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1 **Levels of dechloranes and polybrominated diphenyl ethers (PBDEs) in human**
2 **serum from France**

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23 **Abstract**

24 Human exposure to dechloranes has been evaluated in Western Europe (France) with the
25 analysis of Dechlorane Plus (DP), Dechloranes (Dec) 602, 603, 604, Chlordene Plus (CP) and
26 Mirex in 48 serum samples collected between 2003 and 2005. While no production source
27 has been identified in Europe until now, detection frequencies for all investigated
28 dechloranes were high, except for Dec 604 which was below detection limit for all
29 samples. The mean DP concentration was 1.40 ± 1.40 ng/g lipid weight (lw), lower than levels
30 reported in serum from Chinese population, but higher than levels reported in Canadian
31 human milk. To the best of our knowledge, this is the first time Σ_5 dechlorane levels are
32 reported for human serum. A specific pattern of contamination was found (Dec 603 > DP >
33 Mirex > Dec 602 > CP) compared to other biota samples that have been analyzed from
34 Europe, with Dec 603 as the most abundant dechlorane (mean level: 2.61 ± 2.63 ng/g lw). Dec
35 603 and CP levels were correlated with age and with levels of some bioaccumulative
36 organochlorine pesticides (OCPs). These results indicate that bioaccumulation properties
37 should be further investigated and taken in consideration when assessing human exposure
38 to dechloranes. For comparison purposes, polybrominated diphenyl ether (PBDE) levels were
39 also measured for BDE-47, -99, -100, -153 and -154 in the serum samples. As expected, BDE-
40 47 and BDE-153 were the major congeners with mean levels of 2.06 ± 1.80 ng/g lw and 1.39
41 ± 0.97 ng/g lw, respectively. The mean Σ_5 PBDE levels (4.32 ± 2.99 ng/g lw) was in the range
42 typical of Western Europe levels, but lower than the mean Σ_5 dechlorane levels (6.24 ± 4.16
43 ng/g lw). These results indicate that the attention to dechloranes should be continued if
44 research indicates toxicological concerns.

45
46 **Keywords**

47 Dechloranes; human biomonitoring; flame retardants; blood serum; PBDEs

48 1. INTRODUCTION

49 Dechlorane or Mirex ($C_{10}Cl_{12}$) was extensively used as a pesticide as well as an additive flame
50 retardant (FR) in the USA during the 1960s and the 1970s. It was banned in the USA in 1978
51 because of its toxicity, persistence and high potential for bioaccumulation (Kaiser, 1978).
52 Consequently, other related compounds such as Dechlorane Plus (DP, $C_{18}H_{12}Cl_{12}$), Dechlorane
53 602 (Dec 602, $C_{14}H_4Cl_{12}O$), Dechlorane 603 (Dec 603, $C_{17}H_8Cl_{12}$), Dechlorane 604 (Dec 604,
54 $C_{13}H_4Br_4Cl_6$) and Chlordene Plus (CP, $C_{15}H_6Cl_{12}$), patented by Hooker Chemicals and Plastics
55 Corp. (Hooker; currently OxyChem, Niagara Falls, New York), became candidates to replace
56 Mirex. All these compounds share a bicyclo [2,2,1] heptene structure, resulting from a Diels-
57 Alder reaction between one or two hexachlorocyclopentadiene molecules (HCCPDs) with
58 various cyclic dienophiles. They all possess flame retardant properties similar to
59 Mirex (International Programme on Chemical Safety, 1984). Whereas the use of DP as a flame
60 retardant (electrical wires, cables coating, computers and polymers) is well established
61 (Betts 2008), listed as a high production volume chemical in the USA (US Environmental
62 Protection Agency, 2006) and as a low production volume chemical in EU (Sverko et al.,
63 2011), little information is available for the use of the other dechloranes. Dec 602 and Dec
64 604 are reported as flame retardant additives for polymeric products and they are listed on
65 the Nondomestic Substances List published by Environment Canada (Canadian
66 Environmental Protection Act, 1999), indicating their current use in commercial products. On
67 the contrary, no direct applications have been reported for Dec 603 or CP to date. They were
68 only referenced as impurities found in technical organochlorine pesticides (OCPs) (Shen et al.,
69 2011). All these compounds are unregulated compounds and represent a possible alternative
70 to other regulated FRs such as the polybrominated diphenyl ethers (PBDEs).

71 The environmental occurrence of dechloranes was first reported in 2006 in North
72 America when DP was detected in air, sediment and fish samples from the Laurentian Great
73 Lakes (Hoh et al., 2006). Different studies were conducted in this particular area (Qiu and
74 Hites 2007; Sverko et al., 2007) potentially contaminated due to the proximity of the
75 manufacturer Oxychem, localized on the Niagara River, the main connecting channel
76 between Lake Ontario and Lake Erie. A relationship between environmental DP levels and
77 the distance from the manufacturing plant was demonstrated, as well as with the local
78 population density (Hites et al., 2010), possibly reflecting the use of DP in electrical
79 equipment. In 2010, other dechloranes such as Dec 602, 603 and 604 were reported in
80 sediment and fish samples from the same area (Shen et al., 2010). CP was later detected in
81 sediments (Shen et al., 2011). Similar studies were also conducted in China. In 2010, Wang et
82 al. collected samples from the vicinity of an important DP manufacturing plant operating
83 since 2003 (Anpon Electrochemical Company, located in Huai'an, Northwest of Shanghai). The
84 influence of the production plant on environmental contamination levels in this region was
85 demonstrated. DP levels were also correlated to the proximity to e-waste recycling plants
86 and various industrial areas (Qi et al., 2010; Wang et al., 2011; Yu et al., 2010). Additionally to
87 DP, Dec 602 was detected in air, soil and sediment samples while Dec 603 and Dec 604 were
88 below detection limits (Wang et al., 2010).

89 Even though the number of studies is still small, and measurements around other potential
90 manufacturing plants have still to be conducted, additional data collected in Korea, Brazil,
91 North Africa, Spain and Germany (de la Torre et al., 2012; de la Torre et al., 2011; Kang et al.,
92 2010; Munoz-Arnanz et al., 2012; Sühling et al., 2013) indicate that DP and related
93 compounds should be considered as possible worldwide contaminants. Furthermore, Möller
94 et al. (2010) reported DP in air sampled in the Atlantic Ocean and suggested that this

95 compound was possibly subject to long range atmospheric transport. The same is observed for
96 Dec 602 as it was recently detected in Arctic Beluga whales (Shen et al., 2012). Two recent
97 review papers described sources, occurrence and behavior of dechloranes in the
98 environment, concluding on the need of more research dedicated to the production of data
99 on exposure and toxicity (Sverko et al., 2011; Xian et al., 2011). Additionally to the fact of
100 considering environmental contamination and geographical distribution, a better
101 understanding of the behavior of DP and related compounds in terms of bioaccumulation
102 and biomagnification is still needed. This is important since structurally similar Mirex was
103 banned and added to the Persistent Organic Pollutant List of the Stockholm convention
104 because, among other criteria, of its bioaccumulative potential (Stockholm Convention,
105 2001). A collection of limited data for aquatic and terrestrial biota was recently reported by
106 Feo and al. (2012). It highlighted the lack of information on the toxicity of DP to aquatic and
107 terrestrial organisms.

108 Even more importantly, virtually no human biomonitoring data are available for any of the
109 dechloranes. The assessment of internal dose exposure by means of measurements of these
110 toxicants in human tissues or fluids is currently unavailable. There have only been a couple of
111 reports published concerning studies conducted in China and Canada. Serum and collected
112 hair samples from workers at a Chinese e-waste recycling facility were analyzed to evaluate
113 DP exposure. Results from these hair samples suggested that direct ingestion of dust could
114 be considered as a major route of DP exposure of the workers (Zheng et al., 2010). In the
115 first study to report DP levels in human serum, DP was detected at concentrations ranging
116 from 7.8 to 465 ng/g lipid weight (lw) (Ren et al., 2009). Lower levels were later reported for a
117 population living in an urban area of South China (2.7 to 91 ng/g lw) (Yan et al., 2012) or in a
118 Halogenated Flame Retardant (HFR) production area of Northeastern China (1.4 to 11 ng/g

119 lw) (He et al., 2013). DP levels were also reported in Canadian human milk, ranging from
120 non-detected (nd) to 8 ng/g lw(Siddique et al., 2012). None of these studies however
121 reported data for the other dechloranes which have been reported to be even more
122 bioaccumulative than DP. Only a recent study by Cequier et al. (2013) reported DP, Dec 602
123 and 603 levels in human serum on a few individual serum samples (n = 10) from Norway.
124 The present study had two objectives. The first was to adapt an existing analytical
125 procedure based on solid-phase extraction (SPE) and gas chromatography coupled to high
126 resolution sector mass spectrometry (GC-HRMS) to isolate and measure levels of Mirex, DP,
127 Dec 602, Dec 603, Dec 604, and CP in human serum samples. The second was to measure
128 levels of these compounds in human serum samples from Western Europe (France) for which
129 data on levels of selected persistent organic pollutants (POPs) such as OCPs were previously
130 reported (Viel et al., 2011). Levels of selected PBDEs have also been measured in the present
131 study to allow comparison with dechlorane levels.

132

133 **2. MATERIALS AND METHODS**

134 **2.1. Serum samples**

135 A total of 48 banked human serum samples of which 24 males and 24 females (mean age 57
136 \pm 13 years, age range 28-86 years) were analyzed for this study. They were collected in
137 France between 2003 and 2005, from people living in the area of a municipal solid waste
138 incinerator in Besançon. Further details about samples and the ethical approval of the study
139 are described in another study (Viel et al., 2011).

140

141 **2.2. Lipid content determination**

142 Enzymatic lipid determinations of unknown samples were performed by a sub-contractor
143 clinical laboratory on a dedicated 1 mL serum sub-sample. Four types of lipids were targeted
144 and measured: triglycerides, total cholesterol, non-esterified (free) cholesterol, and
145 phospholipids B. Sample sizes were as follow: triglycerides (2 μ L), total cholesterol (2 μ L),
146 non-esterified (free) cholesterol (50 μ L), and phospholipids B (20 μ L). A well documented
147 summation method was used to estimate the total lipid concentration (Akins et al., 1989).
148 The total lipid content was expressed in g/L. For the inter-conversion of volumetric and
149 gravimetric data, a value of 1.026 g/mL was used for serum specific gravity.

150

151 **2.3. Chemicals**

152 *Syn-DP*, *anti-DP* and *syn-DP*¹³C₁₀ labeled (99%) standards were supplied by Cambridge Isotope
153 Laboratories (CIL, Andover, MS, USA). Dec 602 (95%), Dec 603 (98%) and Dec 604 (98%) were
154 purchased from Toronto Research Chemical Inc. (Toronto, ON, Canada) and CP was from
155 Wellington Laboratories (Guelph, ON, Canada). Mirex was purchased from Cluzeau InfoLabo
156 (France). The EC-4058 solution of PCBs mixture containing CB-209 ¹³C₁₂ (99%) and the EC-1414
157 solution of CB-80 ¹³C₁₂ (99%), from CIL, were used as surrogate and instrumental (recovery)
158 labeled standards, respectively. For BDE-47, 99, 100, 153 and 154 measurements, the BDE-
159 CVS-F calibration solutions, the MBDE-MXFS labeled surrogate stock and the MBDE-MXFR
160 labeled recovery stock (¹³C₁₂ standards) were purchased from Wellington Laboratories.
161 Hexane was Picograde reagent (LGC Promochem, Wesel, Germany). Nonane (analytical
162 standard grade, Fluka) was purchased from Sigma-Aldrich (St Louis, MO, USA). Anhydrous
163 sodium sulfate was from Acros Organics (Geel, Belgium) and sulphuric acid 95-97% was
164 Baker analyzed reagent (J.T. Baker, Deventer, Holland). Silica gel 60 (0.063-0.200mm) for
165 column chromatography was purchased from Merck (Darmstadt, Germany).

166

167 **2.4. Sample preparation**

168 Sample sizes of 10 g were extracted using solid-phase extraction (SPE) on non-end capped
169 isolute C18 cartridges (1g/6 mL) (Argonaut-Sopachem, Brussels, Belgium). The C18 cartridges
170 were eluted with 3 x 5 mL of hexane. More details on the SPE protocol can be found
171 elsewhere (Focant et al., 2006). The 15 mL hexane extracts were then loaded on a multi-
172 layers column made, from bottom to top, of 2 g of 22 % sulphuric acid silicagel, 1 g of
173 activated silica and 1g of sodium sulfate. Further elution with 15 mL of hexane was
174 performed. The evaporation of the pooled fractions was carried out using a PowerVap 6
175 system (Fluid Management Systems Inc., Watertown, MA, USA) equipped with specific
176 evaporation tubes to which GC vials are screwed and can easily be disconnected once the
177 final evaporation volume of 500 μ L is reached. After adding the keeper solvent (nonane),
178 gentle room temperature evaporation in a dust protected hood was performed to reach a
179 final volume of 10 μ L of nonane. Procedural blank samples consisted in 10 mL of Milli-
180 Q[®]water (Millipore, Brussels, Belgium) that followed the same procedure. A blank was
181 included with each series of 8 unknown samples.

182

183 **2.5. Measurement**

184 Samples were analyzed with a GC-HRMS system (MAT95 XL, Thermo Finnigan MAT, Bremen,
185 Germany) connected by a heated transfer line (275°C) to a CE Trace GC (ThermoQuest)
186 equipped with an A2000S autosampler (Thermo). The GC column was a ZB-5 (15m x 0.25mm
187 I.D., 0.25 μ m df) (Phenomenex, Utrecht, The Netherlands). Helium was used as the carrier
188 gas at a constant flow rate of 1 mL/min. One and two microliters of the final extract (for
189 dechloranes and PBDEs analysis, respectively) were injected into a split/splitless injector held

190 at 280°C, in splitless mode. For dechlorane measurements, the GC oven temperature was
191 maintained at 140°C for 2 min, ramped at 30°C/min to 280°C then at 5°C/min to 300°C and
192 held for 10 min. For PBDE measurements, the GC oven temperature was maintained at
193 140°C for 1 min, ramped at 15°C/min to 180°C, then at 10°C/min to 290°C and finally at
194 80°C/min to 350°C and held for 2 min. The MS ion source temperature was 250°C and
195 Electron Ionization (EI) was performed with 70 eV. The HRMS instrument was operated in the
196 selected ion monitoring (SIM) mode. Two ions were monitored for both native and
197 labeled species at m/z 271.8102/273.8072 for dechloranes, 276.8269/278.8240 for *syn*-DP
198 ¹³C₁₀, 295.9157/297.9127 for surrogate CB-209 ¹³C₁₂ and 301.9626/303.9597 for
199 recovery ¹³C₁₂ CB-80. For PBDE measurements, the monitored ions were m/z
200 483.7131/485.7111 and 495.7533/497.7513 for native and labeled tetra-BDEs (47 and
201 recovery 77), 403.8046/405.8026 and 415.8449/417.8429 for penta-BDEs (99 and 100),
202 481.7151/483.7131 and 493.7553/495.7533 for hexa-BDEs (153, 154, and recovery
203 138). Monitored ions were chosen based on signal intensity, specificity and jump between
204 m/z values allowed during the analysis according to the magnet settling time. Samples were
205 analyzed randomly. Calibration stability was ensured by injecting both low and high level
206 calibration points of the curve every 20 samples. Both instrumental and procedural blanks
207 were monitored. More details regarding the GC-HRMS procedure can be obtained in a
208 previous report (Focant et al., 2001).

209

210 **2.6. Quality assurance and quality control (QA/QC)**

211 All samples were processed in an ISO17025 BELAC accredited laboratory. The compounds
212 were identified based both on retention time of the corresponding standard with maximum
213 variation of 2 sec and mass spectral data. Isotope ratio between the two monitored ions was

214 checked to ensure proper identification. The limits of quantification of the method
215 (LOQ) were calculated based on a signal-to-noise (S/N) ratio equal to 6. For compounds
216 detected in procedural blanks, the mean procedural blank value was subtracted from the
217 samples and the limit of quantification was set at 3 times the standard deviation of the
218 procedural blank. A QC serum sample was included with each series of 8 unknown samples.
219 This internal QC was made of a pool of non-fortified human serum of 1030 adults (30-65
220 years old), collected between March and July 2005 in 8 different areas in France (Frery et al.,
221 2007).

222

223 **2.7. Statistical analyses**

224 Statistical analyses were performed using XLSTAT 2013. According to the Shapiro Wilk-test,
225 the data significantly deviated from normal distribution ($p < 0.05$). The non-parametric
226 Spearman's rank correlation coefficients (r_s) were calculated to assess relationships between
227 the different levels of compounds as well as with age. The Mann-Whitney U test was used
228 for comparison between males and females or younger and older people. Concentrations
229 were lipid normalized before statistical analysis and samples below LOQ were assigned with
230 the LOQ value.

231 **3. RESULTS AND DISCUSSION**

232 **3.1. Method performances**

233 The sample preparation procedure was derived from our routine approach for measurement
234 of selected polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans
235 (PCDFs), and polychlorinated biphenyls (PCBs) in human serum (Focant et al.,
236 2006). Recovery rates were calculated using CB-80 $^{13}\text{C}_{12}$ as instrumental standard. The

237 average surrogate standard recoveries ranged from 40% to 71% for CB-209 $^{13}\text{C}_{12}$ and from
238 33% to 61% for *syn*-DP $^{13}\text{C}_{10}$. Because of the comparable structures and lipophilicity of the
239 dechloranes, similar recovery rates can be expected for the other dechloranes. These values
240 are similar to what has previously been reported for dechlorane measurements in
241 environmental and biological samples using similar analytical approaches (Shen et al., 2010;
242 Shen et al., 2011; Baron et al., 2012). A more precise calculation would require proper ^{13}C -
243 labeled internal standard to be used, but these compounds are not yet available. For PBDEs,
244 recovery rates ranged from 55 to 81%, in accordance to one of our previous studies (Pirard
245 et al., 2003).

246 For dechloranes, retro Diels-Alder HCCPD ion fragments were selected for quantification and
247 isotope ratio checks. Typical chromatograms for dechloranes in standard solutions and in real
248 serum samples are available in supplementary data (Figure S1). The variation of the isotope
249 ratio between the two monitored ions was within $\pm 15\%$ and $\pm 30\%$ of the theoretical value for
250 PBDEs and dechloranes, respectively. LOQs of the methods, on a lipid weight basis, are listed
251 in Table 1. The method allowed the measurement of all analytes, except Dec 604 for which
252 the instrumental LOD of $0.3 \text{ pg}/\mu\text{L}$ was not suited to the very low levels in serum samples.
253 QC charts obtained for dechloranes and PBDEs, for the 6 QC samples that were analyzed
254 during the time of unknown sample analyses are shown in Figure 1. Values were
255 normalized and presented in z-score units. Upper and lower control limits (UCL/LCL)
256 corresponded to 3σ , while warning limits were set at 2σ . For each compound, each QC was
257 included within 2σ of the total average. The mean \pm SD (ng/g lw) of dechlorane and PBDE
258 levels in the non-fortified pool serum are reported in Table 2. No (certified) reference
259 materials are available so far for dechloranes. The reproducibility of the measurements was
260 acceptable with CV ranging from 11% to 32%, with CV for BDE-47 slightly higher (37%) due to

261 lower control of the blank levels in our laboratory at the time of the study. Despite the fact
262 that *syn*-DP $^{13}\text{C}_{10}$ was used, the CV for *syn*-DP was higher than for other dechloranes for
263 which no ^{13}C -labeled internal standards were available. Furthermore, for the other
264 dechloranes, when quantifications were tested on either *syn*-DP $^{13}\text{C}_{10}$ or CB-209 $^{13}\text{C}_{12}$, better
265 correlation coefficients and lower CVs were always obtained with CB-209 $^{13}\text{C}_{12}$. This was
266 verified by calibration checks over time. As reported also by others, stability issues might be
267 present for the *syn*-DP $^{13}\text{C}_{10}$ standard solution, but this requires further investigation to be
268 verified.

269

270 **3.2. Levels of dechloranes in human serum**

271 DP, Dec 602, Dec 603, CP, and Mirex were detected in almost all the serum samples while
272 Dec 604 was below detection limit for all samples. Detection frequency, mean, median, and
273 range values are reported in Table 1. DP levels (median: 1.20, range: nd - 7.04 ng/g lw) are
274 higher but consistent with levels reported by Siddique et al. (2012) in their study on human
275 milk from Canada (median: 0.6, range: nd - 8.0 ng/g lw). Studies from China reported DP
276 levels with median values 10 to 40 times higher for e-waste recycling plant workers (Ren et
277 al., 2009) and 5 times higher for women living close to e-waste recycling sites (Ben et al.,
278 2013). For both of these studies, direct occupational exposure to DP was expected according
279 to its use and production for the electronic market in North America and China. The reason for
280 the presence of dechloranes in human serum samples from Europe is not clear. DP, Dec 602
281 and Dec 603 were also detected in human serum samples from Norway (Cequier et al.,
282 2013). Direct exposures by contact to commodities containing dechloranes and/or long
283 range transport are possible hypothesis but no robust data are available so far to further
284 explore them. Dec 603 surpassed all other dechloranes in terms of concentration (median

285 value of 2.01 ng/g lw, 39% of the Σ_5 Dechloranes). Mirex, the banned product, was present
286 at measurable levels in all samples with a median value of 1.06 ng/g lw.

287 No literature data are available for comparison of relative concentration pattern of Mirex,
288 DP, Dec 602, Dec 603, Dec 604, and CP levels in serum. To our knowledge, this study is the
289 first to report levels for these Σ_5 dechloranes (5.21 ng/g lw) in human serum. Levels of Mirex
290 were rarely reported in human serum studies focusing on OCPs, as Mirex concentrations are
291 usually below LODs (Kang and Chang, 2011). The comparison within the dechlorane family
292 showed a relative concentration pattern of Dec 603 > DP > Mirex > Dec 602 > CP
293 (Figure 2). Among the few studies available on dechlorane levels, this is the first time Dec 603
294 is reported as the most abundant dechlorane. In biota studies, Mirex usually remains the
295 most abundant dechlorane, with levels 10 to 40 times higher than the other dechloranes in
296 samples from Canada or Brazil, while a smaller difference is observed in samples from Spain
297 (de la Torre et al., 2012; Guerra et al., 2011; Shen et al., 2010). In our study, Mirex and DP
298 were detected at relatively similar levels, higher than Dec 602. Similar results were reported
299 by de la Torre et al. (2012) for their study on Franciscana Dolphin from Brazil. Mirex was the
300 most abundant dechlorane, but DP and Dec 603 were reported at higher levels than Dec
301 602. In the study of Cequier et al. (2013), DP levels in human serum from Norway were
302 similar to levels reported in the present study, and around 2 times higher than levels of Dec
303 602 and Dec 603, the only other dechloranes reported in that study. DP was detected at
304 lower levels than Dec 602 in bird eggs or fish samples from both Spain and Canada (Baron et
305 al., 2012; Guerra et al., 2011). Dec 602 has already been suggested to possibly be more
306 bioavailable or bioaccumulative than DP based on their estimated octanol-water partition
307 coefficients (K_{ow}) and bioconcentration factors (BCF) (Shen et al., 2010). These results
308 support the hypothesis that not only the geographical localization influences the pattern of

309 contamination levels. The higher level of Dec 603 compared to Dec 602 could be related not
310 only to a higher level of exposure but also to a specific biotransformation or bioaccumulation
311 in mammals or humans. In the study of de la Torre et al. (2012) on mammals, they obtained
312 the highest biotransformation half-life (HL; day) value for Dec 603 (138000), followed by DP
313 (33100) > CP (12630) > Dec 602 (2752) > Dec 604 (1219) > Mirex (109).

314 Another mammal study on Arctic Beluga whales reported Dec 602 at low levels (0.08 to 0.3
315 ng/g lw) while DP, Dec 603, and Dec 604 were not detected (Shen et al., 2012). The exposure
316 level certainly remains an important factor to take in consideration, like it is the case for
317 biotransformation as dechlorinated products were also detected. Therefore, more
318 investigations are needed to fully integrate factors such as exposure level, bioavailability,
319 bioaccumulation, and biotransformation to better understand the relative distribution of the
320 various dechloranes in human serum samples.

321 Dec 602 was detected in all human serum samples while Dec 604 was not detected at all.
322 Such a situation was also reported in other biota studies (Baron et al., 2012; de la Torre et al.,
323 2012; Shen et al., 2012). Although the presence of Dec 604 in samples is likely dependent on
324 bioaccumulation parameters, it could also be a possible marker of production source
325 proximity. The study of Shen et al. in Canada (2010) demonstrated a relationship between
326 samples located in the Niagara area, close to the manufacturer Oxychem, and contamination
327 of Dec 602 and Dec 604. Similar trends obtained for Dec 602 and Dec 604 possibly reflected
328 usage patterns of these compounds in some flame retarded polymers. A production source
329 in Europe is nevertheless possible as Dec 604 has been already reported in biota
330 samples from Spain (Guerra et al., 2011).

331 Spearman's correlation coefficients were used to investigate possible relationships between
332 the different dechlorane levels (Table 3). Correlation values with statistical significance ($p <$

333 0.05* or $p < 0.01^{**}$) were obtained between all the reported dechloranes, except between
334 DP and Mirex. CP and Dec 603 showed the strongest correlation ($r_s = 0.83$ with $p < 0.01$), as
335 well as CP and Dec 602 ($r_s = 0.71$ with $p < 0.01$). The lowest but significant value ($r_s = 0.29$
336 with $p < 0.05$) was obtained between DP and Dec 602. DP has been reported as a potential
337 flame retardant in use in Europe. The reason for the lack of correlation between DP and
338 Mirex is not clear. One can think that although DP is exclusively used as a FR, Mirex was also
339 mainly used as a pesticide and this would therefore result in a different type of exposure.
340 The ban of Mirex could also be impacting the correlation, but should also do for the other
341 dechloranes such as Dec 602, Dec 603, and CP, unless the novel aspect of their use
342 counterbalances this effect. Whether the presence of dechloranes in human serum is related
343 to their use as FRs in Europe or from use as pesticides remains undefined. Balance between
344 contamination from exposure and bioaccumulation must be considered. Additionally, one
345 has to keep in mind that no production sources have been located in Europe to date,
346 opening the discussion to possible long range transport as another source of exposure.

347

348

349 **3.3. Comparison of dechlorane and PBDE levels in human serum**

350 Levels of BDE-47, 99, 100, 153 and 154 are listed in Table 1. The \sum_5 PBDE levels ranged from
351 1.63 to 15.02 ng/g lw, with a median value of 3.46 ng/g lw. BDE-47 and BDE-153 were the
352 most abundant PBDEs with a contribution of 45% and 33% to the total amount, respectively.
353 The relative concentration pattern is BDE-47 > BDE-153 > BDE-99 \approx BDE-100 > BDE-154 (Figure
354 2). Similar results with predominant BDE-47 and BDE-153 have been reported in human
355 serum studies from Sweden, Korea, Greece or Slovakia (Chovancova et al., 2012; Guvenius et
356 al., 2003; Kalantzi et al., 2011; Lee et al., 2007). Several studies from both the US and Europe

357 differently reported patterns related to the commercial PentaBDE mixture content, with a
358 major contribution of BDE-47 and BDE-99 (Antignac et al., 2009; Frederiksen et al., 2009;
359 Sjödin et al., 2004). Such differences may be related to possible variations in routes of
360 exposure and use of PBDE mixtures. As for the case of the Canadian milk samples (Siddique
361 et al., 2012), the median DP level (1.20 ng/g lw) was lower than the \sum_5 PBDEs (3.46 ng/g lw).
362 However, once other dechloranes are included, the mean \sum_5 dechlorane level (5.21 ng/g lw)
363 is higher than the mean \sum_5 PBDE level. Dec 602, Dec 603, and CP therefore appear to be
364 important congeners to measure if one has to estimate a global dechlorane exposure.
365 Focusing on DP only might lead to an under estimation of the real dechlorane exposure. Such
366 data indicate that the attention devoted to dechloranes should be continued if research
367 indicates toxicological concerns.

368 PBDE levels were correlated (Table 3) except for BDE-154 that was only correlated with BDE-
369 100 ($r_s = 0.31$, $p < 0.05$). The \sum_5 PBDE level was slightly lower than the \sum_5 dechlorane level
370 (Table 1) with median values of 3.46 ng/g lw and 5.21 ng/g lw, respectively. Potential
371 relationships between dechloranes and PBDEs levels were evaluated (Table 3). The results
372 demonstrated correlations between CP and all PBDEs, except BDE-154 (not correlated with
373 the other PBDEs). BDE-153 was correlated with Dec 602, Dec 603 and CP. A study on PBDEs
374 47, 99, and 153 metabolism mediated by human liver microsomes reported that only BDE-47
375 and BDE-99 were metabolized. This study provided a possible explanation for the high
376 bioaccumulation rate of BDE-153 in humans (Lupton et al., 2009). The hypothesis is that the
377 correlation obtained could result from a similar behavior of these dechlorane compounds.
378 Different results were obtained by de la Torre et al. (2012) when they evaluated the
379 correlation between dechloranes and PBDEs in marine mammal samples for Brazil. They only
380 reported correlations between DP and PBDEs. However, levels and relative concentration

381 patternsof PBDEs were different. Siddique et al. (2012)also reported correlations between
382 PBDEs and DP for breast milk samples from Canada but not with a consistent pattern. The
383 PBDE pattern was similar toour study although the levels were 5 times higher.

384

385 **3.4.Comparison of dechlorane and OCP levels in human serum**

386 Individual and Σ_5 of dechlorane or PBDE levels did not statistically differ between males and
387 females. Age was not correlated with PBDE levels, in accordance with previous observations
388 (Kalantzi et al., 2011), while significant correlations were found between age and Dec 603,
389 CP and Mirexlevels (Table 3).When the samples were split in two groups ($n_1 = n_2 = 24$), with
390 agerangesof 29-58 years for the first group and 59-86 years for the second group, levels of
391 Dec 603 and CP statistically differed ($p < 0.05$) with higher levels for the second group.

392 Because OCPs are persistent and bioaccumulative compounds, it is interesting to note that
393 only Dec 603 and CP demonstrated relationships with some OCP levels already reported for
394 these samples(Viel et al., 2011)Significant statistical correlations ($p < 0.05$) were found
395 between Dec 603 and beta-HCH ($r_s = 0.35$), Dec 603 and trans-nonachlor ($r_s = 0.36$), CP and
396 beta-HCH ($r_s = 0.33$) as well as CP and trans-nonachlor ($r_s = 0.35$). Beta-HCH is considered as
397 a byproduct (5-14%) of gamma-HCH (of Lindane), a well-used pesticide. Beta-HCH isomer
398 correlated with Dec 603 and CP while no correlation was found with the gamma- isomer.
399 Some studies reported greater bioaccumulation of the beta-isomer over the gamma-isomer
400 (Kolarikova et al., 2013). A similar behavior was observed with trans-nonachlor. Although
401 trans-and cis-nonachlor are both chlordane derivatives, correlations were found only with
402 the trans-isomer. Some studies have already reported higher bioaccumulation of the trans-
403 isomer over the cis-isomer (Bondy et al., 2000). Also, food web magnification factors
404 (FWMFs) were determined for beta-HCH and trans-nonachlor (Skarphedinsdottir et al.,

405 2010). The correlation of Dec 603 and CP with these specific OCP isomers could be related to
406 both exposure and bioaccumulation properties. Dec 603 and CP are known to be present as
407 impurities in technical products. In the study of Shen et al. (2011), Dec 603 was observed in
408 technical Aldrin and Dieldrin while CP was found only in technical Chlordene and Chlordane,
409 at levels lower than 1%. The higher levels of Dec 603 in the Lake Erie of Canada were
410 suggested to be related to the use of Aldrin and Dieldrin. Lower levels of CP were detected
411 compared to Dec 603 in our samples which is similar to other studies on dechlorane levels
412 including CP. However, in terms of exposure, Aldrin, Dieldrin or Chlordane were banned in
413 France in 1992 (INERIS, 1992). Results of monitoring studies performed in 2000 and 2005
414 were optimistic for the eradication of these pesticides (INERIS, 2007) and to our knowledge,
415 no preferential use of Aldrin or Dieldrin over Chlordane was reported.

416

417

418 **3.5. Levels of DP isomers**

419 *Syn*- and *anti*-DP isomers were analyzed separately. Higher levels and frequency of detection
420 were obtained for the *anti*-isomer (Table 1). The *anti*-DP fraction (f_{anti} , amount of *anti*-DP in
421 total DP) was calculated for 33 samples and ranged from 0.65 to 0.86, with a mean value of
422 0.75 ± 0.07 (RSD = 9.3%). In several studies, the f_{anti} value was compared with the reported
423 ratio of commercial DP products, to assess potential differences between isomers behavior.
424 According to Ben et al. (2013), the technical DP f_{anti} value should be comprised between 0.60
425 and 0.80, based on variation reported from various batches or manufacturers (Hoh et al.,
426 2006). Our results are included in this range and therefore support the hypothesis of
427 non-specific isomer bioaccumulation, although sources of exposure for Europe have not been
428 identified yet. However, the evaluation of a potential isomer bioaccumulation based on

429 sample measurements and technical values comparison should be done carefully. A study on
430 rats and DP exposure reported similar f_{anti} values that ranged between 0.75 and 0.80 for
431 muscle, liver and serum samples but it was also demonstrated that these DP f_{anti} values
432 decreased significantly with higher levels of exposure (Li et al., 2013). A similar behavior was
433 obtained for the study on Peregrine Falcon eggs sampled in Spain and Canada (Guerra et al.,
434 2011). Lower DP f_{anti} values were obtained for samples from Canada, when the DP levels
435 were 10 to 50 times higher than levels reported in Spain. Both f_{anti} value and DP level should
436 be taken into consideration for the evaluation of a potential stereoselective bio-
437 accumulation.

438

439 **4. CONCLUSIONS**

440 This study is the first report of Σ_5 dechlorane levels in Western European (France) human
441 serum. Despite the fact that no production sources have been identified in Europe to date, DP
442 and related dechloranes were detected. A specific pattern of contamination was found, and
443 Dec 603 was reported with high levels, compared to other biota samples that have been
444 analyzed from Europe. Results demonstrated that bioaccumulation properties should be
445 taken in consideration in addition to possible routes of human exposure. Dose-toxicity data
446 are needed for these chemicals in order to initiate proper human risk assessment. The
447 hypothesis of long range transport has also to be considered until more information on
448 production and use are made available for Europe. Nevertheless, our study indicates that at
449 least part of the European population might be exposed to dechloranes. This is further
450 supported by recent levels reported from a preliminary study performed in Norway (Cequier
451 et al., 2013). In addition, the Σ_5 dechlorane level is higher than the Σ_5 PBDE level. Because
452 unregulated dechloranes are reported to present similar physico-chemical properties and

453 cost advantages over brominated flame retardants (Oxychem, 2007), efforts should be made
454 to better understand their behavior as they might become the next family of FR to consider
455 for human biomonitoring.

456

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461

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