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1 **Prenatal exposure to Endocrine Disrupting Chemicals and risk of being born Small for**
2 **Gestational Age: pooled analysis of seven European birth cohorts**

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51

52 **Running title**

53 Endocrine Disrupting Chemicals and SGA

54 **ABSTRACT**

55 **Background and aims**

56 There is evidence that endocrine disrupting chemicals (EDCs) have developmental effects at
57 environmental concentrations. We investigated whether some EDCs are associated with the
58 adverse birth outcome Small for Gestational Age (SGA).

59 **Methods**

60 We used PCB 153, *p,p'*-DDE, HCB, PFOS and PFOA measured in maternal, cord blood or
61 breast milk samples of 5446 mother-child pairs (subset of 693 for the perfluorinated
62 compounds) from seven European birth cohorts (1997-2012). SGA infants were those with
63 birth weight below the 10th percentile for the norms defined by gestational age, country and
64 infant's sex. We modelled the association between measured or estimated cord serum EDC
65 concentrations and SGA using multiple logistic regression analyses. We explored effect
66 modification by child's sex and maternal smoking during pregnancy.

67 **Results**

68 Among the 5446 newborns, 570 (10.5%) were SGA. An interquartile range (IQR) increase in
69 PCB 153 was associated with a modestly increased risk of SGA (odds ratio (OR) of 1.05
70 [95% CI: 1.04-1.07]) that was stronger in girls (OR of 1.09 [95% CI: 1.04-1.14]) than in boys
71 (OR of 1.03 [95% CI: 1.03-1.04]) (*p*-interaction = 0.025). For HCB, we found a modestly
72 increased odds of SGA in girls (OR of 1.04 [95% CI: 1.01-1.07] per IQR increase), and an
73 inverse association in boys (OR of 0.90 [95% CI: 0.85-0.95]) (*p*-interaction = 0.0003).
74 Assessment of the HCB-sex-smoking interaction suggested that the increased odds of SGA
75 associated with HCB exposure was only in girls of smoking mothers (OR of 1.18 [95% CI:
76 1.11-1.25]) (*p*-interaction = 0.055). Higher concentrations of PFOA were associated with
77 greater risk of SGA (OR of 1.64 [95% CI: 0.97-2.76]). Elevated PFOS levels were associated
78 with increased odds of SGA in newborns of mothers who smoked during pregnancy (OR of

79 1.63 [95% CI: 1.02-2.59]), while an inverse association was found in those of non-smoking
80 mothers (OR of 0.66 [95% CI: 0.61-0.72]) (p -interaction = 0.0004). No significant
81 associations were found for p,p' -DDE.

82 **Conclusions**

83 Prenatal environmental exposure to organochlorine and perfluorinated compounds with
84 endocrine disrupting properties may contribute to the prevalence of SGA. We found
85 indication of effect modification by child's sex and smoking during pregnancy. The direction
86 of the associations differed by chemical and these effect modifiers, suggesting diverse
87 mechanisms of action and biological pathways.

88

89 **Key words:** Endocrine Disrupting Chemicals (EDCs); Small for Gestational Age (SGA);
90 Pooled analysis.

91

92 **1. INTRODUCTION**

93 A suboptimal intra-uterine environment can affect fetal growth and contribute to the risk of
94 developing adult diseases (Barker 1998). The fetus depends on an accurate hormone balance
95 for its development (Diamanti-Kandarakis et al. 2009). Concern has risen since several
96 endocrine disrupting chemicals (EDCs), particularly those with estrogenic activity, are
97 suspected of disrupting the programming of endocrine signaling pathways during
98 development (Newbold 2011). Maternal exposure to EDCs has been associated with fetal
99 growth (de Cock and van de Bor 2014; Tang-Peronard et al. 2011). During gestation, fetuses
100 are exposed to the accumulated maternal body burden of persistent organic pollutants with
101 endocrine properties, including: polychlorinated biphenyls (PCBs),
102 dichlorodiphenyldichloroethylene (*p,p'*-DDE), hexachlorobenzene (HCB), perfluorooctane
103 sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Despite regulatory measures and due to
104 their long half-lives, these compounds are still ubiquitous in the environment and detected in
105 a variety of human tissues and fluids (Malisch and Kotz 2014). The human elimination half-
106 lives of PCB 153, *p,p'*-DDE, HCB, PFOS and PFOA are >10 years (Ritter et al. 2011), ~5
107 years (Ferreira et al. 2011), ~6 years (To-Figueras et al. 2000), ~5 years (Olsen et al. 2007),
108 and 3.5 years (Olsen et al. 2007), respectively. Due to their high lipophilicity (organochlorine
109 compounds) or amphoteric properties (perfluorinated compounds) these compounds are
110 transported via the placenta to the fetus and can also reach the infant through maternal milk
111 (Stefanidou et al. 2009; WHO/UNEP 2013).

112 Up to date, most epidemiological studies have investigated associations between EDCs and
113 birth weight or other continuous measures like birth length, head circumference, gestational
114 age, and most of them reported significant inverse associations, i.e. lower birth weight, birth
115 length and head circumference for increased EDC concentrations, including HCB (Eggesbo et
116 al. 2009), PCBs (Govarts et al. 2012) and perfluorinated compounds (Bach et al. 2015;

117 Johnson et al. 2014). However, there is much variation in studies reporting on these
118 associations with several studies observing no significant association (Berkowitz et al. 1996;
119 Gladen et al. 2003; Khanjani and Sim 2006; Longnecker et al. 2005; Wolff et al. 2007).
120 Moreover, although birth weight is accurately measured, its interpretation is not always
121 obvious (EURO-PERISTAT 2013). Investigating infants born small for gestational age
122 (SGA) has advantages since it is a clinical outcome, and therefore has clear implications for
123 public health (Lee et al. 2013). Only a few studies, have looked at the association of EDCs
124 and SGA (Basterrechea et al. 2014; Eggesbo et al. 2009; Lauritzen et al. 2017; Longnecker et
125 al. 2005; Manzano-Salgado et al. 2017). Longnecker *et al.* (Longnecker et al. 2005) found a
126 significant positive association of PCBs with SGA while no significant association was found
127 for birth weight. The HUMIS cohort found a positive association close to significance of
128 HCB with SGA (Eggesbo et al. 2009), while Basterrechea *et al.* (Basterrechea et al. 2014)
129 found no significant association for HCB. In a recent Scandinavian study, prenatal exposure
130 to PFOA, PCB 153 and HCB were significantly associated with higher odds for SGA
131 (Lauritzen et al. 2017). Manzano-Salgado *et al.* (Manzano-Salgado et al. 2017) found no
132 significant associations between some perfluorinated compounds and SGA, whereas PFOS
133 exposure was associated with low birth weight in boys.

134 In the present study, we harmonized and pooled data from seven European birth cohorts with
135 organochlorine measures and four of them with measures of the perfluorinated compounds,
136 providing a large study sample to investigate the association between the selected EDCs and
137 SGA. This allowed us to examine the hypothesis that EDCs influence fetal growth.

138

139 **2. METHODS**

140 ***2.1. Description of cohorts***

141 Within the EU-FP7 OBELIX project, five European birth cohorts were available for our
142 pooled analysis: FLEHS I and II (FLEMish Environment and Health Study), HUMIS (HUman
143 Milk Study), LINC (LInking EDCs in maternal Nutrition to Child health) and PCB cohort of
144 Flanders, Norway, The Netherlands and Slovakia respectively. We invited two additional
145 cohorts, INMA (INfancia y Medio Ambiente; Environment and Childhood) (Spain) and
146 PELAGIE (Endocrine disruptors: longitudinal study on pathologies of pregnancy, infertility
147 and childhood) (France), resulting in seven European birth cohorts. Cohort participants were
148 sampled from the general population and included births from 1997 to 2012. The INMA
149 cohort was considered as two populations based upon the matrix (one available per child)
150 used for the EDC measurements (maternal or cord serum). This makes a total of 8 study
151 populations. Our study population sample was restricted to live-born singleton births, with
152 available exposure levels and information on at least one birth outcome. In total, we used
153 EDC measurements from 5446 women. Table 1 lists cohort characteristics, while
154 Supplemental Material, Table S1 contains cohorts' descriptions and references. Each cohort
155 study was approved by the national ethical committee. Mothers provided written informed
156 consent prior to participation.

157

158 ***2.2.Exposure assessment***

159 All cohorts provided concentrations from the selected exposure markers if available. PCB 153
160 was selected as a marker of overall exposure to PCBs (used in many industrial applications),
161 since it is the most abundant congener (Hagmar et al. 2006) and highly correlated with most
162 of the congeners, *p,p'*-DDE because it is the most persistent metabolite of the widely used
163 insecticide DDT (Agency for Toxic Substances and Disease Registry (ATSDR) 2002), and
164 HCB, another organochlorine pesticide widely used as fungicide. PFOS and PFOA were
165 included as markers for exposure to the perfluorinated compounds which are used as

166 fluorosurfactants in consumer products such as teflon, stain-resisting fabrics and fire-fighting
167 foams. Information on chemical-analytical methods and their limits of
168 detection/quantification (LODs/LOQs) together with the lipid analysis method of the sampled
169 matrices is given in the Supplemental Material, p.6-7 and Table S2. Concentrations below the
170 LOD/LOQ were replaced with LOD/LOQ divided by $\sqrt{2}$ (Hornung and Reed 1990). Cohorts
171 with $\geq 50\%$ of samples below the LOD/LOQ for an exposure biomarker were excluded from
172 the analysis of that exposure biomarker.

173 Since cord serum levels are considered the best proxy of organochlorine exposure during fetal
174 life (Korrick et al. 2000), we estimated the equivalent concentrations in cord serum from the
175 concentrations measured in maternal serum or breast milk.

176 The non-dioxin-like organochlorine compounds PCB 153, *p,p'*-DDE and HCB were
177 measured in cord plasma or serum for FLEHS I & II, the PCB cohort and PELAGIE, in breast
178 milk for HUMIS, in cord plasma or breast milk for the LINC cohort, and in cord or maternal
179 serum for the INMA cohort. For the recalculation of PCB 153 and *p,p'*-DDE to cord serum
180 levels, we used conversion factors obtained from a previous study (Govarts et al. 2012):

181 Cord serum level (ng/L) = 0.20 x maternal serum level (ng/L)

182 Cord serum level (ng/L) = 1.20 x breast milk level (ng/g fat)

183 For HCB, we obtained conversion factors from available data in the literature (Palkovicova
184 Murinova et al. 2017; Patayova et al. 2013):

185 Cord serum level (ng/L) = 0.265 x maternal serum level (ng/L)

186 Cord serum level (ng/L) = 2.18 x breast milk level (ng/g fat)

187 Due to variability between the published milk/maternal serum HCB concentration ratios
188 (Palkovicova Murinova et al. 2017), a sensitivity analysis was performed using the minimum
189 and maximum ratios of 0.848 and 1.87, respectively, which resulted in a conversion factor of
190 1.42 and 3.13, respectively, for the conversion of breast milk levels to cord serum levels.

191 The perfluorinated compounds PFOS and PFOA were measured in breast milk samples for
192 HUMIS and the PCB cohort, in cord plasma for FLEHS II and in cord plasma or breast milk
193 for the LINC cohort. Based on the recently published partitioning coefficients for breast
194 milk:plasma of 0.014 and 0.058 and fetal:maternal plasma concentrations of 0.45 and 0.78 for
195 PFOS and PFOA respectively in Verner *et al.* (Verner et al. 2016), the following conversion
196 factors were obtained:

197 For PFOS: Cord serum level (ng/L) = 32 x breast milk level (ng/L)

198 For PFOA: Cord serum level (ng/L) = 13 x breast milk level (ng/L)

199

200 ***2.3. Outcome variable***

201 The outcome of interest was SGA, calculated as birth weight below the 10th percentile of birth
202 weight for each week of pregnancy defined by available country- and sex-specific reference
203 weight curves (FLEHS I and II: The Flemish Centre for the Study of Perinatal Epidemiology
204 2001-2010; HUMIS: (Skjaerven et al. 2000); INMA: (Carrascosa et al. 2008); LINC: (Visser
205 et al. 2009); PCB cohort: (Kucera et al. 1998); PELAGIE: (Audipog Sentinel Network 2008)).
206 An overview of the country- and sex-specific reference percentiles used for each cohort is
207 given in the Supplemental Material, Table S3 and Table S4. Birth weight was extracted from
208 medical records collected in the birth cohorts and information on gestational age was
209 estimated from the questionnaires based on date of the last menstrual period and/or by
210 ultrasound. For HUMIS and some of the INMA cohorts, the data obtained from the last
211 menstrual period were replaced by ultrasound determination if the discrepancy between the
212 two methods exceeded 7-14 days (Table 1).

213

214 ***2.4. Statistical analysis***

215 After harmonizing and pooling the data, we assessed correlations between exposures using
216 Spearman's correlation coefficient. For the outcome SGA, we fitted a multiple logistic
217 regression model to estimate the association with each EDC independently, adjusting for
218 confounders, using a generalized estimating equation (GEE) that accounts for correlation
219 from between-cohort variation. A p -value < 0.05 was taken as significance level for the EDC
220 estimate. Potential confounders and known determinants of birth weight were included in the
221 models based on literature (Bailey and Byrom 2007; Goldenberg et al. 1997; McCowan and
222 Horgan 2009). These included sex of the newborn (male/female), maternal pre-pregnancy
223 body mass index (BMI; <18.5 kg/m², $18.5 < 25$ kg/m², $25 < 30$ kg/m², and ≥ 30 kg/m²), maternal
224 height (<163 cm, $163 < 169$ cm, ≥ 169 cm), smoking status during pregnancy (non-smoking,
225 smoking as derived from questionnaire information), maternal education (maximum
226 secondary school, higher education), maternal age at delivery (<25 years, $25 < 30$ years, $30 < 35$
227 years, ≥ 35 years) and parity (0, 1 and ≥ 2). Missing values were not imputed. We additionally
228 evaluated sex and smoking status as potential effect modifiers of EDC exposures as indicated
229 by several previous studies (Casas et al. 2015; Eggesbo et al. 2009; Hertz-Picciotto et al.
230 2005; Lamb et al. 2006; Sonneborn et al. 2008; Vafeiadi et al. 2014). Effect modification was
231 analyzed in models including main effects and cross-product terms. A p -value < 0.05 was the
232 significance level suggesting an interaction. Moreover, we tested for heterogeneity in the
233 exposure-effect association between the cohorts by fitting a model with the interaction term
234 between cohort and exposure. Not all cohorts or only a subset of some cohorts had
235 information on maternal gestational weight gain (GWG) (Table 1). We performed a
236 sensitivity analysis to explore the effect of GWG on the EDC-SGA associations, except for
237 the perfluorinated compounds, which do not accumulate in fat tissue. As information on
238 ethnicity is missing for some of the cohorts (FLEHS I & II, LINC and PELAGIE), but
239 probably a high percentage is Caucasian, a sensitivity analysis was performed excluding the

240 Roma participants as they constituted about 21% of the PCB cohort (Table 1). Furthermore,
241 we reran the final analysis restricting to studies where EDCs have been measured in cord
242 blood for the non-dioxin-like organochlorine compounds without applying conversion factors.
243 Moreover, multipollutant models were studied for the pooled database including PCB 153,
244 *p,p'*-DDE and HCB as these pollutants were measured in all 7 birth cohorts. We did not
245 attempt to include also the perfluorinated compounds in the multipollutant model due to small
246 sample size with all exposures and covariates available (N = 344). We checked for
247 collinearity with variance inflation factors greater than 5 (Kleinbaum et al. 2013) and
248 condition index greater than 30 (Belsley 1991) suggesting a problem of collinearity.
249 For each pollutant model, the assumption that the exposure is linearly related to the log-odds
250 of the binary outcome SGA was not rejected (*p*-value > 0.05) by restricted cubic splines,
251 therefore the exposure concentrations were introduced into the model as a continuous
252 variable. To quantify the exposure-response association, the estimates are presented as odds
253 per interquartile range (IQR) increase of cord serum contaminant concentration.
254 All statistical analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC,
255 USA). R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to
256 construct the figures.

257

258 3. RESULTS

259 Table 1 summarizes the characteristics of all 8 study populations. The median birth weight
260 and gestational age were 3350 grams (3405 grams for boys and 3300 grams for girls) and 40
261 weeks, respectively. INMA babies were the lightest and HUMIS and LINC babies the
262 heaviest. The percentage of mothers who indicated they smoked during pregnancy varied
263 across the cohorts (4% for LINC to 30% for INMA). In the PCB cohort, 46.5% of the mothers
264 were <25 years at delivery, while in the other cohorts this proportion was between 4.1 and

265 16.6%. Overall, most women delivered their first child (38-61%). The proportion of
266 overweight/obese women was higher in HUMIS (33%) compared to the other cohorts. There
267 were 570 (10.5%) SGA-babies. The proportion of SGA across the cohorts varied between 7.0-
268 13.6%, except in the LINC cohort (4 SGA-babies, 4.8%). Information on GWG was available
269 for between 0 (FLEHS II)-97.5% (HUMIS) of the participants in the different cohorts (Table
270 1).

271

272 Overall correlations between biomarkers for prenatal organochlorine compounds were
273 moderate to high ($r = 0.63$ and $r = 0.64$ for respectively PCB 153 and p,p' -DDE with HCB; r
274 $= 0.73$ for PCB 153 with p,p' -DDE), whereas the correlations between the two perfluorinated
275 compounds were lower ($r = 0.47$) (Supplemental Material, Table S5). Correlations between
276 other exposure biomarkers were small (r ranging from 0.12 to 0.35), except for PFOA with
277 p,p' -DDE ($r = 0.59$) (Supplemental Material, Table S5).

278

279 *3.1. Non-dioxin-like organochlorine compounds*

280 The median (range of cohort medians) cord serum concentrations for PCB 153, p,p' -DDE and
281 HCB in the pooled cohort populations were 88.0 ng/L (30.0 for LINC to 271.8 ng/L for PCB
282 cohort), 258.0 ng/L (49.7 for HUMIS to 1015.3 ng/L for PCB cohort) and 63.8 ng/L (24.4 for
283 HUMIS to 178.4 ng/L for PCB cohort), respectively (Table 2). In FLEHS II and LINC, the
284 detection frequency for HCB was only 50% and 33% respectively (Table 2) and these cohorts
285 were excluded from the HCB analyses. For the INMA Menorca cohort the LOQ of 484.1
286 ng/L for HCB measured in cord serum was much higher compared to the other cohorts with
287 cord serum measures (LOQ ranged between 1.4-79 ng/L) (Supplemental Material, Table S2),
288 so this sub-cohort was also excluded from the HCB analyses.

289 Figure 1 show the adjusted association between chlorinated persistent organic pollutants
290 (PCB 153, *p,p'*-DDE and HCB) and SGA. PCB 153 showed a stronger significant increased
291 odds of SGA in girls (odds ratio (OR) of 1.09 [95% CI: 1.04, 1.14]) than in boys (1.03 [95%
292 CI: 1.03, 1.04]) (*p*-interaction = 0.025) (Figure 1). For HCB, a significant increased odds of
293 SGA was found in girls (OR of 1.04 [95% CI: 1.01, 1.07]), while a decreased odds of SGA
294 was found in boys (OR of 0.90 [95% CI: 0.85, 0.95]) (*p*-interaction = 0.0003) (Figure 1).
295 Additionally, there was an indication of effect modification by smoking for HCB as there was
296 a significant association between HCB and SGA among children from smoking mothers (OR
297 of 1.03 [95% CI: 1.01, 1.06]) compared to an inverse association among children from non-
298 smoking mothers (OR of 0.97 [95% CI: 0.93, 1.00]) (*p*-interaction = 0.02) (Supplemental
299 Material, Table S6). There was an indication of a three-way interaction HCB-sex-smoking (*p*-
300 interaction = 0.055). The association remained significant in girls from smoking mothers (OR
301 of 1.18 [95% CI: 1.11-1.25]), but not those from non-smoking mothers (OR of 0.99 [95% CI:
302 0.94-1.05]). There was an inverse association between HCB and SGA for boys, regardless of
303 maternal smoking status (Supplemental Material, Table S6). There was no effect modification
304 indicated by smoking status for either PCB 153 or *p,p'*-DDE in association with SGA. No
305 statistically significant association was found for *p,p'*-DDE with SGA (Figure 1). Sensitivity
306 analysis ran removing EDCs measured in breast milk (HUMIS and subset of LINC) and
307 maternal serum (subset of INMA) yielded similar results (data not shown). The sensitivity
308 analysis using the minimum and maximum factor for the conversion of HCB breast milk to
309 cord serum levels resulted in identical estimated odds ratios and 95% CIs compared to the
310 median conversion factor as used in the original models (Supplemental Material, Table S7).
311 Multipollutant models including PCB 153, *p,p'*-DDE and HCB slightly changed the estimated
312 odds ratios of the pollutants (Supplemental Material, Table S8), but did not alter the
313 interpretation of the results. Only the increased odds of SGA in girls declined for HCB when

314 adjusting for PCB 153 and *p,p'*-DDE. Although these exposures were significantly correlated,
315 their variance inflation factors were around 1.3 and the largest condition index was equal to
316 18.8, indicating that the problem of collinearity was avoided in this large study population
317 (N=4377).

318

319 *3.2. Perfluorinated compounds*

320 For the perfluorinated compounds, the pooled median cord serum concentration was 1984
321 ng/L (960 for PCB cohort to 2700 ng/L for FLEHS II) for PFOS and 550 ng/L (312 for
322 HUMIS to 1500 ng/L for FLEHS II) for PFOA (Table 3). The adjusted pooled analysis of
323 perfluorinated compounds showed PFOA exposure associated with a higher odds of having an
324 SGA-baby (OR of 1.64 [95% CI: 0.97, 2.76]) (Figure 2). The association between PFOA and
325 SGA was stronger for mothers who smoked during pregnancy with an OR of 2.18 (95% CI:
326 1.02, 4.64) versus 1.51 (95% CI: 0.87, 2.63) in non-smoking mothers, although not
327 statistically significant (*p*-interaction = 0.33). Significant effect modification by maternal
328 smoking during pregnancy was observed for the association between PFOS and SGA (*p*-
329 interaction = 0.0004): newborns of non-smoking mothers had a significant decreased odds of
330 SGA (OR of 0.66 [95% CI: 0.61, 0.72]) associated with PFOS exposure, while those of
331 smoking mothers had an increased odds of SGA (OR of 1.63 [95% CI: 1.02, 2.59]) (Figure 2).
332 There was no effect modification indicated by child's sex for either PFOS or PFOA.

333

334 There was some evidence (*p*-interaction < 0.05), of effect modification by cohort, but the
335 direction of the estimates was not heterogeneous (data not shown). In general, additional
336 adjustment for GWG had no influence on the associations between EDCs and SGA, although
337 the estimates slightly reduced for PCB 153 (Supplemental Material, Table S9). The estimated

338 odds ratios changed slightly, but the interpretation of the results remained when fitting the
339 final models again excluding the Roma participants (Supplemental Material, Table S10).

340

341 **4. DISCUSSION**

342 We examined the association between prenatal exposure to different EDCs and SGA in seven
343 European birth cohorts (eight study populations). This is the first epidemiological study to
344 pool different birth cohorts for assessing the association between different EDCs and the
345 clinical outcome SGA. Exposure to PCB 153 was associated with a significantly increased
346 risk of SGA, with a stronger association in girls. For HCB, we found significant increased
347 odds of SGA for girls, while the odds of SGA was significantly decreased in boys. The
348 association of HCB with SGA in girls was, however, only observed in newborns of smoking
349 mothers. We also observed PFOA concentrations associated with increased odds of having an
350 SGA-baby. Furthermore, the association was even stronger in newborns of mothers who
351 smoked during pregnancy. Also PFOS was associated with increased odds of SGA in
352 newborns of mothers who smoked during pregnancy, while an inverse association was
353 observed in newborns of non-smoking mothers. No significant associations were found for
354 *p,p'*-DDE. In addition, we found that maternal gestational weight gain only had a small to no
355 influence on these associations.

356

357 *4.1. Adverse outcome SGA*

358 This is the largest study to date on the associations between some EDCs and the adverse birth
359 outcome SGA. SGA represents a fetus that is relatively small according to its gestational age.
360 This is important since intra-uterine growth restriction is a risk factor for neonatal
361 complications, neurobehavioral disorders, insulin resistance, central adiposity, as well as
362 metabolic conditions and cardiovascular disorders in adulthood (Barker et al. 1989; Hofman

363 et al. 2004; Lundgren and Tuvemo 2008; Oelberg 2006). As SGA is by definition an outcome
364 that occurs in about 10% of the population, it is difficult to explore exposure-response
365 analysis in separate, rather small cohorts. As the associations have to be adjusted for several
366 important confounders, the chance of observing (quasi-) complete separation in the data
367 points is high, i.e. when the outcome variable separates a combination of predictor variables
368 completely (to a certain degree). For binary outcomes with a rather low prevalence such as the
369 one studied here, pooling different databases results in more power to explore associations.
370 Quasi-complete separation of data points was observed in some of the cohort separate
371 analyses of the current study, namely PELAGIE for all organochlorine analyses, HUMIS and
372 the PCB cohort for the perfluorinated compounds, therefore the obtained estimates were not
373 reliable (Allison 2008). However, this was not a problem for the pooled analyses.

374 As SGA was calculated based on country-specific birth weight for gestational age reference
375 curves, the classification is country-dependent. The birth weights from the obtained reference
376 percentiles are variable across countries. This was expected as there is a north-south gradient
377 for birth weight in Europe, i.e. the Nordic countries having higher birth weights and countries
378 from Southern Europe having lower birth weights (OECD 2012). This gradient is both
379 reflected in the obtained country-specific reference percentiles as in our cohort data, i.e. the
380 HUMIS cohort (Norway) having the highest median birth weight and in general higher
381 reference birth weights and the INMA (Spain) and PCB cohort (Slovakia) having the lowest
382 median birth weight and reference birth weights. The variation in birth weight across
383 countries is as such taken into account.

384

385 *4.2. Non-dioxin-like organochlorine compounds*

386 In the current pooled analysis, significantly higher odds of SGA were observed with
387 increasing PCB 153 concentrations, and no significant associations were found for *p,p'*-DDE.

388 The positive association of PCBs with SGA was also observed by Lauritzen *et al.* and
389 Longnecker *et al.* (Lauritzen *et al.* 2017; Longnecker *et al.* 2005). Recently, a significant
390 inverse association between environmental exposure to PCB 153 and birth weight was found
391 in a pooled analysis of 9000 mother-child pairs, enrolled in 11 European birth cohorts (Casas
392 *et al.* 2015), but none found for *p,p'*-DDE. All our cohorts, except the LINC cohort were
393 included in those analyses. Casas *et al.* (Casas *et al.* 2015) also showed a stronger effect of
394 PCB 153 in girls whose mothers smoked during pregnancy. In our study a stronger
395 association was also seen in girls, but no effect modification by smoking was indicated. This
396 stronger effect of PCB 153 in girls was previously found in a study by Lamb *et al.* (Lamb *et*
397 *al.* 2006), but other studies have also reported a stronger effect in boys (Hertz-Picciotto *et al.*
398 2005; Lauritzen *et al.* 2017; Sonneborn *et al.* 2008). These studies were, however, too small to
399 explore effect modification by sex (n between 150-1057).

400 Our findings that HCB was significantly associated with increased odds of being SGA for
401 girls and decreased odds for boys are somewhat consistent with results found in a recent
402 Greek study (Vafeiadi *et al.* 2014). In that study, HCB measured in maternal serum during
403 pregnancy had a significant inverse association with birth weight in girls, while there was no
404 statistically significant association found in boys. Moreover, that study observed stronger
405 associations between HCB and birth weight among babies of smokers or ex-smokers
406 compared to non-smokers, which was also observed in our study. Similar results were
407 observed by Eggesbø *et al.* (Eggesbo *et al.* 2009), where the inverse association between HCB
408 and birth weight was present only among smokers. We observed a three-way interaction sex-
409 smoking-HCB. To our knowledge, such a finding has not been previously reported. Vafeiadi
410 *et al.* (Vafeiadi *et al.* 2014) also conducted a multipollutant model including the sum of 6 PCB
411 congeners, *p,p'*-DDE and HCB and showed that the association with birth weight was mainly
412 driven by HCB. However, no collinearity diagnostics were mentioned and the analysis was

413 conducted in a sample size of 522 newborns. In our pooled multipollutant model including
414 PCB 153, *p,p'*-DDE and HCB, the interpretation of the results of the single pollutant models
415 was not affected, and both PCB 153 and HCB appeared to drive the association with SGA.
416 The association of HCB with SGA in girls was, however, less strong when mutually adjusting
417 for PCB 153 and *p,p'*-DDE.

418

419 *4.3. Perfluorinated compounds*

420 The association between increasing PFOA concentrations and the increased odds of having an
421 SGA-baby are consistent with the conclusion of a recent systematic review of Bach *et al.*
422 (Bach *et al.* 2015). In 14 studies with PFOA/PFOS measurements in maternal blood during
423 pregnancy or in umbilical cord blood, *in utero* PFOA exposure was associated with decreased
424 birth weight, even though the magnitude of the association differed and many results were not
425 statistically significant. In a meta-analysis of 9 out of 18 studies on PFOA exposure in relation
426 to fetal growth a significant decrease in birth weight (-18.9 g (95% CI: -29.8, -7.9)) was found
427 for a 1 ng/mL increase in serum or plasma PFOA (Johnson *et al.* 2014). In a recent
428 Scandinavian study, prenatal exposure to PFOA was associated with higher odds for SGA
429 (Lauritzen *et al.* 2017). For PFOS exposure the association with birth weight was observed in
430 some studies, while others found no significant association (Bach *et al.* 2015; Lauritzen *et al.*
431 2017; Manzano-Salgado *et al.* 2017). In our study, PFOS was associated with SGA in
432 newborns of smoking mothers, while an inverse association was observed in those of non-
433 smoking mothers. For both PFOS and PFOA we found indication of effect modification by
434 smoking, but this was not considered in any previous studies.

435 In the recent report of US-EPA (US-EPA 2016) on the health effects of PFOA was concluded,
436 that the association observed between PFOA plasma/serum concentration and birth weight is
437 possibly explained by the influence of the glomerular filtration rate (GFR) (Verner *et al.*

438 2015; Vesterinen et al. 2015). Women who give birth to babies with low birth weight have
439 lower GFR. A lower GFR in turn decreases the removal of PFOA from the blood. Therefore,
440 it is possible that women who give birth to babies with a lower birth weight have higher
441 serum PFOA concentrations because of a lower GFR. However, as we did not see the same
442 effect for PFOS in our study, it seems that the observed association between PFOA and SGA
443 could not solely be attributed to confounding. In a recent Spanish study (Manzano-Salgado et
444 al. 2017) maternal GFR measured early during pregnancy did not confound the estimated
445 associations between perfluorinated compounds and birth outcomes.

446

447 *4.4.Mechanisms*

448 Identifying the mechanisms whereby EDCs influence weight homeostasis and energy balance
449 remains an important area of research. It is clear from our results that not all endocrine
450 disrupting compounds exert similar effects. Indeed, there are a variety of direct mechanisms
451 such as binding to nuclear receptors or indirect mechanisms by which these chemicals may
452 interfere with weight homeostasis and energy balance. Various PCB congeners bind to the
453 estrogen receptor, acting as agonists or antagonists and change normal fetal programming
454 (Newbold et al. 2009). PCB metabolites are high-affinity ligands for the thyroid hormone
455 transport protein transthyretin (Cheek et al. 1999). *p,p'*-DDE binds to the androgen receptor
456 (Kelce et al. 1995; Xu et al. 2013), while PFOA promotes adipocyte differentiation as a
457 peroxisome proliferator-activated receptor gamma (PPAR γ) ligand (White et al. 2011;
458 Yamamoto et al. 2015). Several studies in rats demonstrated the thyroid-disrupting effect of
459 the pesticides DDT (Scollon et al. 2004) and HCB (Alvarez et al. 2005; van Raaij et al.
460 1993a; van Raaij et al. 1993b), as they decreased serum levels of thyroid hormones. High
461 maternal free thyroxine levels during the first half of pregnancy were related to lower birth
462 weight and increased risk of SGA newborns, suggesting that maternal thyroid function may

463 affect fetal growth, even within the normal range. Sexual dimorphism appears to be present in
464 the relationship between maternal thyroid metabolism and fetal intrauterine growth, with
465 stronger associations in male infants (Leon et al. 2015; Vrijkotte et al. 2017). PPAR γ is the
466 main regulator of placental metabolism, controlling the amounts of maternal nutrients that go
467 across to the fetus and hence will influence fetal growth (Xu et al. 2007). Estrogens are
468 known to play an important role for placental angiogenesis, which is crucial for transport of
469 nutrients to the fetus (Albrecht and Pepe 2010). It has been shown that obesogenic EDCs can
470 alter the epigenome of multipotent stromal cells, which is preprogrammed toward an
471 adipogenic fate (Janesick and Blumberg 2011, 2012). Other proposed endocrine disrupting
472 mechanisms are changes in glucocorticoids and steroid hormones that may affect neuronal
473 cells and release of brain-produced substances that bind to nuclear receptors and may affect
474 energy regulation (Harris and Seckl 2011). The exact target tissue is unknown and probably
475 involves multiple target sites, e.g. adipocytes, brain, liver, stomach, pancreas, and the effects
476 may be age, dose and sex dependent. Our results suggested that sex and smoking during
477 pregnancy were potential effect modifiers on SGA, although mechanisms underlying these
478 potential interactions remain unclear. For HCB, even opposite effects were found in girls
479 (significant increased risk of SGA) versus boys (significant decreased risk of SGA). It is
480 difficult to hypothesize the mechanism through which this effect modification is caused.
481 Since HCB is a known EDC it might also disrupt sex hormone pathways, and as such a
482 finding specific to girls or boys would not be unexpected. The biological mechanism
483 underlying the possible modifying effect of sex and smoking remains to be established.

484

485 *4.5. Confounders and Risk factors*

486 Maternal gestational weight gain (GWG) will dilute the EDC concentrations in maternal
487 blood and is also overall positively associated with birth weight of the child, and may

488 therefore be a confounder of the associations between EDCs and birth weight (Verner et al.
489 2013). Associations between GWG and cord serum concentrations of Σ PCBs, 4,4'-DDE and
490 HCB have been reported (Vizcaino et al. 2014). We evaluated whether GWG confounded the
491 associations of the EDCs with SGA in the subset of the pooled data having information on
492 GWG (Table 1). Maternal GWG influenced the association between EDCs and SGA to a
493 limited extent in this study. The estimated odds ratios did not change substantially after
494 additional adjustment for GWG for *p,p'*-DDE and HCB. For PCB 153, the odds ratios slightly
495 reduced but remained significant when correcting for GWG, indicating a degree of partial
496 confounding.

497

498 In a previous paper exploring the association between PCBs and birth weight in the PCB
499 cohort, effect modification was observed by Roma ethnicity where maternal PCB
500 concentrations were associated with lower birth weight in Roma boys (Sonneborn et al.
501 2008). Information on ethnicity is however not known for four of the seven birth cohorts, but
502 the percentage of Caucasian participants within these cohorts is likely very high, and for
503 HUMIS and INMA respectively 94% and 96% of the participants were Caucasian. In the PCB
504 cohort about 21% of the population was Roma and in the HUMIS cohort there was also one
505 Roma participant. As such we decided to do a sensitivity analysis excluding the Roma
506 population from the final models. The interpretation of the EDC-SGA associations was not
507 influenced in this sensitivity analysis.

508

509 There are many established risk factors for babies who are SGA (McCowan and Horgan
510 2009). The confirmed maternal risk factors identified in the models for SGA in this study
511 include small maternal height, low maternal pre-pregnancy BMI, smoking during pregnancy
512 and nulliparity. All the models were adjusted for these identified risk factors and additionally

513 for maternal education, maternal age at delivery and child's sex. Some potential risk factors
514 such as cocaine use, vitamin status, mother/father born SGA were not available in the
515 questionnaires or there were not enough cases present in the cohorts (e.g. pre-eclampsia,
516 hypertension). In the pooled model, mothers smoking during pregnancy had about 2.5 times
517 higher odds of having an SGA-baby than non-smoking mothers, adjusting for the other factors
518 in the model. For an increase of PCB 153, HCB, PFOS and PFOA with the IQR, we obtain
519 respectively an odds ratio of: 1.09 (girls) and 1.03 (boys) for PCB 153 (for an increase of 125
520 ng/L); 1.04 for HCB in girls (for an increase of 127 ng/L); 1.6 (smoking mothers during
521 pregnancy) for PFOS (for an increase of 1808 ng/L) and of 1.5 (non-smoking mothers during
522 pregnancy) and 2.2 (smoking mothers during pregnancy) for PFOA (for an increase of 901
523 ng/L). The results indicate that smoking, a well-known risk factor for SGA, is more strongly
524 associated with SGA, than the pollutants studied. On the other hand almost all babies had
525 measurable EDC concentrations and hence are exposed. In addition, for the perfluorinated
526 compounds the odds of SGA in those already exposed to maternal smoking were rather
527 substantial.

528

529 *4.6.Strengths and Limitations*

530 The particular strength of this study was that by pooling the results, information was obtained
531 on the risks of being born small for gestational age. The pooled analysis included more than
532 5000 mother-child pairs for the analysis of the prenatal growth effects of PCB 153, HCB and
533 *p,p'*-DDE; and nearly 700 for the perfluorinated compounds (PFOA and PFOS). As such, a
534 large enough sample size was attained to explore effect modification by child's sex and
535 smoking. For outcome parameters that are not highly prevalent but clinically relevant, pooling
536 of data is very useful. However, pooling data from different cohorts could lead to effect
537 modification by cohort due to underlying heterogeneity of the populations. The direction of

538 the estimates was however not heterogeneous when including the interaction term with cohort
539 in the models. By pooling data from different cohorts over Europe we obtained considerable
540 variability in exposure levels. Nevertheless, as the birth cohorts span a fifteen year period
541 from 1997-2012, the exposure to the selected EDCs could have changed over time, i.e.
542 changes in behaviors or manufacturing practices that could have reduced exposure over time,
543 and this might have affected the analysis. As such, a decrease over time of the non-dioxin-like
544 organochlorine compounds (Schoeters et al. 2017) appears to attribute to the low detection
545 frequency of HCB in the most recent cohorts FLEHS II (2008-2009) and LINC (2011-2012)
546 together with the relatively high quantification limit in cord serum versus milk samples which
547 have higher lipid content. There is a potential of exposure misclassification induced by
548 different methods of measuring the exposures across the cohorts. The organochlorine
549 compounds were measured by different laboratories using different methodologies, however
550 the LODs/LOQs were very similar, typically within a range of a factor of 2, except for HCB
551 within the INMA Menorca cohort, which was therefore excluded from the analyses. For the
552 perfluorinated compounds, the sensitivity of the analyses in cord plasma differed between the
553 two laboratories, but as the detection frequency for all cord plasma measures was 100% this
554 would not have led to misclassification. The analysis of perfluorinated compounds in breast
555 milk samples were performed in the same laboratory. Although biomarker concentrations
556 were measured in different laboratories, these labs performed their analysis according to
557 internal lab quality systems and participated in international ring tests to verify their analytical
558 results and to ensure the comparability of their data. As different biological matrices (cord
559 plasma/serum, maternal serum and breast milk) were used to assess EDC exposure, variation
560 is introduced with respect to the period of exposure it represents. Conversion factors were
561 used to estimate the corresponding cord serum levels. However, while the EDCs studied are
562 persistent, mobilization of these during different periods of pregnancy could lead to variation

563 in the levels. The conversion of available pollutant concentrations in maternal serum or breast
564 milk to cord serum levels may introduce estimation error in the pollutant concentrations.
565 However, we also performed our analysis in a subset of the dataset with EDCs measured in
566 cord blood without applying any conversion factor as a sensitivity analysis and this did not
567 change the conclusions. For HCB the sensitivity analysis, using the minimum and maximum
568 factor for the conversion of breast milk to cord serum levels yielded identical results to those
569 from the original model using the median conversion factor. A further weakness of the study
570 is that the chemicals were included one by one in the statistical models, which does not reflect
571 what happens in the real world situation in which multiple exposures and stressors may act or
572 counteract. We cannot exclude that highly correlated exposure biomarkers act as a proxy for
573 each other. However, the pooled database of 7 birth cohorts offered a large enough sample
574 size to study PCB 153, *p,p'*-DDE and HCB in a multipollutant model. The interpretation of
575 the association between individual exposures and SGA was independent of the other
576 exposures; identical results were obtained from the single versus multipollutant models.
577 Although these exposures were significantly correlated, the problem of collinearity was
578 avoided in this large study population (N=4377). This concurs with a recent simulation study
579 that shows that for properly specified models, total effect estimates remained unbiased even
580 when the exposures are highly correlated (Schisterman et al. 2017). Furthermore, we cannot
581 exclude the possibility of unmeasured confounding, both by other exposures and by other
582 possible factors. As only measures of PCB153, HCB, *p,p'*-DDE, PFOS and PFOA were used,
583 it is possible that the effects observed may be due to other, correlated chemicals that were not
584 measured, such as other PCB congeners or perfluorinated compounds as perfluorononanoic
585 acid (PFNA) or perfluorohexane sulfonic acid (PFHxS). Another limitation is differential
586 determination of gestational age. For some of the cohorts gestational age was estimated from
587 the date of the last menstrual period which is less accurate than ultrasound determination

588 (Butt and Lim 2014). Also smoking status during pregnancy was derived from questionnaire
589 information and could be under reported.

590

591 **5. CONCLUSIONS**

592 A pooled analysis of 7 European birth cohorts found that prenatal environmental exposures to
593 organochlorine and perfluorinated compounds with endocrine properties, may contribute to
594 the prevalence of SGA. Child's sex and smoking during pregnancy were identified as
595 potential effect modifiers in these associations. The EDCs studied did not all exhibit
596 associations in the same direction, suggesting diverse mechanisms of action and biological
597 pathways.

598

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604

605 **Competing financial interests**

606 The authors declare they have no competing financial interests.

607

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821 TABLES

822 Table 1: Characteristics of the 8 study populations

Characteristics	FLEHS I (Belgium, 2002-2004)	FLEHS II (Belgium, 2008-2009)	HUMIS (Norway, 2002-2006)	INMA cord (Spain, 1997-2008)	INMA mat (Spain, 2004-2008)	LINC (The Netherlands, 2011-2012)	PCB cohort (Slovakia, 2002-2004)	PELAGIE (France, 2002-2006)
N ^a	1105	242	440	1287	860	84	1034	394
Small for gestational age								
Yes	113 (10.2%)	17 (7.0%)	60 (13.6%)	129 (10.0%)	91 (10.6%)	4 (4.8%)	127 (12.3%)	29 (7.4%)
No	992 (89.8%)	225 (93.0%)	380 (86.4%)	1158 (90.0%)	769 (89.4%)	80 (95.2%)	907 (87.7%)	365 (92.6%)
Birth weight (g)	3390 (1245-5575)	3530 (2175-4950)	3614 (2015-5100)	3250 (1200-4880)	3290 (770-4785)	3600 (2130-4950)	3350 (950-5060)	3370 (1070-4760)
Gestational Age (GA) (weeks)	39 (31-42)	40 (34-42)	40 (35-44)	40 (30-42)	40 (28-42)	40 (34-42)	40 (30-43)	40 (27-42)
Determination of GA								
1 st day last menstruation				964 (74.9%)		84 (100%)	1034 (100%)	
Ultrasound								394 (100%)
Combination			440 (100%)	323 (25.1%)	860 (100%)			
Missing (%)	100%	100%	0%	0%	0%	0%	0%	0%
Term								
Preterm (<37 weeks)	38 (3.4%)	5 (2.1%)	10 (2.3%)	52 (4.0%)	29 (3.4%)	3 (3.6%)	25 (2.4%)	10 (2.5%)
Term (37-42 weeks)	1067 (96.6%)	237 (97.9%)	406 (92.3%)	1217 (94.6%)	822 (95.6%)	81 (96.4%)	1007 (97.4%)	384 (97.5%)
Over term (>42 weeks)	0 (0%)	0 (0%)	24 (5.5%)	18 (1.4%)	9 (1.1%)	0 (0%)	2 (0.2%)	0 (0%)
Child gender								
Boy	577 (52.2%)	126 (52.1%)	227 (51.6%)	676 (52.5%)	427 (49.7%)	50 (64.1%)	526 (50.9%)	200 (50.8%)
Girl	528 (47.8%)	116 (47.9%)	213 (48.4%)	611 (47.5%)	433 (50.4%)	28 (35.9%)	508 (49.1%)	194 (49.2%)
Missing (%)	0%	0%	0%	0%	0%	7.1%	0%	0%
Maternal age at delivery (years)	29.6 (18.1-44.0)	30.2 (18.2-42.4)	29 (16-42)	31.1 (16.7-44.5)	31.8 (17.8-43.8)	31.3 (23.1-40.4)	25.5 (17.9-44.9)	30.4 (20.1-44.9)
Missing (%)	0.5%	0%	0%	1.2%	0.1%	6.0%	0.8%	0%
Maternal age at delivery								
<25 years	157 (14.3%)	27 (11.2%)	73 (16.6%)	107 (8.4%)	35 (4.1%)	5 (6.3%)	477 (46.5%)	33 (8.4%)
25<30 years	425 (38.7%)	89 (36.8%)	176 (40.0%)	398 (31.3%)	234 (27.2%)	22 (27.9%)	339 (33.0%)	150 (38.1%)
30<35 years	404 (36.8%)	93 (38.4%)	127 (28.9%)	529 (41.6%)	392 (45.6%)	35 (44.3%)	164 (16.0%)	150 (38.1%)
≥35 years	113 (10.3%)	33 (13.6%)	64 (14.6%)	238 (18.7%)	198 (23.1%)	17 (21.5%)	46 (4.5%)	61 (15.5%)
Missing (%)	0.5%	0%	0%	1.2%	0.1%	6.0%	0.8%	0%
Maternal pre-pregnancy BMI (kg/m ²)	22.4 (14.0-44.6)	22.3 (16.0-47.4)	23.1 (16.6-43.8)	22.5 (15.8-49.6)	22.4 (14.9-53.8)	22.5 (17.7-36.5)	21.2 (14.5-40.7)	21.4 (16.5-37.6)

Characteristics	FLEHS I (Belgium, 2002-2004)	FLEHS II (Belgium, 2008-2009)	HUMIS (Norway, 2002-2006)	INMA cord (Spain, 1997-2008)	INMA mat (Spain, 2004-2008)	LINC (The Netherlands, 2011-2012)	PCB cohort (Slovakia, 2002-2004)	PELAGIE (France, 2002-2006)
Missing (%)	3.0%	0.8%	1.8%	1.2%	0%	2.4%	4.4%	1.0%
Maternal pre-pregnancy BMI								
<18.5 kg/m ²	60 (5.6%)	15 (6.3%)	14 (3.2%)	53 (4.2%)	43 (5.0%)	2 (2.4%)	126 (12.8%)	29 (7.4%)
18.5<25 kg/m ²	737 (68.8%)	169 (70.4%)	275 (63.7%)	911 (71.7%)	598 (69.5%)	63 (76.8%)	680 (68.8%)	303 (77.7%)
25<30 kg/m ²	201 (18.8%)	36 (15.0%)	99 (22.9%)	224 (17.6%)	158 (18.4%)	10 (12.2%)	128 (13.0%)	43 (11.0%)
≥30 kg/m ²	74 (6.9%)	20 (8.3%)	44 (10.2%)	83 (6.5%)	61 (7.1%)	7 (8.5%)	54 (5.5%)	15 (3.9%)
Missing (%)	3.0%	0.8%	1.8%	1.2%	0%	2.4%	4.4%	1.0%
Maternal gestational weight gain (kg)	13 (0-35)	/	14 (-3-31)	13.2 (-5.7-37.1)	13.5 (-7.4-30.4)	13 (-6-23)	14 (1-35)	13 (3-31)
Missing (%)	50.2%	100%	2.5%	36.8%	6.6%	9.5%	27.1%	38.3%
Maternal height (cm)	167 (149-184)	168 (148-183)	168 (149-199)	162 (135-185)	163 (145-180)	171 (158-187)	165 (133-186)	164 (146-190)
Missing (%)	2.0%	0.8%	0.7%	1.2%	0%	1.2%	0%	0%
Maternal height								
<163 cm	281 (26.0%)	50 (20.8%)	84 (19.2%)	656 (51.6%)	389 (45.2%)	6 (7.2%)	362 (35.0%)	154 (39.4%)
163-169 cm	406 (37.5%)	90 (37.5%)	172 (39.4%)	422 (33.2%)	312 (36.3%)	17 (20.5%)	407 (39.4%)	152 (38.9%)
≥169 cm	396 (36.6%)	100 (41.7%)	181 (41.4%)	193 (15.2%)	159 (18.5%)	60 (72.3%)	265 (25.6%)	85 (21.7%)
Missing (%)	2.0%	0.8%	0.7%	1.2%	0%	1.2%	0%	0.8%
Parity								
0	670 (60.6%)	98 (40.5%)	184 (41.8%)	667 (51.8%)	481 (56.1%)	31 (38.3%)	438 (42.5%)	172 (43.7%)
1	297 (26.9%)	80 (33.1%)	172 (39.1%)	489 (38.0%)	323 (37.7%)	31 (38.3%)	338 (32.8%)	142 (36.0%)
≥2	138 (12.5%)	64 (26.5%)	84 (19.1%)	131 (10.2%)	54 (6.3%)	19 (23.5%)	255 (24.7%)	80 (20.3%)
Missing (%)	0%	0%	0%	0%	0.2%	3.6%	0.3%	0%
Maternal education								
Secondary education or less	847 (78.6%)	91 (38.6%)	156 (35.5%)	932 (73.5%)	541 (63.1%)	27 (33.3%)	952 (92.3%)	142 (36.0%)
Higher education	230 (21.4%)	145 (61.4%)	283 (64.5%)	336 (26.5%)	316 (36.9%)	54 (66.7%)	79 (7.7%)	252 (64.0%)
Missing (%)	2.5%	2.5%	0.2%	1.5%	0.3%	3.6%	0.3%	0%
Maternal smoking during pregnancy								
Yes	179 (16.2%)	29 (12.2%)	51 (11.6%)	383 (30.1%)	234 (27.8%)	3 (3.7%)	158 (15.3%)	56 (14.4%)
No	923 (83.8%)	208 (87.8%)	389 (88.4%)	891 (69.9%)	607 (72.2%)	78 (96.3%)	876 (84.7%)	333 (85.6%)
Missing (%)	0.3%	2.1%	0%	1.0%	2.2%	3.6%	0%	1.3%
Ethnicity								
Caucasian			415 (94.3%)	1223 (96.1%)	834 (97.0%)		799 (78.9%)	
Inuit			3 (0.7%)					

Characteristics	FLEHS I (Belgium, 2002-2004)	FLEHS II (Belgium, 2008-2009)	HUMIS (Norway, 2002-2006)	INMA cord (Spain, 1997-2008)	INMA mat (Spain, 2004-2008)	LINC (The Netherlands, 2011-2012)	PCB cohort (Slovakia, 2002-2004)	PELAGIE (France, 2002-2006)
Roma Other Missing (%)	100%	100%	1 (0.2%) 4 (0.9%) 3.9%	49 (3.9%) 1.2%	26 (3.0%) 0%	100%	214 (21.1%) 2.0%	100%
Sample type ^b Cord blood Maternal blood Breast milk	1105 (100%)	242 (100%)	440 (100%)	1287 (100%)	860 (100%)	66 (78.6%) 61 (72.6%)	1026 (99.2%) 210 (20.3%)	394 (100%)
Caesarean section Yes No Missing (%)	53 (4.8%) 1052 (95.2%) 0%	11 (4.6%) 230 (95.4%) 0.4%	60 (13.6%) 380 (86.4%) 0%	151 (12.8%) 1032 (87.2%) 8.1%	101 (14.4%) 599 (85.6%) 18.6%	3 (3.6%) 81 (96.4%) 0%	100%	50 (12.9%) 337 (87.1%) 1.8%

823 Continuous measures described by median (min-max); categorical measures described by frequencies (%).

824 Abbreviations: SGA, Small for Gestational Age; BMI, body mass index.

825 ^aNumber of live-born singleton births with exposure levels and information on at least one outcome.

826 ^bSome mothers of the PCB and LINC cohort had more than one biological sample (cord blood and breast milk), however to assess exposure, only one sample
827 type was used depending on the compound.

828

829 Table 2: Concentration of the PCB 153, *p,p'*-DDE and HCB (ng/L) exposure biomarkers in cord serum, actual or obtained by conversion, of the
830 8 study populations

Study population	PCB 153 (ng/L)					<i>p,p'</i> -DDE (ng/L)					HCB (ng/L)					
	n	Mean ± SD	Median	P25-P75	n<LOD/ n<LOQ (%)	n	Mean ± SD	Median	P25-P75	n<LOD/ n<LOQ (%)	n	Mean ± SD	Median	P25-P75	n<LOD/ n<LOQ (%)	
FLEHS I ^a	1048	73.1 ± 56.3	60.0	30.0-105.0	206 (19.7%)	1094	315.4 ± 347.4	220.0	130.0-376.0	19 (1.7%)	1027	48.4 ± 35.6	40.0	20.0-61.0	249 (24.3%)	
FLEHS II ^a	242	62.9 ± 35.8	53.0	38.0-78.0	7 (2.9%)	242	207.6 ± 212.1	153.5	93.0-238.0	0 (0%)	242	Not calculated ^d				121 (50%)
HUMIS ^b	440	43.5 ± 20.8	39.0	30.6-52.0	0 (0%)	440	74.4 ± 108.4	49.7	34.1-79.7	0 (0%)	440	26.2 ± 9.7	24.4	20.2-29.3	0 (0%)	
INMA cord ^a	1216	157.1 ± 112.5	136.0	91.4-194.2	111 (9.1%)	1217	959.3 ± 1761	486.6	266.7-1007	20 (1.6%)	886	300.1 ± 373.8	177.0	93.7-340.2	156 (17.6%)	
INMA mat ^c	859	52.7 ± 34.6	46.4	30.8-66.1	56 (6.5%)	857	212.1 ± 325.6	131.1	82.3-205.6	5 (0.6%)	860	76.7 ± 62.5	59.8	34.0-98.0	80 (9.3%)	
LINC ^{ab}	79	36.0 ± 20.1	30.0	<LOQ-42.0	30 (38.0%)	79	101.6 ± 94.6	79.0	42.0-114.1	13 (16.5%)	79	Not calculated ^d				53 (67.1%)
PCB cohort ^a	1026	394.1 ± 459.7	271.8	169.3-449.9	2 (0.2%)	1025	1309 ± 1194	1015	554.7-1678	8 (0.8%)	1017	274.1 ± 363.0	178.4	102.8-313.6	39 (3.8%)	
PELAGIE ^a	394	126.7 ± 77.4	110.0	75.0-160.0	0 (0%)	393	254.4 ± 336.3	180.0	100.0-300.0	74 (18.8%)	394	37.3 ± 22.6	32.5	<LOQ-51.0	99 (25.1%)	
Combined	5304	151.7 ± 246.7	88.0	45.0-170.0	412 (7.8%)	5347	603.6 ± 1114	258.0	117.0-646.3	139 (2.6%)	4624	148.5 ± 265.2	63.8	30.0-156.6	623 (13.5%)	

831 Abbreviations: PCB, polychlorinated biphenyl; *p,p'*-DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; SD, standard deviation; P, percentile;

832 LOD, limit of detection; LOQ, limit of quantification

833 ^aObserved cord serum concentrations

834 ^bEstimated cord serum concentrations based on measured concentrations in breast milk

835 ^cEstimated cord serum concentrations based on measured concentrations in maternal serum

836 ^dFor exposure biomarkers with ≥ 50% of the measures < LOD or LOQ, the mean (SD) and median were not calculated. This cohort was excluded in the
837 analysis of that exposure biomarker.

838

839 Table 3: Concentration of the perfluorinated compounds (ng/L) in cord serum, actual or obtained by conversion, of the OBELIX birth cohorts

Cohort	PFOS (ng/L)					PFOA (ng/L)				
	N	Mean ± SD	Median	P25-P75	n < LOD/LOQ (%)	n	Mean ± SD	Median	P25-P75	n < LOD/LOQ (%)
FLEHS II ^a	208	2950 ± 1542	2700	1700-3800	0 (0%)	210	1651 ± 676	1500	1100-2100	0 (0%)
HUMIS ^b	196	2899 ± 1343	2624	1968-3520	0 (0%)	196	381 ± 293	312	228-442	13 (6.6%)
LINC ^{ab}	80	1624 ± 696	1600	1000-2058	0 (0%)	80	881 ± 470	805	560-1122	0 (0%)
PCB cohort ^b	204	1217 ± 985	960	576-1440	22 (10.8%)	207	433 ± 294	403	221-533	35 (16.9%)
Combined	688	2267 ± 1484	1984	1200-3008	22 (3.2%)	693	839 ± 723	550	299-1200	48 (6.9%)

840 Abbreviations: PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; SD, standard deviation; P, percentile; LOD, limit of detection; LOQ, limit of

841 quantification

842 ^aObserved cord serum concentrations

843 ^bEstimated cord serum concentrations based on measured concentrations in breast milk

844 **FIGURE LEGENDS**

845 **Figure 1: Adjusted odds ratio (OR) (95% CI) for IQR increase of cord serum PCB 153,**
846 ***p,p'*-DDE and HCB with SGA**

847

848 Abbreviations: OR, Odds Ratio; CI, Confidence Interval; IQR: interquartile range; PCB:
849 polychlorinated biphenyl; *p,p'*-DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene;
850 SGA: Small for Gestational Age

851 Global estimate: Estimate for IQR increase in exposure in model adjusted for maternal education,
852 maternal age at delivery, maternal height, maternal pre-pregnancy BMI, smoking during pregnancy,
853 parity and child's sex;

854 Estimate girls/boys: Estimate for IQR increase in exposure for girls/boys in model with interaction
855 term for child's sex adjusted for maternal education, maternal age at delivery, maternal height,
856 maternal pre-pregnancy BMI, smoking during pregnancy and parity;

857 *p*-interaction sex-PCB 153 = 0.025; *p*-interaction sex-*p,p'*-DDE = 0.006 and *p*-interaction sex-HCB =
858 0.0003.

859

860

861 **Figure 2: Adjusted odds ratio (OR) (95% CI) for IQR increase of cord serum PFOS and**
862 **PFOA with SGA**

863

864 Abbreviations: OR, Odds Ratio; CI, Confidence Interval; IQR: interquartile range; PFOS,
865 perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; SGA: Small for Gestational Age

866 Global estimate: Estimate for IQR increase in exposure in model adjusted for maternal education,
867 maternal age at delivery, maternal height, maternal pre-pregnancy BMI, smoking during pregnancy,
868 parity and child's sex;

869 Estimate non-smoking/smoking: Estimate for IQR increase in exposure for non-smoking/smoking in
870 model with interaction term for smoking during pregnancy adjusted for maternal education, maternal
871 age at delivery, maternal height, maternal pre-pregnancy BMI, parity and child's sex;

872 *p*-interaction smoking-PFOS = 0.0004; *p*-interaction smoking-PFOA = 0.33.

873

874