wong, L.Y.; Bishop, A.M.; Calafat, A.M. Variability of urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour collections. *Environ. Health Perspect.* **2011**, *119*, 983–988. [[CrossRef](#)] [[PubMed](#)]
84. Federal Department of Home Affairs (FDHA). Human Biomonitoring in Switzerland. Report of the Federal Council from November 18, 2009 on Human Biomonitoring in Switzerland in Response to the Moser Postulate 08.3223 on the Implementation of a Body Burden Analysis to Chemical Substances. 2009. Available online: <https://www.bag.admin.ch/dam/bag/en/dokumente/chem/chemikalien-alltag/bundesratsbericht-von-2009-zum-human-biomonitoring.pdf> (accessed on 20 February 2020).
85. FDHA. Human Biomonitoring in Switzerland. Current Situation and Long-Term Prospects. Interim Report. [In German]. Available online: <https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und-gesundheit/chemikalien/chemikalien-im-alltag/human-biomonitoring/human-biomonitoring-projekte-in-der-schweiz.html> (accessed on 20 February 2020).



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).