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1 **Characterisation of pregnant women exposure to halogenated parabens and bisphenols**
2 **through water consumption**

3

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28

29 ABSTRACT:

30 Exposure of pregnant women to endocrine disruptor compounds, such as parabens and bisphenol A
31 is of concern for foetal transition. Their halogenated degradation products, mainly coming from
32 water treatment plans, could be problematic as well, depending on their occurrence in drinking
33 water in the first place. Thus, 25 halogenated compounds were synthesised in order to investigate 60
34 substances (Bisphenols, parabens and their degradation products) in 325 drinking water samples
35 coming from a French cohort study of pregnant women. Analysis was performed by tandem mass
36 spectrometry coupled to gas chromatography (GC-MS/MS) after SPE extraction and derivation of
37 the contaminants. Results indicate that parabens (methylparaben, n-propylparaben, ethylparaben
38 and n-butylparaben), bisphenols S, A and F, and their degradation product, 4-hydroxybenzoic acid,
39 were detected up to several hundred ng/L in drinking water, with detection frequencies between 16
40 and 88%. Regarding halogenated degradation products, the highest detection frequencies were
41 found for monochlorinated products (about 50% for 2-chlorobisphenol A), which were quantified
42 up to several tens of ng/L. Such analytical approaches with broader spectrum of monitoring (i.e.
43 chemical hazards and their degradation products) constitute in the beginning of a solution to
44 exhaustively answer the questions related to the characterization of the human chemical exposome.

45
46 **Key words:** Exposome, Endocrine disruptor, drinking water, GC-MS/MS

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50 Statement of Environmental Implication

51 Parabens and Bisphenol A are become ubiquitous chemical hazards. Whereas parabens are chemical
52 products often used in small amounts as preservatives in cosmetics, pharmaceuticals and food,
53 bisphenols were mainly used as basic building block for production of plastics and coatings. Their
54 toxicity was demonstrated for human health (endocrine disruption) and marine environment. They
55 could also be halogenated after waste water treatment plans. These by-products sometimes present
56 higher toxicities than their parent compounds. Therefore, this study allows to reveal for the first
57 time their occurrence in drinking water, which were sampled from pregnant women, who are both
58 at risk and vigilant.

59

60 **1 Introduction**

61 Parabens and bisphenols, described as Endocrine Disrupting Chemicals (EDCs), are chemicals
62 hazards of concern. Parabens health effects are reported in vitro, e.g. on malignant ovarian [1] or
63 breast tumor [2]) or adiposity [3] and in vivo, e.g. on anogenital distance or ovary weights [4] or
64 prostate cancer [5], whereas bisphenol adverse effects are reported on bisphenol A (BPA) and
65 mainly on its S and F substitutes[6], focusing on their hormonal activity [7] their reproductive
66 toxicities [8]. The toxicity of bisphenol and paraben degradation products or derivatives is also of
67 concern, with the classification of chlorinated BPA as EDCs [9]. The estrogenic activity of Cl_xBPA
68 was more studied and higher than in parent compounds [10, 11]. These compounds could act as RX
69 receptor disruptors [12] but also with other nuclear receptors [10, 13, 14]. Parabens and some
70 chlorinated parabens exhibited estrogenic activities using hER competitive enzyme-linked
71 immunosorbent assay [15, 16] or a two-hybrid assay with the yeast cells transfected with hER α for
72 brominated parabens, but few studies were found for their interaction with nuclear receptors [17].
73 The internal exposure of the general population, and of pregnant women cohorts more specifically,
74 has been already demonstrated, both for parabens and bisphenols in blood and urine [18-21].
75 Indeed, Human are mainly exposed to parabens through personal care products whereas bisphenols
76 are prevalent in numerous food and environmental matrices [22]. However, their degradation
77 products have been little studied, except as disinfection by-products [23] whereas their half-lives are
78 longer than those of their parent compounds [24, 25]. As halogenated derivatives appear during the
79 water chlorination treatment plans [12, 26-28], the presence of such halogenated derivatives in
80 drinking water is expected. Actually, these substances (bisphenols and parabens) were ubiquitous
81 found in water resources, soils, sediments, sludge. Their phenolic moiety is described as very
82 reactive with chloride and bromide radicals during water treatment plans, promoting chlorinated
83 and brominated by-products. These results have been already confirmed by pilot studies and
84 halogenated parabens were already quantified in raw sewage water [29] However, the residual

85 contribution of parent and halogenated by-products of BPA and parabens in drinking water from a
86 well-characterized cohort now deserves to be known. As the population most susceptible to EDCs
87 exposure remains the early childhood years, the characterization of the exposure of pregnant women
88 to these chemical hazards via drinking water seemed relevant in the first place.

89 To the best of our knowledge, no study reports halogenated bisphenols and parabens in the
90 pregnancy external exposome [23, 30-32]. Therefore, we investigate 60 compounds including BPA
91 and its substitutes BPAF, BPB, BPE, BPF, BPS, parabens, halogenated derivatives of BPA and
92 parabens and their degradation products in 325 drinking-water samples from a French pregnant
93 women cohort. A dedicated GC-MS/MS method was developed to better characterise the drinking
94 water exposure of women of childbearing age.

95 **2 Experimentals**

96 *2.1 Pregnant women sample collection and ethical considerations*

97 Pregnant French women were enrolled in the Endocrine Disruptors Deux-Sèvres (EDDS) cohort
98 study. Drinking water samples were collected during pregnancy. The EDDS cohort recruitment
99 begun in 2011 and has been described elsewhere [33]. Briefly, eligible subjects were pregnant
100 women who declared pregnancy before 14 weeks of pregnancy. Women lived in one of the 87
101 municipalities of Deux-Sèvres (France) where drinking-water was exclusively produced from
102 surface water, because EDDS cohort objectives focused on emerging chemical contaminants that
103 were more frequently found in surface water than groundwater [34, 35]. They received 1-hour visits
104 by a trained interviewer during the second and third trimester of pregnancy. Dermal water exposure
105 and ingestion frequency of tap or bottled water were particularly investigated by a questionnaires
106 expressly designed for the study. Samples of tap water were collected at home, into two 250 mL jar,
107 filled for half in the bathroom and for half in the kitchen, and at work, both at second and third
108 trimesters of pregnancy. Five samples of water treatment plan in the department were collected

109 during the study (10/05/2012, 10/07/2012, 8/10/2012, 13/03/2014, 25/11/2014). Informed consent
110 was filled in by pregnant women and her partners, and the study was approved by the ethical
111 committee with the IRD n° 2011-A00194-37.

112 2.2 *Br_xCl_ybisphenol A and Br_xCl_yparabens synthesis*

113 The synthesis of Br_xCl_yBPA has been presented previously [36]. All Br_xCl_yparabens were described
114 according general synthetic routes. All chloroparaben compounds were synthesized with sulfuryl
115 chloride and their bromo analogues with Br₂. These reagents, parabens, BPA, BPAF, BPB, BPE,
116 BPF, BPS were purchased from Sigma-Aldrich. Detailed synthesis purification procedures and
117 characterization (¹H, ¹³C, LC-MS, CLHP) data are provided in the supplementary file n°1.

118 2.3 *Drinking water samples*

119 325 drinking water samples, corresponding to the entire set of samples originating from EDDS
120 cohort, were analyzed by the analytical strategy developed in this work. These analyses were
121 performed under reproducibility conditions since fifteen series of samples were considered over a
122 period of two months.

123 2.4 *Solvents, reagents and commercial standard solutions*

124 ¹³C₆-n-butyl-4-hydroxybenzoate was used as internal standard and was purchased by CIL
125 (Tewksbury, MA,USA). 2-hydroxy-4-methoxy-benzophenone-d₅ was used as external standard and
126 was purchased by CDN Isotopes (Quebec, Canada). SPE Chromabond HR-X, 0.5 g, 6 mL, were
127 from Macherey-Nagel (Hoerdt, France). Methanol was purchased by VWR (Fontenay-sous-Bois,
128 France), Water HPLC grade was provided from Panreac (Lyon, France) and acetonitrile was
129 purchased by Carlo Erba (Val-de-Reuil, France). N-methyl-N(trimethylsilyl)-trifluoroacetamide
130 (MSTFA) was provided from Fluka-Merck (Darmstadt, Germany).

131 **2.5 Sample preparation**

132 Samples of 150 mL water aliquots were prepared in a polypropylene flask with 0.2 ng of internal
133 standards mixture (¹³C-bisphenol A, ¹³C-bisphenol S, ¹³C-bisphenol F, ¹³C-2,2',6,6'-tetrachloro
134 bisphenol A, ¹³C-2,2',6,6'-tetrabromo bisphénol A, ¹³C-methyl-4-hydroxybenzoate, ¹³C-butyl-4-
135 hydroxybenzoate, n-heptyl-4-hydroxybenzoate-d₄). Each sample was purified on a preconditioned
136 SPE (6 mL methanol and 6 mL water). After drying the cartridge under moderate vacuum (<15
137 mbar), analytes were eluted with 10 mL methanol / acetonitrile mixture (50:50, v/v). external
138 standard (2 ng) was added before evaporation to dryness . Derivatization was achieved by adding 20
139 μL of MSTFA reagent into the vial and heated for about 30 min at 45°C.

140 **2.6 GC-MS/MS analysis**

141 An Agilent 7890 gas chromatograph, equipped with an Optima-17-MS column (30 m x 0.25 mm
142 i.d., 0.25 μm film thickness) (Macherey Nagel, Hoerd, France), was coupled to a triple quadrupole
143 mass analyzer Agilent 7000 (Agilent Technologies, Santa Clara, USA). The temperature program
144 was set as follows: 100°C (2 min) and 16°C min⁻¹ until 320°C (5 min). Injector and transfer line
145 were set at 280°C and 320°C, respectively. Source temperature was set at 250°C. Electron energy
146 was set at 70 eV. Helium was used as carrier gas at 1 mL min⁻¹. Argon was used as collision gas at
147 1.5 mL min⁻¹. Injection was performed in the pulsed splitless mode at 300°C (40 psi, 1.5 min), with
148 2 μL. Three transitions per analyte were monitored (cf. supplementary material). Data acquisition
149 and data processing were performed using the version B07.00 Mass Hunter constructor software
150 (Agilent Technologies, Santa Clara, USA). Two transitions were monitored per compound in SRM
151 mode (cf. Table S3).

152 2.7 QA/QC analysis

153 Quantification of compounds was carried out after identification (2002/657/EC criteria)[37] ,
154 according to the isotopic dilution process. Calibration was checked within the concentration range
155 [0-33.3] ng/L, nine calibration points, on the basis of RRF repeatability (RSD<20%). Method
156 performances were estimated on the basis of the current ISO 11352:2013 standard[38], using a
157 quality control sample spiked at 0.5 ng/150 mL and analysed 8 times all over the analysis campaign.
158 Within-laboratory reproducibility, trueness and combined uncertainty were determined from this
159 QC results.

160 Background contamination was checked, on the basis of the control of intra-laboratory
161 environmental contamination, considered as a major critical issue [39]. Numerous contamination
162 sources have been already highlighted for other ubiquitous contaminants, such as analytical
163 measurement devices, SPE columns, glassware, plastic ware, solvents. Therefore, from the various
164 sources of contamination, the strategy applied in the present study consisted in a systematic control
165 of the environmental contamination for each compound of interest, in each batch of samples. Three
166 procedural blank samples were included in each batch of analysis, and allowed the calculation of an
167 average concentration and its relative standard deviation (RSD), if significant signals were observed
168 with a S/N>3.

169 Limits of detection (LOD) and quantification (LOQ) were determined with a S/N ratio of 3 on the
170 first and the second transition, respectively. Only one consensual LOQ value was reported for each
171 analyte, which corresponds to the highest calculated LOQ value (upperbound approach), excluding
172 the outliers and always above the blank contamination level and the median value of the LOQs.

173 3 Results

174 All the results are synthetized and reported in **Table 1**.

Table 1 : First occurrence of parabens, bisphenols and their degradation products in drinking water, EDDS cohort

Compound	n quantified	Detection frequency	LOQ (ng/L)	uncertainty (at 3.3 ng/L)	P50 (ng/L)	P75 (ng/L)	P95 (ng/L)	P99 (ng/L)
bisphenol S	280	86%	0,7	85%	3,9	7,0	15,5	55,0
bisphenol A	95	29%	23,2	117%	<LOQ	25,8	63,0	229
bisphenol F	51	16%	0,7	59%	<LOQ	<LOQ	1,2	3,0
bisphenol AF	7	2%	1,0	133%	<LOQ	<LOQ	<LOQ	1,8
bisphenol B	1	0%	0,3	96%	<LOQ	<LOQ	<LOQ	<LOQ
bisphenol E	1	0%	0,4	112%	<LOQ	<LOQ	<LOQ	<LOQ
2-chloro BPA	167	51%	0,4	84%	0,4	1,1	5,0	15,6
2-bromo BPA	84	26%	0,3	164%	<LOQ	0,3	8,3	43,2
2,6-dichloro BPA	80	25%	0,6	98%	<LOQ	<LOQ	10,2	100
2,2'-dichloro BPA	43	13%	0,8	72%	<LOQ	<LOQ	1,6	8,9
2'-bromo-2,6-dichloro BPA	33	10%	0,3	62%	<LOQ	<LOQ	0,6	2,2

2-bromo-2',6'-dichloro BPA	20	6%	0,4	76%	<LOQ	<LOQ	0,4	0,9
2,2',6'-trichloro BPA	17	5%	0,5	53%	<LOQ	<LOQ	0,5	1,3
2,2'-dibromo BPA	15	5%	0,7	193%	<LOQ	<LOQ	<LOQ	83,2
2,6-dibromo BPA	15	5%	0,5	175%	<LOQ	<LOQ	<LOQ	8,2
2,2',6,6'-tetrachloro BPA	14	4%	0,4	53%	<LOQ	<LOQ	<LOQ	1,5
2-bromo-2'-chloro BPA	8	2%	0,5	59%	<LOQ	<LOQ	<LOQ	1,0
2-chloro-2',6'-dibromo BPA	7	2%	0,7	171%	<LOQ	<LOQ	<LOQ	3,0
2-chloro-2',6'-dibromo BPA	6	2%	0,7	171%	<LOQ	<LOQ	<LOQ	1,2
2,2'-dibromo-6,6'-dichloro BPA	5	2%	0,1	66%	<LOQ	<LOQ	<LOQ	0,2
2,6-dibromo-2',6'-dichloro BPA	4	1%	0,7	57%	<LOQ	<LOQ	<LOQ	0,7
2-bromo-6-chloro BPA	4	1%	0,4	60%	<LOQ	<LOQ	<LOQ	0,6
2-chloro-2',6,6'-tribromo BPA	4	1%	0,3	72%	<LOQ	<LOQ	<LOQ	0,3
2,2',6'-tribromo BPA	3	1%	1,3	126%	<LOQ	<LOQ	<LOQ	<LOQ
2-bromo-2',6,6'-trichloro BPA	1	0%	0,4	59%	<LOQ	<LOQ	<LOQ	<LOQ

ethyl 3-chloro-paraben	119	37%	0,6	39%	<LOQ	0,8	1,7	2,6
methyl 3-bromo-paraben	54	17%	0,1	18%	<LOQ	<LOQ	0,4	1,9
methyl 3-bromo-5-chloro-paraben	41	13%	0,5	54%	<LOQ	<LOQ	2,1	4,4
methyl 3,5-dichloro-paraben	39	12%	0,7	26%	<LOQ	<LOQ	2,3	7,9
methyl 3-chloro-paraben	16	5%	0,9	32%	<LOQ	<LOQ	<LOQ	1,9
methyl 3,5-dibromo-paraben	10	3%	6,8	42%	<LOQ	<LOQ	<LOQ	12,8
butyl 3,5-dichloro-paraben	7	2%	0,4	35%	<LOQ	<LOQ	<LOQ	0,8
propyl 3-bromo-paraben	6	2%	0,3	68%	<LOQ	<LOQ	<LOQ	0,4
propyl 3,5-dibromo-paraben	4	1%	1,4	41%	<LOQ	<LOQ	<LOQ	2,1
butyl 3,5-dibromo-paraben	3	1%	0,9	77%	<LOQ	<LOQ	<LOQ	<LOQ
ethyl 3,5-dichloro-paraben	3	1%	0,3	24%	<LOQ	<LOQ	<LOQ	<LOQ
butyl 3-bromo-paraben	2	1%	0,3	27%	<LOQ	<LOQ	<LOQ	<LOQ
ethyl 3,5-dibromo-paraben	2	1%	1,4	52%	<LOQ	<LOQ	<LOQ	<LOQ
ethyl 3-bromo-paraben	2	1%	0,5	18%	<LOQ	<LOQ	<LOQ	<LOQ
propyl 3,5-dichloro-paraben	2	1%	0,4	92%	<LOQ	<LOQ	<LOQ	<LOQ

propyl 3-chloro-paraben	2	1%	0,3	22%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
butyl 3-chloro-paraben	1	0%	0,3	35%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
propyl 3-bromo-5-chloro-paraben	1	0%	0,3	37%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
butyl 3-bromo-5-chloro-paraben	0	0%	1,0	40%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
ethyl 3-bromo-5-chloro-paraben	0	0%	1,4	44%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
4-hydroxybenzoic acid	135	42%	24,7	174%	<LOQ	55,1	114	259	
3-chloro 4-hydroxybenzoic acid	128	39%	0,9	95%	<LOQ	1,6	4,0	5,2	
3,5-dibromo-4-hydroxybenzoic acid	92	28%	2,8	120%	<LOQ	3,8	29,9	50,5	
3,5-dichloro 4-hydroxybenzoic acid	76	23%	1,4	134%	<LOQ	<LOQ	11,7	24,0	
3-bromo-4-hydroxybenzoic acid	47	14%	0,8	87%	<LOQ	<LOQ	3,0	7,2	
methyl paraben	285	88%	6,0	22%	19,0	32,6	81,7	362	
n-propyl paraben	280	86%	1,5	12%	7,7	14,4	48,7	136	
ethyl paraben	271	83%	1,3	27%	5,0	9,7	19,9	36,5	
n-butyl paraben	207	64%	1,0	16%	1,5	3,1	10,8	15,3	
iso-butyl paraben	11	3%	1,0	18%	<LOQ	<LOQ	<LOQ	2,7	

benzyl paraben	7	2%	0,6	138%	<LOQ	<LOQ	<LOQ	<LOQ	1,0
n-pentyl paraben	4	1%	1,3	66%	<LOQ	<LOQ	<LOQ	<LOQ	1,4
iso-propyl paraben	0	0%	1,0	21%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
n-heptyl paraben	0	0%	0,9	55%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

176 3.1 Performances of the analytical method

177 The GC-MS/MS acquisition method was assessed enough selective to provide confident results
178 regarding the correct analyte identification. An extracted ion chromatogram is given in Figure S1 to
179 illustrate the separation quality of halogenated parabens which have never been shown before. The
180 sensitivity of the analytical method was considered fit for purpose for our study, with LOQs
181 generally below the ng/L concentration level, as reported by Valbonesi *et al.* [40], except for BPA
182 and 4-hydroxybenzoic acid (cf. Table S1). Actually, their well-known contamination background
183 was detected in all samples [41, 42], coming from the environmental contamination, which
184 artificially increased the LOQ value (around [20-25] ng L⁻¹). To the best of our knowledge, this
185 issue of BPA contamination is not well reported in the literature either because LOQ of other
186 methods are higher the background contamination (LOQ=500 ng/L, [43]) or using the signal to
187 noise ratio of 3 to determine a technical LOQ without taking into account the environmental
188 contamination, as determined in the study of Valbonesi *et al.* [40] for example, with LOQ close to
189 the ng/L. In the implemented experimental conditions, no background contamination was observed
190 for the other compounds throughout the analysis campaign, neither in analytical measurement
191 devices nor in the laboratory environment, demonstrating the non-ubiquitous status of these
192 compounds. LOQs of halogenated compounds are also similar to those found by Fan *et al.* [44],
193 with levels below ng/L on chlorinated BPA in drinking water.

194 The resulting extended uncertainties, expressed within a 95% confidence range, were determined in
195 the range of 24% for n-propyl-4-paraben and 375% for 2,2',6-trichloro BPA, for which no labelled
196 internal standard was used (cf. Table S1), with the worst uncertainties reported for brominated
197 bisphenols and compounds with highest LOQ (close or above 1 ng/L). Recoveries yields are also
198 given for information in Table S2. They are included in the range [96-114] % depending on the
199 compound monitored.

200

201 *3.2 General occurrence of contaminants in drinking water samples*

202 Four compounds were high frequently detected (above 66 %): bisphenol S and methyl/ethyl/n-
203 propyl-parabens; 5 compounds were regularly detected (within 33-66%): 2-dichloroBPA,
204 ethylchloro/nbutyl-parabens, 3-chlorohydroxybenzoic acid and hydroxybenzoic acid and 47 were
205 detected at lower frequencies. Four compounds were never detected: butyl/ethyl 3-bromo-5-chloro-
206 parabens and iso-propyl/n-heptyl-parabens.

207 *3.3 Occurrence of bisphenols and parabens in drinking water samples*

208 The detection frequency of BPS and methyl-, n-propyl- and ethyl-parabens are above 80% while n-
209 butyl-paraben appears in 60 % and BPA in 29% of the samples.

210 The medians of the water concentrations are in the range of [1.5-19] ng L⁻¹. The highest
211 concentrations are found methylparaben > n-propylparaben > ethylparaben > bisphenol S > n-
212 butylparaben. Maximal concentrations (at the 99th percentile) were above 100 ng L⁻¹ for
213 methylparaben > BPA > n-propylparaben.

214 BPA presents the highest measured concentrations within the bisphenol group whereas bisphenol S
215 is found much more frequently, probably thanks to its lower LOQ, at significant level (at P50: from
216 3.9 ng L⁻¹ to 55 ng L⁻¹).

217 Methyl-, propyl-, ethyl- and butyl-parabens were very frequently detected, with consistent
218 concentrations, particularly for methyl- and n-propylparaben. The 4-hydroxybenzoic acid, which
219 represents the main degradation product of parabens, was also frequently detected (42 %) at level
220 up to several hundred of ng L⁻¹.

221 3.4 Quantification of Br_xCl_y parabens in 325 water samples

222 The most frequently detected compound was ethyl-3-chloroparaben which was clearly detected and
223 quantified in 37% of the analyzed samples. Their corresponding 75th percentile and 99th percentile
224 values were 0.8 and 2.6 ng L⁻¹ respectively, with a maximal concentration at 18.6 ng/L. Indeed, the
225 sensitivity of the method has allowed the systematic detection of ethyl-3-chloroparaben at ppt level
226 whereas the ethyl-3-bromoparaben was much less detected (in only 2 % of samples). Then, methyl-
227 Br_xCl_y-parabens were detected more frequently (in the [5-20] % of detection frequency range) and
228 in higher concentrations, up to several ng L⁻¹, than other halogenated parabens, i.e. ethyl, propyl and
229 butyl ones.

230 Propyl- and butyl-Br_xCl_y-parabens were significantly less frequently detected than methyl- and
231 ethyl- ones, with detection frequencies ranges below 2 %, depending on the halogen substitution.
232 However, when concentrations were measurable, they could reached several ng/L in drinking water,
233 like for propyl-3,5-dibromoparaben with 99th percentile at 2.1 ng L⁻¹.

234 3.5 Quantification of Br_xCl_y bisphenols in 325 water samples

235 The most frequently detected and identified compound was 2-chloroBPA with a detection
236 frequency of 51 % and a concentration range of [0.4-16] ng/L (until the 99th percentile). In parallel
237 2-bromoBPA was quantified in 26 % of the samples studied on a concentration range of [0.3-43]
238 ng/L (until the 99th percentile). Both dichloroBPAs (2,2'-dichloroBPA and 2,6-dichloroBPA) were
239 also detected with significant detection frequencies of 13 % and 25 % and until 9 ng L⁻¹ and 100 ng
240 L⁻¹, respectively. Mixed chlorinated and brominated molecules were also unambiguously identified
241 with lower frequencies, from 1/325 to 10 % for 2-bromo-2',6,6'-trichloro BPA and 2'-bromo-2,6-
242 dichloro BPA, respectively.

243 3.6 Quantification of Br_xCl_y -hydroxybenzoic acid in the 325 drinking water samples

244 The halogenated degradation products of 4-hydroxybenzoic acid were also monitored, based on
245 their mono- and di- Br/Cl substitution. The monochlorinated compound was the more frequent
246 degradation product found (39 % of detection frequency) followed by the dibrominated one (28 %),
247 the dichlorinated one (23 %) and the monobrominated one (14 %). The highest concentrations were
248 found for the dihalogenated forms (Br_2 or Cl_2) where drinking water concentrations reached up to
249 several tens of $ng\ L^{-1}$, whereas the monohalogenated forms stay below $10\ ng\ L^{-1}$.

250 4 Discussion

251 4.1 Uncertainty measurement

252 Whereas several studies has already reported endocrine disruptor concentrations in drinking water
253 [40, 45, 46], uncertainty measurement remain poorly described in the associated articles. Indeed,
254 recoveries and accuracy has been often preferred than uncertainties in old studies, to assess the
255 quantification performances, like for BPA [42] or for chlorinated parabens [28]. Indeed, Li *et al.*
256 [41] have developed a method focused on BPA quantification in water report accuracy values
257 determined on spiking levels well above ng/L , i.e. in the range of [300-20000] ng/L . At such high
258 concentrations, BPA uncertainties were described at $\pm 40\ %$ in the range of [500-2000] ng/L , far
259 away the environmental contamination level and the level of interest in drinking water.

260 In our study, uncertainties could reach several hundred percent, notely for degradation products. As
261 labelled halogenoparabens and labelled of mix chloro- and bromo-bisphenols were not available as
262 analytical standards, uncertainty measurement was led with non-mimetic internal standard for
263 several compounds. Consequently, several extended uncertainties appeared very high. Nevertheless,
264 the knowledge about the performances of this developed method firstly allows to assess the
265 frequency of detection of halogenated bisphenols and parabens in drinking water. Then, each

266 quantification value is always given with its associated uncertainty, according to the expectation of
267 the ISO 17025:2017 standard [43]
268 .

269 4.2 *Native compounds of bisphenols and parabens*

270 The significant occurrence of bisphenols and parabens in the drinking water samples assessed in
271 this work, particularly those of bisphenol S and methyl/n-propyl/ethyl parabens, confirms the great
272 interest to monitor these native substances in drinking water.

273 This study reveals first higher BPS detection frequency and the highest concentrations for BPA in
274 drinking water in the 325 collected drinking water samples, BPS detection frequencies of 86 %
275 found in this study are considerably higher than those found in India [47] (29 %) or in China [48]
276 where BPS has been never detected, whereas BPA detection frequencies found in this study (29 %)
277 are below those found in the two last papers, i.e. 40 %. The other BPs analogues are more rarely
278 found in the drinking water samples, despite a detection frequency of 16 % for BPF, which was not
279 yet reported at this level in other studies. BPA concentrations still the highest quantified BP in the
280 samples of this study (P99=229 ng/L) compared to BPs analogues. The concentration range
281 quantified in the present study is in accordance with that reported by that reported in drinking water
282 samples from China (4.7–512 ng/L) [44], France (2–16.9 ng/L [45] and 28 ng/L [49]), and South
283 Africa (23 ng/L [49]). The prevalence of BPS regarding BPA in this study could be explained both
284 by the highest LOQ found for BPA, censoring the lowest contamination levels of BPA, and the
285 prohibition of BPA use in favor of BPS or BPF (which only reaches 19 % of detection frequency)
286 when the sampling was made. The polarity of BPS ($\log P = 1.9$), higher than the one of BPA
287 ($\log P=3.3$), could also play a part in its higher contamination of drinking water. The occurrence of
288 each bisphenol seems to be rather linked to their technical use, the highest concentrations being
289 observed for BPA, and a lower but frequent detection for BPS.

290 Concerning parabens, this present study reports equivalent detection frequencies that those reported
291 in Vietnam [50] (around [80-100] %) for methyl-, ethyl-, propyl- and butylparabens but much
292 higher detection frequencies than that reported in Egypt [46], or in Spain and in Morocco [51],
293 which did not exceed 20 % of detection for methyl-, propyl- and butylparaben. Concentrations in
294 methylparaben determined in this study are similar to the results found in Brazil in 2018, in the
295 range of [90-242] ng/L [52], but higher than the concentrations found in the Mediterranean basin,
296 *i.e.* around 50 ng/L in Egypt in 2020 [46], [17-40] ng/L in Spain in 2015 [53] or in Vietnam in
297 2022[50]. Whereas the drinking water concentrations of n-propylparaben (P99=136 ng/L) were
298 higher than that reported by Radwan et al. [46], the n-butylparaben concentrations are closed
299 between both studies.

300 Parabens were usually used as preservatives in cosmetics and pharmaceuticals, but also in food
301 commodities and industrial products. Their widespread production and use has led to their aqueous
302 environment leaking. These products were ubiquitous found in water resources, either from
303 wastewater treatment discharges or as a runoff from atmosphere particles [54]. The occurrence and
304 the concentration of parabens in drinking water samples seems to be also linked to their polarity, the
305 highest polar paraben (methylparaben) being detected in more concentrations and in more samples
306 than the less polar ones. However, methyl- and ethyl-parabens are still the prevalent parabens in the
307 environment [53]. This observation can also explain their prevalence in these drinking water
308 samples.

309 *4.3 Halogenated parabens*

310 Ethyl-3-chloroparaben and methyl-Br_xCl_y-parabens were the most commonly found halogenated
311 parabens in the drinking water samples. As mentioned above, their high occurrence is explained by
312 the fact that their precursors (methyl and ethyl-parabens) being the most ones present in the
313 environment [53]. Ethylchloroparaben was the most frequently detected halogenated by-products,

314 i.e. quantified in 37 % of the drinking water samples in the range of [0.6-2.6] ng/L whereas
315 halogenated methylparabens were found with lower detection frequencies (from 3 to 17 %). Higher
316 concentrations were reported for dihalogenated than monohalogenated methylparabens, with
317 highest concentrations for dibrominated (up to 12.8 ng/L), then for dichlorinated (from 0.7 to 7.9
318 ng/L) and for bromochloro-methylparaben (from 0.5 to 4.4 ng/L). Higher occurrence of
319 dihalogenated compared to monohalogenated parabens have already been reported in wastewater
320 and sludge samples [28] but never in drinking water samples. The concentration of Br_xCl_yparaben
321 obviously depends to the initial concentration of the native paraben, to the bromide concentration in
322 water and to the potential chlorination treatment, simultaneously. In this study, we have observed
323 that these three conditions were often united, and this work has demonstrated the great interest to
324 monitor not only parabens but also halogenoparabens for the next Human exposure studies.

325 4.4 Halogenated bisphenols

326 Halogenated bisphenols were commonly found in the drinking water samples of this study,
327 particularly 2-chlorobisphenol A, 2-bromobisphenol A and both dichloroBPA (2,2'-dichloroBPA
328 and 2,6-dichloroBPA), whereas they has not been detected ten years ago in drinking water sample
329 from the same location (only 8 drinking water samples) [45]. Nevertheless, the same chlorinated
330 compounds are commonly found in tap water (n=21) of patient underwent a breast surgery [36], but
331 with higher detection frequency and concentrations in this present study for mono- and
332 dichlorinated compounds. In details, quantitative results were given in our study and in the study of
333 Dumas *et al.* [36] at 51% vs 24% for monochloroBPA, 13-25% vs 9% for dichloroBPA, 5% vs 9%
334 for trichloroBPA, 4% vs 33% for tetrachloroBPA, respectively. This last compound could come
335 from another source because of its use as flame retardant, which could lead to an overestimation of
336 its concentration in their studied samples. The chlorinated BPA detection frequencies found in this
337 study are still much lower than those found in China by Fan *et al.* in 2013 [44]. Actually, mono-

338 and dichloroBPA has been almost systematically detected in this last study, while tri- and
339 tetrachloroBPA were detected in more than half of the Chinese drinking water samples. The
340 chlorinated BPA concentrations found in the present study were similar to those reported in the
341 study of Fan *et al.*, except for dichloroBPA, and particularly for the 2,6-dichloroBPA isomer, for
342 which concentrations were significantly higher ([0,6-100] ng/L) in this study, whereas they didn't
343 exceed 6 ng/L in the Fan study [44]. Finally, all the halogenated BPA degradation products were
344 detected at least once in all the 325 samples of the present study. Once again, the simultaneous
345 monitoring of all these halogenated forms in the same analysis is of great interest to better
346 characterize the Human exposure to pollutants. Moreover, recent toxicological studies on
347 halogenated BPA demonstrated an ER α reduced activation, and significant impacts on PPAR γ and
348 inflammatory response (IL6 and IL8 expression) for selected halogenated BPA species [55], which
349 confirms the interest of following all halogenated compounds simultaneously.

350 *4.5 Halogenated hydroxybenzoic acid degradation products*

351 The monochlorinated compound is the most frequently degradation product detected. Terasaki et al.
352 already published concentrations of dichlorohydroxybenzoic acid and monochlorohydroxybenzoic
353 acid in river water from Japan at [12-150] ng/L and [11-74] ng/L, respectively [56], which are in the
354 same order of concentration as the present study The detection frequency of brominated by-
355 products were found equivalent to the chlorinated ones, at concentrations up to 50 ng/L for
356 dibromohydroxybenzoic acid. This result has never been published before. As hydroxybenzoic acid,
357 its halogenated forms could come from other chemicals and cannot be directly linked to only the
358 paraben degradation pathway in drinking water. Actually, 3,5-dibromo-4-hydroxybenzoic acid has
359 already been described as a soil degradation product of benzonitrile herbicides such as bromoxynil
360 and ioxynil [57]. Therefore, the monitoring of such halogenated hydroxybenzoic acid compounds
361 could cover several origins, performing a quick overview of several chemical families

362 simultaneously. At that time, these compounds can be easily monitored with the multiresidue
363 method.

364 4.6 *Strengths and limits*

365 The 60 compounds studied present quite different physicochemical properties, which lead to
366 questionable quantitative performances:

- 367 - Indeed, the greater the number of compounds to be monitored, the more difficult it is to
368 maintain excellent quantitative performance. However, additional internal standards
369 mimetic of halogenated bisphenols and parabens should improve the measurement
370 quality.
- 371 - The environmental contamination management should be improved in order to reduce
372 LOQ at their minimum for all the ubiquitous compounds which can come from different
373 sources at different concentrations through the lab. For each substance, source
374 contamination assessment and reduction are a huge but relevant work to investigate
375 contaminants at ultra-trace levels.
- 376 - This multiresidue method allows the monitoring of a wide range of BPA by-products but
377 does not cover others halogenated BPA substitutes degradation products. That would be
378 very relevant to cover a wide range of potential chemicals since native compounds (BPS
379 and F particularly) are found in the study samples. Using a time of flight mass
380 spectrometer would be able to increase the number of analytes monitored
381 simultaneously, paying attention to the LOQs which may not perform as well as in QqQ.
382 This also shows that classical analytical approaches of the targeted type (i.e. with a
383 priori) considerably limit knowledge of the reality of the exposome and therefore
384 constitute a major obstacle to the study of possible causal links between exposure to
385 certain chemical substances and certain pathologies suspected of being associated. The

386 development of analytical approaches without a priori (e.g. suspect screening and non-
387 targeted screening) constitute in this sense the beginning of a solution to exhaustively
388 answer the questions related to the characterization of the human chemical exposome.

389 - It should be considered at this stage to characterize the toxicity of the hazards revealed in
390 our study. The use of New Approach Methodologies (NAM) based on (Q)SAR models
391 (e.g., Leadscope, DEREK), Read-across (e.g., OECD QSAR Toolbox), in vitro High
392 Throughput Screening (e.g., ToxCast, Tox21) or HTS assays (bioactivity evaluation at
393 the molecular or cellular level) could allow to approach the type of toxicity of these
394 chlorinated decontamination products relatively quickly. With the availability of
395 exposure data via drinking water consumption, this better knowledge of the hazards
396 should make it possible to better characterise the associated risk and, if necessary, to be
397 able to enlighten the various stakeholders, e.g. drinking water producers, health
398 authorities, the population including women of childbearing age.

399 **5. Conclusion**

400 Sixty native and halogenate derivatives of BPA and parabens have been reported in drinking water
401 collected from pregnant women, with significant detection frequencies for monochlorinated BPA,
402 methylparaben and ethylparaben; and detection of a numerous halogenated degradation products
403 over the 44 monitored in the 325 drinking water samples included in this study. Thanks to a
404 dedicated analytical strategy especially developed for the study, using GC-MS/MS measurement,
405 and the synthesis of purified standards, our study demonstrates the great interest to monitor
406 halogenated bisphenols and parabens in drinking water samples to improve the external exposure
407 knowledge of pregnant women. Most of recent studies have focused on BPA and, to a lesser extend
408 parabens, or other EDs (such as triclosan, benzophenone, dichlorophenol) [58] but no one deal with
409 their halogenated derivatives to the best of our knowledge. In parallel, recent toxicological data
410 reinforce the interest of continuing to measure the Human exposure of these halogenated

411 contaminants[55]. Based on these first results, extended EDC list is available to work on the
412 association between the pregnant women exposure and birth outcomes.

413

414 *Authors contributions*

415 PC and BLB contributed to, and were responsible for, initiating, coordinating and conducting the
416 project and studies. MD contributed to the preparation of the halogenated BPA and Parabens,
417 coordinated by PC. MAL and VM are principal investigators of the EDDS Cohort. MAL, AD, NV,
418 PPE, VM contributed to collecting drinking water samples during pregnancy. BLB contributed to
419 coordinating the analytic development. YD, EB, BV, TG and PM contributed to developing the
420 method for the identification and quantification of the 60 targeted molecules on gas chromatograph
421 coupled to a triple quadrupole mass analyzer, YD and EB contributed to data interpretation. MAL,
422 YD, EB and PC contributed to manuscript preparation. EB and PC contributed to submitting the
423 manuscript.

424 Declaration of Interest

425 The authors declare that they have no known competing financial interests or personal relationships
426 that could have appeared to influence the work reported in this paper.

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