Exposure assessment to parabens, bisphenol A and perfluoroalkyl compounds in children, women and men by hair analysis

Julia Martín*, Juan Luis Santos, Irene Aparicio, Esteban Alonso

Corresponding author: Julia Martín

Address: Departmento de Química Analítica, Escuela Politécnica Superior, Universidad de Sevilla, C/ Virgen de África, 7, E–41011 Sevilla, Spain

E-mail: jbueno@us.es

Phone-number: +34-9-5455-6250

ABSTRACT: Population is continuously exposed to endocrine disrupting compounds present in everyday products such as parabens, bisphenol A (BPA), and perfluoroalkyl compounds (PFCs). The aims of this study were, first, to evaluate human exposure to three parabens (methylparaben (MeP), ethylparaben (EtP) and propylparaben (PrP)), BPA and six PFCs (perfluorobutanoic acid, perfluoropentanoic acid, perfluorohexanoic acid, perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) through the analysis of hair samples from children, women and men and, then, to evaluate possible relationships between pollutant concentration in hair and age, gender, smoking and dyeing habits or hair colour. Hair samples were collected from 42 volunteers from Seville (Spain) (10 children, 16 women and 16 men). Six of the monitored pollutants (MeP, EtP, PrP, BPA, PFHpA and PFOS) were detected in at least 76% of the samples analysed. The highest concentrations and frequency of detection (100% of the samples) corresponded to MeP and PrP (up to 14187 and 9009 ng/g, respectively). BPA was found in 83% of the samples at concentrations in the range from 24 to 1427 ng/g whereas PFCs were detected at concentrations in the range from 0.6 to 15.5 ng/g, being PFHpA and PFOS the ones most frequently detected (86% and 76%, respectively). Concentrations of BPA and parabens in adults were statistically higher than those in children. The results of this study reveal the suitability of hair for biomonitoring endocrine disrupting compounds of high concern (PFCs, parabens and BPA) to which population is internally or/and externally but continuously exposed.

Keywords: Endocrine disrupting compounds; Parabens; Bisphenol A; Perfluoroalkyl compounds; Hair analysis; Human biomonitoring

1. Introduction

In the last years, there has been an increasing concern about certain chemicals present in everyday products that are suspected to involve human health risks (Alves et al., 2014; Calafat et al., 2015). Endocrine disrupting chemicals (EDCs) such as bisphenol A (BPA), parabens, perfluoroalkyl compounds (PFCs), phthalates and triclosan (Gore et al., 2019; Katsikantami et al., 2016; Álvarez-Muñoz et al., 2018; Karzi et al., 2018a;2018b) are widely used in a variety of products including food packaging and processing materials, consumer goods, and personal care products such as cosmetics, soaps and fragrances. The main exposure routes to these pollutants are ingestion, inhalation and dermal contact but also perinatal transmission through placenta and breast milk, in the case of foetuses, newborns and babies. Nevertheless, exposition routes are conditioned not only by the commercial applications of the contaminant but also by its physical-chemical properties (Alves et al., 2014, Heffernan et al., 2015; EFSA 2015; Pahigian et al., 2018).

BPA is extensively used in the production of epoxy resins and polycarbonate plastics used in digital media, electronic equipment, medical devices, dental fillings, thermal receipts, water pipes and toys (Dekant and Völkel, 2008; Halden, 2010; Tzatzarakis et al., 2015). Humans can be exposed to BPA not only through the use of materials containing BPA but also via food contaminated with BPA and/or derivatives through plastic packaging materials (Tzatzarakis et al., 2017). In this regard, in 2011, the Commission Regulation (EU) No 10/2011 (EU, 2011a), on plastic materials and articles intended to come into contact with food, fixed a migration limit of 0.6 mg kg^{-1} for BPA in food contact materials whereas the Commission Directive 2011/8/EU banned its use in plastic infant feeding bottles (EU, 2011b). Epidemiological studies have associated high urinary concentrations of BPA in adults and children with obesity and larger waist

circumference (Nicolucci et al., 2013; Wong and Durrani, 2017). Parabens are added as antimicrobial preservatives to a wide variety of products especially personal care products such as shampoo, creams, deodorants, hairspray and other cosmetics. They can also be present in machine wash liquids/detergents, automotive care products, paints and coating or adhesives, fragrances and air fresheners (ECHA, 2019). Therefore, the main exposure route to parabens is dermal contact but also ingestion and inhalation (ECHA, 2019). In the European Union, paraben concentration in cosmetics has been limited to 0.8 % (w/w) for paraben mixtures and 0.4 % (w/w) for individual compounds (European Union Regulation No. 1223/2009).

Methylparaben (MeP), ethylparaben (EtP) and propylparaben (PrP) are the parabens most frequently used in cosmetics and food processing (Jiménes-Díaz et al., 2011; Jackson, 1996) and the ones reported at the highest concentration levels in other biological matrices (Raza et al., 2018; Jiménez-Díaz et al., 2014). PFCs are water, oil and dirt repellents used in stain- and water-resistant coatings (carpets, clothing and frying pan), in firefighting foams, in lubricants and paints, in food packaging and in waxes and cleaners (Fromme et al., 2009; EPA, 2019). They are persistent and highly bioaccumulative. PFCs have even been detected in drinking water to the point that in February 2019, the United States Environmental Protection Agency has announced a per- and polyfluoroalkyl substances action plan to protect public health from the presence of these pollutants in drinking water (EPA, 2019). Exposure routes to PFCs are inhalation (indoor air and dust) and ingestion of food, especially fish, eggs and meat products, and drinking water, especially well water and tap water (Jian et al., 2017).

Biomonitoring in humans is commonly carried out through blood analysis (Angerer et al., 2006, 2007) but, in the last years, special attention has been focused on non-invasive matrices such as saliva, hair and nails, as alternatives to blood, since they offer

advantages with respect to sampling, handling, and ethical aspects, while ensuring similar reliability and sensitivity (Schramm, 2008; Appenzeller et al., 2012; Król et al., 2013; Alves et al., 2014). Among them, hair is considered a promising biomarker for biomonitoring of chemicals (Appenzeller et al., 2012) that present advantages such as easy sampling, transport and storage and can provide information on short to long-term exposure (from weeks to months or even years, depending on hair length) Moreover, hair biomonitoring is suitable for adults but also for children, babies, elderly and/or sick people. Hair analysis has allowed to assess past acute exposure to organophosphate pesticides by hair segmental analysis (Tsatsakis et al., 2012) and to provide information about "endogenous exposition" (sorption of the pollutants from blood) and "exogenous exposition" (sorption or deposition of the pollutants from the atmosphere) (Zhang et al., 2007). Therefore, biomonitoring in hair samples provides information about integral exposition to pollutants including inhalation from atmospheric pollution.

Nowadays, hair analysis is used in forensic and clinical analysis for the detection of drugs of abuse, pharmaceuticals and inorganic compounds but its application to other organic pollutants has been scarcely evaluated and limited to a few groups of pollutants such as pesticides, polybrominated diphenyl ethers, polycyclic aromatic hydrocarbons, dioxins and polychlorinated biphenyls (Appenzeller et al., 2012).

Therefore, the aim of this work was to evaluate the suitability of estimating the burden to parabens, BPA and PFCs through the analysis of hair samples from children and adults and to evaluate the existence of relationships between biomonitoring data and age, gender, smoking habits and hair colour or dyeing habits. Target pollutants monitored were three parabens (MeP, EtP and PrP), BPA and six PFCs (perfluorobutanoic acid, perfluoropentanoic acid, perfluorohexanoic acid, perfluoroheptanoic acid (PFHpA), perfluoroctanoic acid (PFOA) and

perfluorooctanesulfonic acid (PFOS). Analytical determination was carried out by a previous reported method (Martín et al., 2016). Concentrations found in hair samples have been compared to those reported in other biological matrices. To our knowledge, this is the first simultaneous biomonitoring study of parabens, BPA and PFCs in human hair.

2. Experimental

2.1. Chemicals and reagents

HPLC-grade acetone, methanol and water were supplied by Romil (Barcelona, Spain). Analytical-grade acetic acid (HAc) (>99%), ammonium acetate and sodium dodecylsulfate (SDS) were obtained from Panreac (Barcelona, Spain). High purity standards of MeP, EtP, PrP, BPA, perfluorobutanoic acid (PFBuA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), PFOA, PFOS and propyl 4-hydroxybenzoate-$^{13}C_6$ (PrP-$^{13}C_6$) (≥99%) were supplied from Sigma-Aldrich (Steinheim, Germany). Bisphenol A-d_{14} (BPA-d_{14}) (99.5%) was obtained from Dr. Ehrenstorfer (Augsburg, Germany). Perfluorooctanoic acid-$^{13}C_8$ (PFOA-$^{13}C_8$) (99%) was supplied by Cambridge Isotope Laboratories (MA, USA). PrP-$^{13}C_6$, BPA-d_{14} and PFOA-$^{13}C_8$ were used as internal standards (I.S.). Individual stock standard solutions were prepared at 1000 mg/L in MeOH and stored at -18 ºC. Working solutions were prepared by dilution of the stock standard solutions in methanol.

2.2. Hair collection and pretreatment

Hair samples were collected from 42 volunteers (10 children, 16 women and 16 men) of general population from Seville, Spain. Detailed information of the volunteers (age, gender, hair colour and colouring, smoking habit and profession) is given in

Supplementary data (Table S1). Hair was cut on the posterior vertex as close to the scalp as possible and wrapped in aluminium foil. Samples were stored in the dark at room temperature until analysis. Paper and plastic containers were avoided to prevent sample pollution. Hair samples were washed first with ultrapure water, then with SDS (0.1%, w/v), and finally twice again with ultrapure water to remove endogenous substances and chemicals adsorbed on hair surface. In each washing step, sonication for 5 min was applied. After that, hair samples were cut in small pieces (2-3 mm), dried at room temperature and, when necessary, wrapped in aluminium foil and stored in the dark at room temperature until analysis.

2.3. Hair treatment and LC-MS/MS analysis

Target compounds were extracted and analysed by a previously reported method (Martín et al., 2016). Washed hair samples (100 mg) were transferred into 10 mL screw-cap glass centrifuge tubes and spiked with 50 ng of each I.S. Then, samples were incubated with 2 mL of MeOH/HAc (85:15, v/v), at 38 °C overnight, to improve the release of the target compounds from hair matrix. After incubation, samples were cooled to room temperature and sonicated for 15 min after addition of acetone (3 mL). The tubes were centrifuged at 2900 g for 10 min and the supernatants were transferred to clean tubes and evaporated to dryness under a nitrogen stream. Extracts were reconstituted in 500 µL of methanol and transferred to automatic LC injector vials. Aliquots of 10 µL were injected into the LC-MS/MS system.

Analytical determination was performed on a 1200 Series LC system (Agilent, USA) coupled to a 6410 Agilent triple quadrupole (QqQ) mass spectrometer (MS). Chromatographic separation was carried out on an Agilent Zorbax Eclipse XDB–C18 Rapid Resolution HT (50 mm × 4.6 mm i.d.; 1.8 µm particle size) column. An

175 electrospray ionization source operating in negative-ion mode was used. MS parameters
176 were as follows: capillary voltage, 3,000 V; drying gas flow rate, 9 L min^{-1}; drying gas
177 temperature, 350 °C; and nebulizer pressure, 40 psi. Instrument control and data
178 acquisition were carried out with MassHunter software (Agilent, USA). Separation was
179 performed by gradient elution with methanol (solvent A) and 5 mM ammonium acetate
180 aqueous solution (solvent B) at a flow rate of 0.6 mL min^{-1} with the column
181 thermostated at 25 °C. The elution program was as follows: 0–20 min, linear gradient
182 from 28 to 95% of solvent A, held for 2 min. In Tables S2 and S3 in Supplementary
183 material, MS/MS settings and validation parameters, respectively, are summarized.
184 More information can be found in a previous reported method (Martín et al., 2016)
185
186 *2.4. Quality assurance and quality control*
187 For each batch of 20 samples analysed (within one day), procedural blank, blank
188 samples spiked at 50, 200 and 500 ng/g for parabens and BPA and at 5, 20 and 50 ng/g
189 for PFCs and a standard solution containing a mixture of the target compounds at 100
190 ng mL^{-1} were processed and injected. The concentrations of all target chemicals in
191 procedural blanks were below the limits of quantitation (LOQs).
192
193 ## 3. Results and discussion
194 *3.1. Parabens, BPA and PFCs distribution in hair samples*
195 In Table 1 can be seen the range of concentrations of each target compound and their
196 arithmetic and geometric means and median values. Individual concentrations are
197 shown in Table S1.
198 MeP, PrP and BPA were the compounds at the highest concentration levels (median
199 concentrations: 822, 256 and 195 ng/g, respectively) and the ones, in addition to PFHpA

200 and PFOS, most frequently detected (frequency of detection from 76 to 100% of the
201 analysed samples) (Table 1). The distribution pattern of parabens in the analysed hair
202 samples was as follow: MeP (mean 2821 ng/g, median 822 ng/g) > PrP (mean 1006
203 ng/g, median 256 ng/g) > EtP (mean 635 ng/g, median 47.2 ng/g), which is consistent
204 with the wide usage and long-term accumulation of these compounds and with the fact
205 that MeP and PrP are the most commonly used parabens in cosmetics and food
206 processing (Jimenez Díaz et al., 2011; Elder, 1984)). There was also observed
207 correlation between MeP (neperian logarithm (Ln) MeP) and PrP (Ln PrP)
208 concentrations (r^2 = 0.54; $p < 0.05$) (Figure 1). This correlation can be explained by
209 their combined use in commercial formulations due to their synergistic effect. Their
210 concentrations have also been reported to be correlated in other samples such as
211 foodstuffs (Liao et al., 2013), dust (Wang et al., 2012) and in urine samples
212 (Asimakopolus et al., 2014). BPA was detected in 83 % of the analysed samples at
213 concentrations in the range from 24 to 1427 ng/g (mean value: 334 ng/g). Although
214 concentration levels of PFCs were lower (mean value: 2.0-8.9 ng/g) than those of
215 parabens (mean: 635-2821 ng/g) and BPA (mean: 334 ng/g), hair biomonitoring
216 revealed human exposure to these EDCs. At least one PFC was detected in each of the
217 42 hair samples analysed. The most frequently detected PFCs were those with the
218 longest alkyl chain: PFHpA, PFOA and PFOS (frequencies of detection: 86%, 57% and
219 76%, respectively). Correlation between the concentrations of PFOA and PFOS was
220 observed (r^2 = 0.50; $p < 0.05$) as can be seen in Figure 1. Perfluoroalkyl acids of short
221 chain (PFBuA, PFPeA and PFHxA) were less frequently detected than those of longer
222 chain but, when detected, they were present at higher concentrations than those of
223 longer chain. A similar behaviour was reported ~~for~~ by Pérez et al. (2012); Alves et al.

224 (2015) and Li et al. (2012 and 2013) in hair samples from the general population in
225 Spain, Belgium and China, respectively.
226
227 *3.2. Influence of age, gender, smoking habits and hair colour or dyeing habits*
228 Figure 2 shows box-and-whisker plots of the distribution levels of selected EDCs in
229 children, women and men hair samples. Lines in each box correspond to the lower
230 (≤5%), median (≤50%) and upper percentile (≤95%). The point inside each box shows
231 the average concentration. The highest and lowest concentrations are represented by the
232 lines extending from each end of the box. Student's *t*-test demonstrated that
233 concentration levels of parabens and BPA in adults and children were significantly
234 higher in adults than in children (t_{cal} = 2.510; 2.311; 2.432; 2.086 and t_{tab} = 2.024;
235 2.040; 2.030; 2.040; $p < 0.05$ for MeP, EtP, PrP and BPA, respectively). A similar
236 distribution pattern was reported in urine samples from mothers (MeP 37.8 ng/mL; PrP
237 13.9 ng/mL) and their children (MeP 6.8 ng/mL; PrP 2.1 ng/mL) (Larsson et al., 2014),
238 but the concentrations in urine from younger children (6–8 years) and older mothers
239 (>41 years) were higher than in urine from older children (9–11 years) and youngest
240 mothers (<37 years) (Larsson et al., 2014). This fact can be due to a higher use of
241 personal care products by younger children and older mothers.
242 Higher levels of MeP and PrP were especially associated to the use of make-up, creams
243 and mouthwash. Levels of EtP were higher in mothers using sunscreen more frequently.
244 Similar trends were also observed by Ashrap et al. (2018) for parabens in urine samples,
245 while BPA concentration had a decreasing trend with increasing age.
246 Gender differences were also found for parabens. The sum of paraben concentrations
247 were higher in woman hair (mean sum: 5725 ng/g) than in man hair (sum mean 4296
248 ng/g) what can be explained by a higher use of personal care products by women in

249 which parabens are used as antimicrobial preservatives (Asimakopoulos et al., 2014;
250 Fisher et al., 2017; Nassan et al., 2017; Ashrap et al., 2018). No gender difference was
251 observed for BPA and PFCs. BPA concentration in male (mean 473 ng/g) and female
252 (297 ng/g) were statistically similar (Student's *t* test: $t_{cal} = 1.141$, $t_{tab} = 2.186$; $p < 0.05$).
253 The same behaviour was reported by other authors in urine (Kim et al., 2011) and breast
254 milk (Dualde et al., 2019) samples. Kim et al. (2011) reported no BPA difference due to
255 sex and socio-demographic factors such as income or smoking habits. In addition,
256 Dualde et al. (2019) did not found relation between BPA concentrations in breast milk
257 and anthropometric variables such as height, weight or gestational age, but found
258 relations with sociodemographic variables like the place of residence. In any case, data
259 in the literature about gender-dependent differences are contradictory. Calafat et al.
260 (2008) reported different BPA urine concentrations in females-males, children-
261 adolescents-adults from U.S. population whereas Karzi et al. (2018a) reported
262 differences in hair samples in Greek adults and children and sex differences in children
263 but not in adults what could be due to different consumption patterns in each country.
264 Based on a self-reported questionnaire data, 23 % of the volunteers in this study had
265 smoking habits. A biomonitoring study of BPA in blood and urine from Chinese
266 workers and their children (He et al., 2009) revealed that BPA levels were influenced by
267 gender and smoking habits. Nevertheless, no significant difference was observed
268 between concentrations of the target pollutants in hair from smokers and non-smokers
269 (Figure 3).
270 The influence of hair pigmentation and dyeing habits have also been evaluated on
271 pollutant concentration in hair because it has been described that melanine content can
272 affect affinity of pollutants to hair structure (Appenzeller et al., 2012). On the one hand,
273 no significant difference depending on melanine content was observed (see Figure S1 in

supplementary material). On the other hand, higher concentrations of MeP and PrP were found in dyed hair: 4387 and 1614 ng/g, respectively, versus 2194 and 816 ng/g, respectively, in non-dyed hair (Fig. 4). Nevertheless, these differences were not statistically significative (MeP: t_{cal}=1.017 and t_{tab}=2.160; PrP: t_{cal}=0.845 and t_{tab}=2.262). Similar results were obtained in a preliminary study from Sako et al. (2015). Adsorption of parabens by hair was as follow MeP>EtP>PrP>BuP. Their results indicated that adsorption of MeP is higher than that of the other parabens and that dyed hairs have higher capacity for paraben adsorption than natural hairs.

3.3. Comparison between biomonitoring of parabens, BPA and PFCs in hair samples and in other biological matrices

In Table 2 is shown an overview of biomonitoring studies of parabens, BPA and PFCs in several biological matrices. Urine is the matrix most commonly used for biomonitoring of the target compounds although serum and hair can reveal associations that cannot be obtained from urine analysis (Karzi et al., 2018a). Parabens and BPA have been biomonitored in breast milk, placental tissue, serum, urine and hair samples whereas PFCs have been biomonitored in breast milk, nails, serum, urine and hair. No study involving simultaneous biomonitoring of BPA, parabens and PFCs in biological matrices has been found in literature.

Parabens

The highest concentrations and variability from one individual to another was reported for parabens. These facts can be explained by the internal and external exposition to these compounds through the use of personal care products and to the differences in personal care products consumption from one individual to another. Hines et al. (Hines et al., 2015) reported that urine was most suitable than breast milk and serum for

299 biomonitoring of parabens. In Table 2, can be seen that the highest concentrations of
300 parabens were reported in both urine and hair matrices. Moreover, distribution pattern
301 of parabens (MeP>PrP>EtP) in this study is consistent with that reported in other
302 biological matrices such as urine (Ashrap et al., 2018; Ferguson et al., 2018;
303 Asimakopolus et al., 2014, Casas et al., 2011), serum and placental tissue (Jiménes-Díaz
304 et al., 2011) and with their use as preservatives in personal care products. Ashrap et al.
305 (2018) reported geometric mean concentrations of parabens in urine samples 2-3-fold
306 higher in women declaring recent use of hand or body creams than in women who did
307 not use hand or body cream. Hair matrix reveals to be a suitable matrix for
308 biomonitoring of parabens that allows a better evaluation of both internal and external
309 exposition through the use of personal care products and both short to long-term
310 exposition.
311 *BPA*
312 BPA has been biomonitored in breast milk, serum, urine and hair samples (Table 2).
313 Dualde et al. (2019) carried out a large biomonitoring study of bisphenols in human
314 milk in Europe. The frequency of detection of BPA was 83% reaching concentration
315 levels up to 42 ng/mL what shows the relevance of biomonitoring of BPA to prevent
316 breastfed babies from exposure to BPA. Authors found significant associations between
317 BPA concentration and the place of residence of the mother and the use of personal care
318 products. Hines et al. (2015) reported the biomonitoring of BPA in urine, serum and
319 breast milk of lactating women. BPA was detected in most of urine samples but was
320 rarely detected in serum samples whereas frequency of detection in milk was higher
321 than 50%. They conclude that serum was not a suitable matrix for biomonitoring of
322 BPA whereas breast milk is limited for biomonitoring of BPA in lactating women. As
323 can be seen in Table 2, concentrations of BPA are higher in hair samples than in urine

samples. Similar concentrations were reported by Tzatzarakis et al. (2015) in hair samples from Greek population (13.1–72.8 ng/g for children and 17.7–192.8 ng/g for adults). Hair reveals to be the best matrix for biomonitoring of BPA, not only because the highest concentration levels have been reported in this matrix (Table 2) but also because it is the matrix most easy to collect and to storage avoiding the use of plastic materials than can contaminate samples with BPA.

PFCs

Previous studies reported the affinity of PFCs for binding to β-lipoproteins, albumin and liver fatty acids, resulting in a high accumulation in blood, liver and kidney (Jones et al., 2003; Lau et al., 2007). Their occurrence in nail and hair samples, mainly composed by keratin, suggests that they might also bind to keratin (Li et al., 2013; Alves et al., 2014; Wang et al., 2018). Wang et al. (Wang et al., 2018) compared the potential of biomonitoring of PFCs in hair, nail and urine samples obtaining statistical correlations between concentrations in nails and hair. Pérez et al. reported that PFCs are also bioacummulated in hair and urine (Pérez et al., 2012) but with different accumulation patterns. Longer chain PFCs, such as PFOS and PFOA, are most frequently detected in hair samples, as obtained in our study (Table 1), whereas shorter chain PFCs, such as PFBuA, are most frequently detected in urine (Pérez et al., 2012). Longer chain PFCs are considered more toxic than shorter chain PFCs, therefore hair should be considered a better matrix for biomonitoring of PCFs. PFCs have been also detected in breast milk (Barbarossa et al. (2013)) at concentrations in the ranges from 0.015 to 0.288 ng/mL for PFOS and from 0.024 to 0.241 ng/mL for PFOA. Nevertheless, breast milk is limited to biomonitoring of PFCs in breastfeeding women.

Conclusions

The present study evidence the utility of hair analysis for biomonitoring of EDCs. All the target pollutants were found in the analysed hair samples indicating ubiquitous exposure to these xenobiotics. Parabens were the main contributors to the total hair burden (mean concentration levels 635-2821 ng/g), BPA was present in 83 % of the analysed samples at concentrations in the range between 24 and 1427 ng/g and PFCs were detected at concentrations in the range between 0.6-15.5 ng/g, being PFOS and PFOA the compounds most frequently detected.

Concentrations of parabens and BPA were significantly different in hair from adults and children (t_{cal} = 2.311; 2.432; 2.086; 2.510 and t_{tab} = 2.040; 2.030; 2.040; 2.024; $p < 0.05$ for MeP, EtP, PrP and BPA, respectively) revealing a higher exposure of adults. No correlation was found between EDC levels and smoking, hair colour or hair dyeing habits. A state of the art review, of the scarce biomonitoring studies of the target compounds in other biological matrices, have demonstrated the suitability of hair samples for biomonitoring BPA, parabens and PFCs.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no competing interests.

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592

593 **FIGURE CAPTIONS**

594 **Figure 1.** Correlations between MeP (Ln MeP) and PrP (Ln PrP) concentrations and

595 PFOA (Ln PFOA) and PFOS (Ln PFOS) concentrations in hair samples (n=42).

596 **Figure 2**. Distribution of EDCs in children (left), women (middle) and men (right).

597 **Figure 3**. Distribution of EDCs in smokers and non-smokers.

598 **Figure 4**. Distribution of EDCs in dyed and non-dyed hair.

Table 1. Concentrations (ng/g) and frequency of detection of parabens, BPA and PFCs in the analysed hair samples (n=42).

Compound	Range (ng/g)	Arithmetic mean (ng/g)	Geometric mean (ng/g)	Median (ng/g)	Frequency of detection (%)
MeP	68.3-14187.3	2820.7	1077.1	822.1	100
EtP	2.9-6565.9	634.8	84.8	47.2	95
PrP	12.5-9009.0	1006.1	345.0	256.3	100
BPA	24.4-1427.5	333.8	200.0	195.1	83
PFBuA	5.8-15.5	8.9	8.5	7.8	14
PFPeA	4.6-13.3	7.4	7.0	6.8	26
PFHxA	2.0-10.6	8.1	7.6	8.9	26
PFHpA	0.6-10.1	3.1	2.3	2.4	86
PFOA	0.6-9.5	2.0	1.5	1.4	57
PFOS	0.7-11.0	2.7	2.0	1.9	76

~~Compound~~	~~Range (ng/g)~~	~~Arithmetic mean (ng/g)~~	~~Geometric mean (ng/g)~~	~~Median (ng/g)~~	~~Frequency of detection (%)~~
~~MeP~~	~~68.3-14187~~	~~2821~~	~~1077~~	~~822~~	~~100~~
~~EtP~~	~~2.9-6565~~	~~635~~	~~84.8~~	~~47.2~~	~~95~~
~~PrP~~	~~12.5-9009~~	~~1006~~	~~346~~	~~256~~	~~100~~
~~BPA~~	~~24.4-1427~~	~~334~~	~~200~~	~~195~~	~~83~~
~~PFBuA~~	~~0.2-15.5~~	~~5.6~~	~~2.7~~	~~6.7~~	~~24~~
~~PFPeA~~	~~2.8-13.2~~	~~7.0~~	~~6.5~~	~~6.3~~	~~29~~
~~PFHxA~~	~~2.0-10.6~~	~~8.1~~	~~7.6~~	~~8.9~~	~~26~~
~~PFHpA~~	~~0.1-10.1~~	~~2.8~~	~~1.8~~	~~2.0~~	~~95~~
~~PFOA~~	~~0.1-9.5~~	~~1.3~~	~~0.8~~	~~0.8~~	~~98~~
~~PFOS~~	~~0.7-11.0~~	~~2.7~~	~~2.0~~	~~1.9~~	~~76~~

Table
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Table 2. Overview of biomonitoring studies of parabens, BPA and PFCs in human biological samples. Concentrations in ng/mL for liquid samples and in ng/g for solid samples.

Matrix	Country	n	Concentration (ng/mL for liquid matrices; ng/g for solid matrices)										Reference
			MeP	EtP	PrP	BPA	PFBuA	PFPeA	PFHxA	PFHpA	PFOA	PFOS	
Breast milk	Italy	37									0.02-0.24	0.015-0.28	Barbarossa et al., 2013
Breast milk	Spain	10	0.9-11.3	0.5-13.2	0.5-37								Rodríguez-Gómez et al., 2014
Breast milk	Spain	10	1.26-16.2	0.97-18.1	1.02-12.6	0.60-2.10							Rodríguez-Gómez et al., 2015
Breast milk	United States	34	0.8-2.3		0.1-0.4	0.3-1.1							Hines et al., 2015
Breast milk	Spain	100				<LOQ-42							Dualde et al., 2019
Nail	China	15								0.55	0.43	0.15-5.09	Li et al., 2012
Nail	China	64									0.14-0.56	0.15-5.09	Li et al., 2013
Nail	China	8									0.18-1.34	57-479	Wang et al., 2018
Placental tissue	Spain	50	2.6	0.8	0.6								Jiménez-Díaz et al., 2011
Serum	China	64									0.23-14.32	0.73-35.1	Li et al., 2013
Serum	United States	34	8.8-42		0.4-5.4	0.3-0.8							Hines et al., 2015
Urine	Australia	2400	74.4-1180	6.3-802	10.2-530								Heffernan et al., 2015
Urine	Brazil	30	0.82-26.15	0.42	0.15-0.63								Jardim et al., 2015
Urine	China	64									4.8-57.4	7-159.9	Li et al., 2013
Urine	China	8					0.29-3.94	0.06-2.23	0.09	0.04	0.04-0.31	1.13-16.5	Wang et al., 2018
Urine	Greece	100	1.2-803	<LOQ-61	<LOQ-565								Asimakopoulos et al., 2014
Urine	Puerto Rico	2166	78.2	2.8	15.4	2.1							Ashrap et al., 2018
Urine	United States	476	186	2.6	43.3								Ferguson et al., 2018

Urine	Spain	120	191	8.8	29.8	2.2							Casas et al., 2011
Urine	Spain	30					78-1495		1.1-49.7	0.5-4.9	0.13-1.79		Pérez et al., 2012
Urine	United States	34	17-968		0.5-279	0.6-31.9							Hines et al., 2015
Hair	Belgium	30					0.027-1.534	0.067-0.086	0.033-0.067	<LOQ	0.09	<LOQ	Alves et al., 2015
Hair	China	15									1.68	6.74	Li et al., 2012
Hair	China	64									0.11-1.95	0.08-6.74	Li et al., 2013
Hair	China	8					0.28-7.81	0.25	0.3	0.28	11.7-59.4	2140-12640	Wang et al., 2018
Hair	Germany	4		810-1980	400-1520								Martín et al., 2015
Hair	Greece	69				13.1-192.8							Tzatzarakis et al., 2015
Hair	Greece	122				2.6-205					<LOQ		Karzi et al., 2018a
Hair	Korea	10	48.3-224.2	11.5-158.3	70.2-214.5								Cho and Song, 2019
Hair	Spain	24					5.9-39.3				0.1-6.1	3.7-7.2	Pérez et al., 2012
Hair	Spain	6	78-624	7.0-42	27-238	24-158		8.2-13	2.0-8.9	1.0-10	0.6-1.6	1.0-2.5	Martín et al., 2016
Hair	Korea	10				17-22.9							Lee et al., 2017
Hair	Spain	6	10.2-33	9	11.6-107	9.2-45			5.5	7.1	10.6-23.9	4.9-9.9	Rodríguez-Gómez et al., 2017
Hair	Spain	42	68.3-14187	2.9-6565	12.5-9009	24.4-1427	0.2-15.5	2.8-13.2	2.0-10.6	0.1-10.1	0.1-9.5	0.7-11.0	This work

n: number of samples; <LOQ: lower than the limit of quantification.

Table
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Matrix	Country	n	Concentration (ng/mL for liquid matrices; ng/g for solid matrices)										Reference
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Breast milk	Spain	10	1.26-16.2	0.97-18.1	1.02-12.6	0.60-2.10							Rodríguez-Gómez et al., 2015
Breast milk	United States	34	0.8-2.3		0.1-0.4	0.3-1.1							Hines et al., 2015
Breast milk	Spain	100				<LOQ-42							Dualde et al., 2019
Nail	China	15								0.55	0.43	0.15-5.09	Li et al., 2012
Nail	China	64									0.14-0.56	0.15-5.09	Li et al., 2013
Nail	China	8									0.18-1.34	57-479	Wang et al., 2018
Placental tissue	Spain	50	2.6	0.8	0.6								Jiménez-Díaz et al., 2011
Serum	China	64									0.23-14.32	0.73-35.1	Li et al., 2013
Serum	United States	34	8.8-42		0.4-5.4	0.3-0.8							Hines et al., 2015
Urine	Australia	2400	74.4-1180	6.3-802	10.2-530								Heffernan et al., 2015
Urine	Brazil	30	0.82-26.15	0.42	0.15-0.63								Jardim et al., 2015
Urine	China	64									4.8-57.4	7-159.9	Li et al., 2013
Urine	China	8					0.29-3.94	0.06-2.23	0.09	0.04	0.04-0.31	1.13-16.5	Wang et al., 2018
Urine	Greece	100	1.2-803	<LOQ-61	<LOQ-565								Asimakopoulos et al., 2014
Urine	Puerto Rico	2166	78.2	2.8	15.4	2.1							Ashrap et al., 2018
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Hair	Belgium	30					0.027-1.534	0.067-0.086	0.033-0.067	<LOQ	0.09	<LOQ	Alves et al., 2015
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Hair	Germany	4		810-1980	400-1520								Martín et al., 2015
Hair	Greece	69				13.1-192.8							Tzatzarakis et al., 2015
Hair	Greece	122				2.6-205					<LOQ		Karzy et al., 2018
Hair	Korea	10	48.3-224.2	11.5-158.3	70.2-214.5								Cho et al., 2019
Hair	Spain	24					5.9-39.3				0.1-6.1	3.7-7.2	Pérez et al., 2012
Hair	Spain	6	78-624	7.0-42	27-238	24-158		8.2-13	2.0-8.9	1.0-10	0.6-1.6	1.0-2.5	Martín et al., 2016
Hair	Korea	10				17-22.9							Lee et al., 2017
Hair	Spain	6	10.2-33	9	11.6-107	9.2-45			5.5	7.1	10.6-23.9	4.9-9.9	Rodríguez-Gómez et al., 2017
Hair	Spain	42	68.3-14187	2.9-6565	12.5-9009	24.4-1427	0.2-15.5	2.8-13.2	2.0-10.6	0.1-10.1	0.1-9.5	0.7-11.0	This work

n: number of samples; <LOQ: lower than the limit of quantification.

Figure

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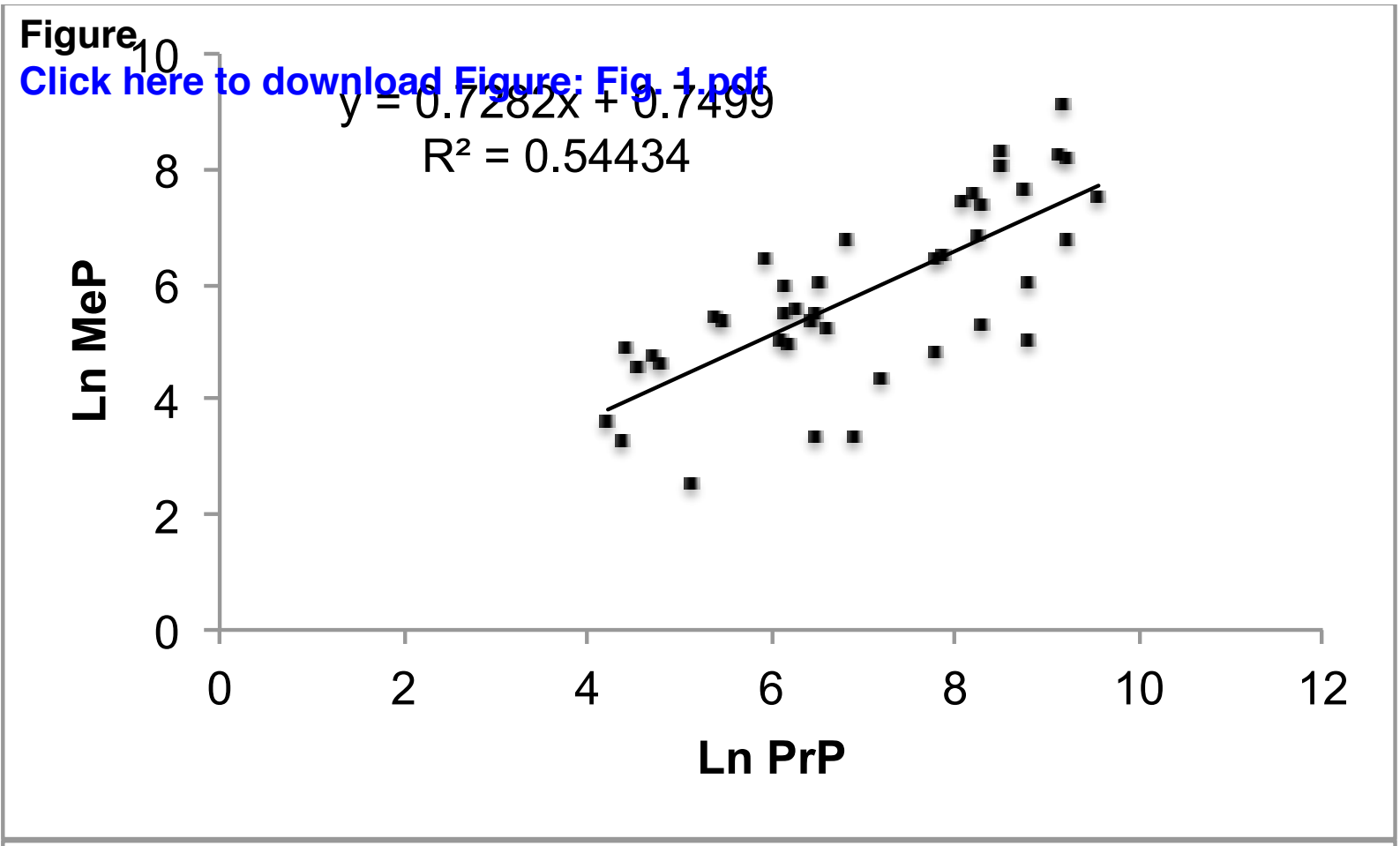

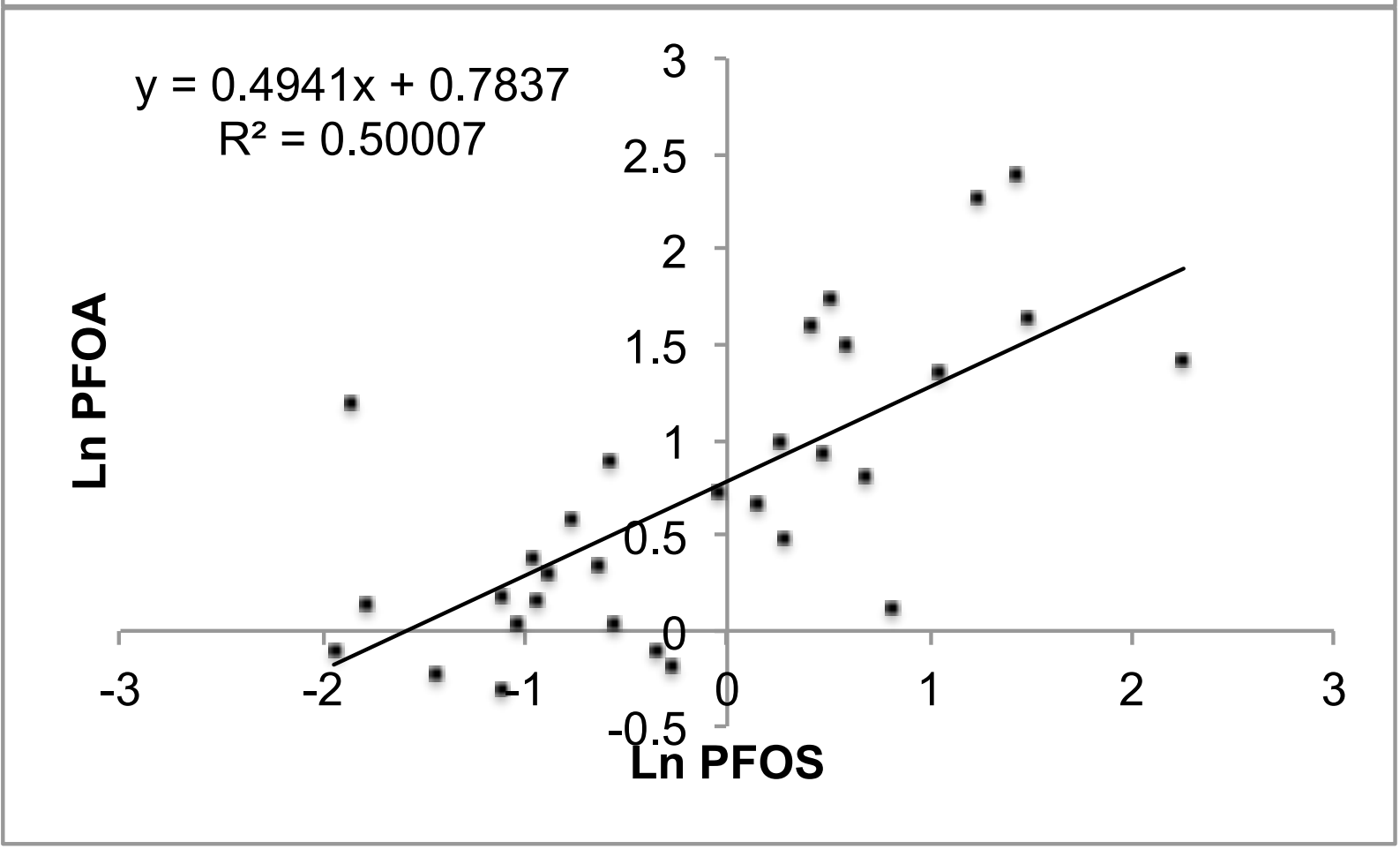

Figure
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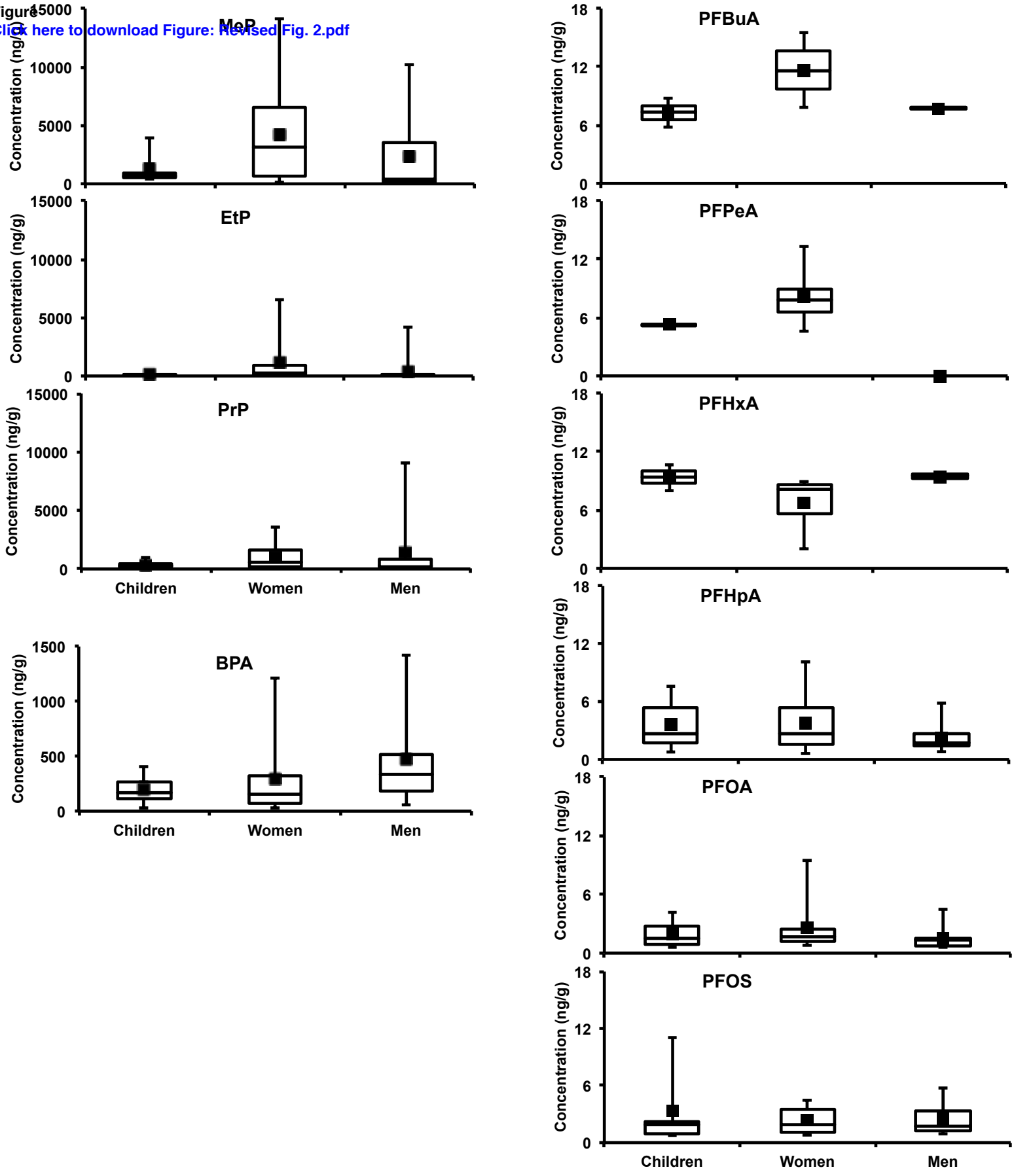

Figure

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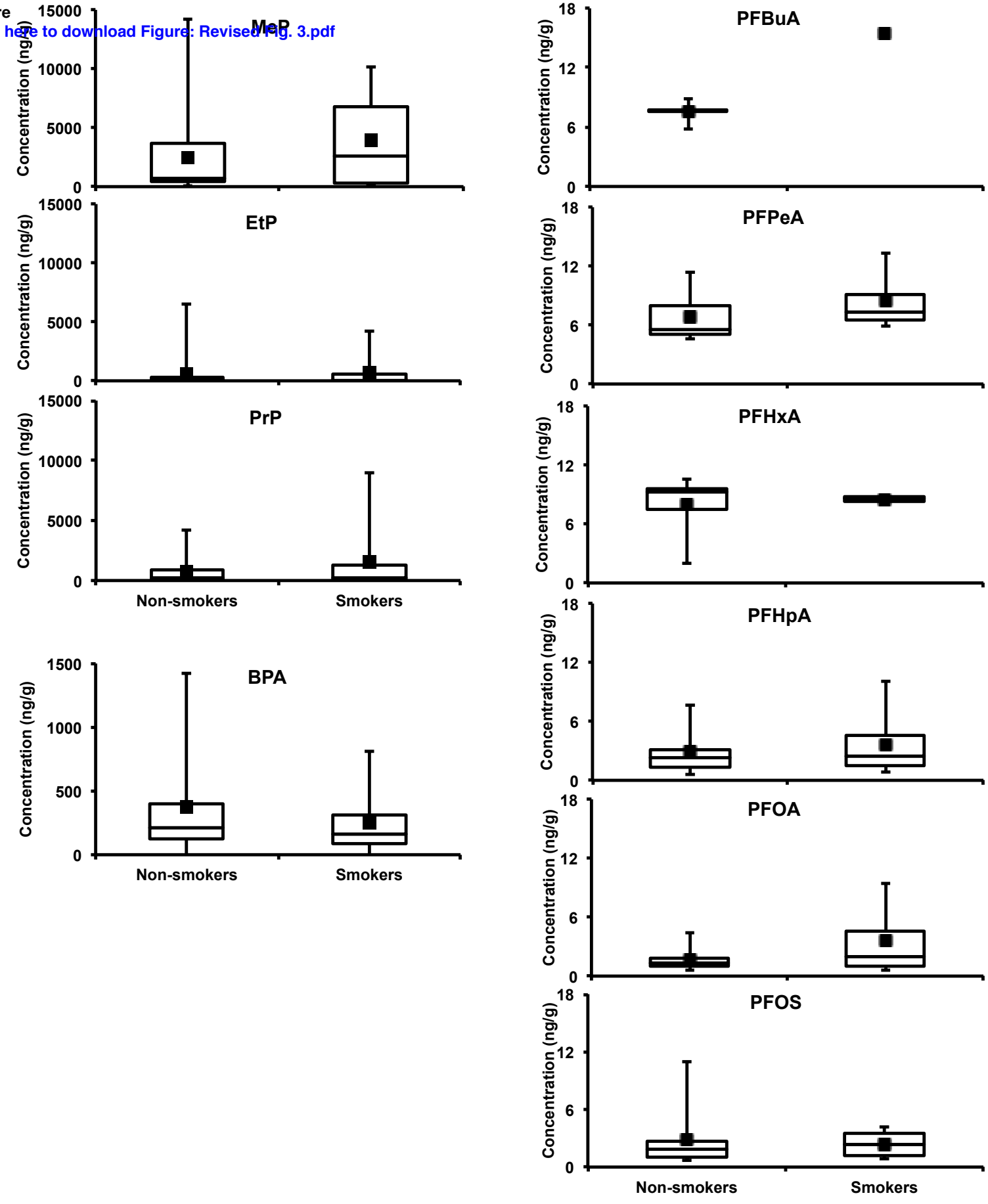

Figure

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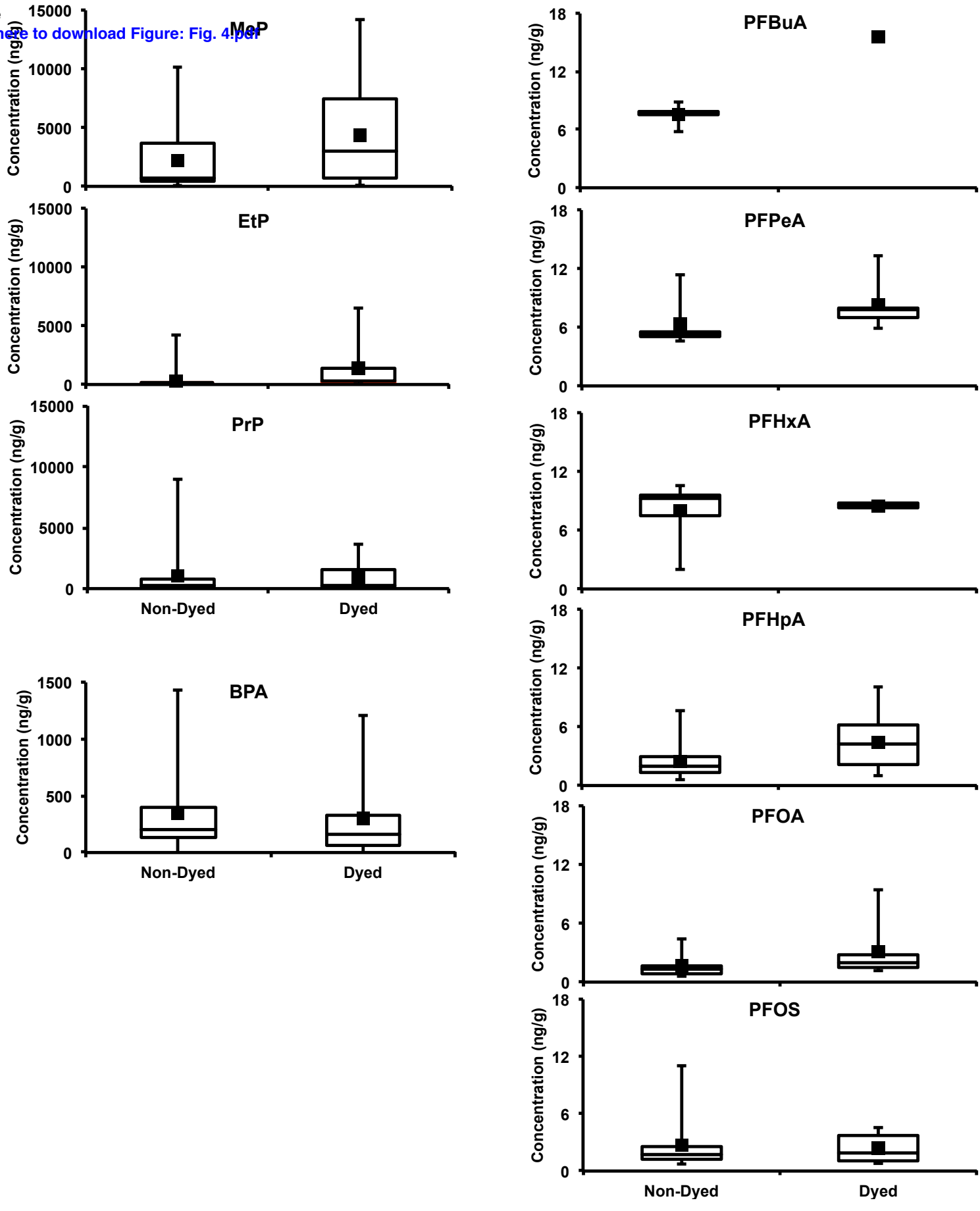

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