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1 **PERINATAL EXPOSURE TO PHENOLS AND POLY- AND PERFLUOROALKYL**
2 **SUBSTANCES AND GUT MICROBIOTA IN ONE-YEAR CHILDREN**

3
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21 **Abstract**

22 The role of the gut microbiota on human health calls for a better understanding of
23 its determinants. In particular, the possible effects of chemicals with widespread exposure
24 other than pharmaceuticals are little known. Our aim was to characterize the sensitivity of
25 the early-life gut microbiota to specific chemicals with possible antimicrobial action.
26 Within SEPAGES French couple-child cohort, we assessed 12 phenols in repeated urine
27 samples from 356 pregnant women and their offspring and 19 poly- and perfluoroalkyl
28 substances (PFAS) in serum from the pregnant women. We collected stool samples in the
29 children at one year of age, in which the V3-V4 region of 16S rRNA gene was sequenced,
30 allowing gut bacterial profiling. Associations of each chemical with α - and β -diversity
31 indices of the gut microbiota, and with relative abundance of the most abundant taxa were
32 assessed using single-pollutant and mixture (BKMR) models. Perinatal exposure to certain
33 parabens was associated with gut microbiota α - and β -diversity and with phyla Firmicutes
34 and Proteobacteria. Suggestive associations of certain phenols with genera of
35 *Lachnospiraceae* and *Enterobacteriaceae* families were observed, but not maintained after
36 correction for multiple testing. Parabens, which have known antimicrobial properties,
37 might disrupt the child gut microbiota, but larger studies are required.

38

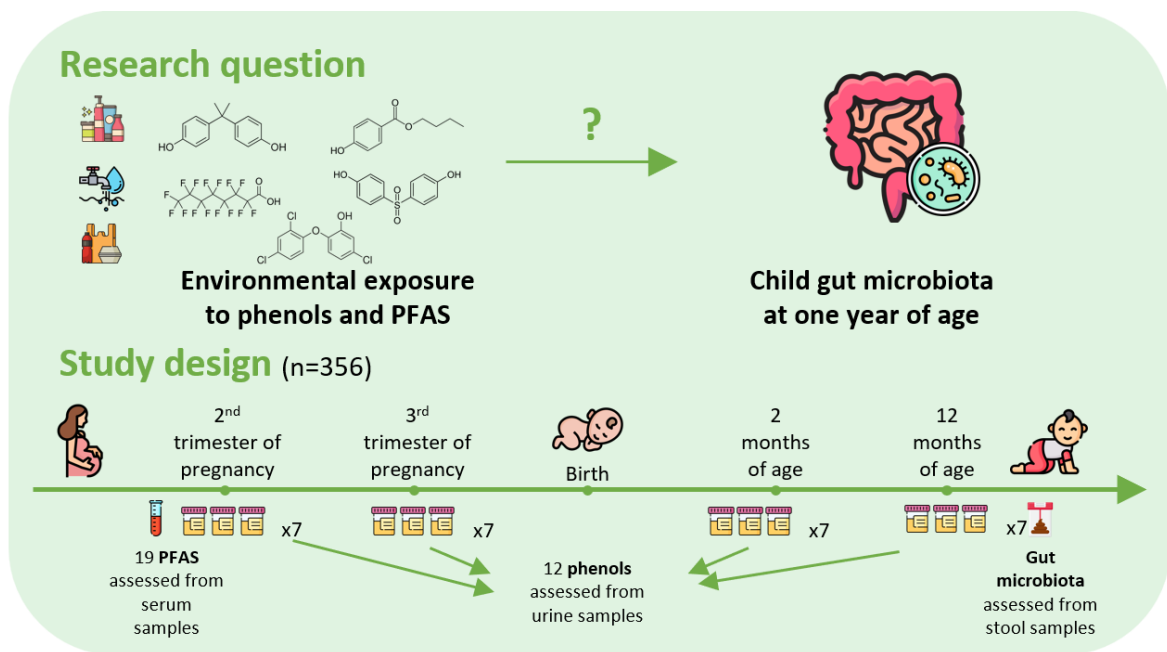
39 **Key words:** couple-child cohort / early-life gut microbiota / environmental exposures /
40 one-year children / perfluoroalkyl substances / phenols.

41 **Synopsis**

42 Growing evidence links the gut microbiota to human health and emphasizes the
43 importance of understanding its determinants. Specific parabens, which are widespread
44 pollutants with a predominantly dietary exposure pathway might influence the gut
45 microbiota diversity in one-year children.

46

47 **Table of Contents graphic**



48
49

50 **Introduction**

51 The microbiota represents all the microorganisms living in a specific environment.
52 In humans, the gut microbiota develops during early childhood before stabilizing around
53 the age of 3 years^{1,2}, it plays a role in digestive, metabolic, trophic, immune and
54 neurological functions throughout life³⁻⁶. Dysbiosis of the gut microbiota has been
55 correlated with many inflammatory and autoimmune conditions^{7,8} and the gut microbiota is
56 also implicated in numerous neuropsychiatric⁹⁻¹³ and neurodevelopmental disorders such
57 as autism spectrum disorders¹⁴⁻¹⁶.

58 It is therefore important to identify controllable causes of gut microbiota dysbiosis.
59 Known determinants of gut microbiota include the mode of delivery¹⁷, breastfeeding^{1,18},
60 diet¹⁹, medical events, age, geographic location and sanitary conditions²⁰. Impact of
61 pharmaceutical drugs on the gut microbiota have been described²¹⁻²⁴, but research on the
62 sensitivity of the gut microbiota to other xenobiotics such as environmental chemicals has
63 little been considered²⁵. A priori worth considering families of substances include those
64 with known antimicrobial properties, such as synthetic phenols. These comprise, among
65 others, parabens and triclosan.

66 Parabens have been used for decades as preservatives in cosmetic and
67 pharmaceutical products, but also as food additives or in cleaning products, due to their
68 antibacterial and antifungal properties²⁶. Skin contacts with cosmetics or body care
69 products containing parabens represents one of the potential exposure routes for the
70 general population; exposure can also occur via the oral route, when consuming food or
71 pharmaceuticals containing parabens or ingesting house dust²⁷⁻²⁹. Triclosan has been used
72 in some cosmetics, personal care products, textiles, and drugs for its antimicrobial
73 properties. Triclosan may be absorbed and reach systemic circulation through the mucous
74 membrane of the oral cavity³⁰, by dermal exposure through the skin^{31,32}, and, after oral

75 exposure, through the gastrointestinal tract^{30,33,34}. A few toxicological studies have
76 investigated the impacts of triclosan exposure on the gut microbiota, mostly in fish or
77 rodent models, showing effects on the microbial diversity and composition³⁵⁻³⁹. Low-dose
78 postnatal exposure to methylparaben, triclosan or their mixture also induced significant
79 changes in the overall bacterial gut microbiota composition in adolescent rats⁴⁰. In humans,
80 Ribado *et al.* found perturbation of maternal but not infant gut microbiota in 17 mother-
81 baby pairs randomly assigned to use triclosan containing products, compared to 22 mother-
82 baby pairs not assigned to triclosan products⁴¹. Bever *et al.* found that the fecal microbiota
83 diversity of 31 exclusively breastfed infants exposed to breast milk with detectable
84 triclosan levels differed compared to their peers exposed to breast milk containing non-
85 detectable amounts⁴².

86 Bisphenols are synthetic chemicals used in the production of polycarbonates, which
87 are transparent, rigid plastics used to make food containers in some countries, and in the
88 production of epoxy resins found in protective coatings and linings for food and beverage
89 cans and vats. The dietary route through migration of bisphenols from packaging and
90 containers into food and beverages consumed is the major source of bisphenol A exposure
91 for the general population. In animal models, effects of exposure to bisphenols A and S on
92 the gut microbiota have been suggested, with alterations described both in terms of
93 bacterial diversity and composition, and leading in some cases to functional profile
94 changes in the microbial community⁴³⁻⁵⁰.

95 Another chemical family of concern regarding health and the gut microbiota in
96 particular are poly- and perfluoroalkyl substances (PFAS), a large family of fluorinated
97 aliphatic compounds widely used as surfactant, water and grease repellents and found in all
98 environmental compartments and in the food chain due to their high persistence^{26,51,52}.
99 Perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are easily

100 absorbed through the gut. They bind to proteins and are distributed mainly to the blood
101 serum, kidney, and liver⁵³. Several PFAS have been measured in human umbilical cord
102 blood, indicating that they can cross the placenta^{54,55}. Zhan et al. demonstrated in 11 weeks
103 old male mice a marked change in the gut microbiota induced by PFOS⁵⁶. In a study by
104 Naspolini et al, infants born by caesarian section showed significant changes in their gut
105 microbiota assessed in meconium associated with high exposures to PFAS⁵⁷. Thompson et
106 al. examined the effects of lifetime exposures to environmental contaminants on the
107 established adult microbiota and found that proximal exposures to perfluorohexane
108 sulfonic acid (PFHxS) and PFOA at age 28 years appeared to be associated with measures
109 of microbiota diversity and taxonomic profiles⁵⁸. In 267 mothers and their one-month
110 infants from NoMIC cohort, Iszatt et al. observed that breast milk PFOS levels in
111 breastfeeding mothers was associated with decreased microbiota phylogenetic diversity
112 and specific richness, and that significant differences existed in community composition
113 between groups with high and low PFOS exposure⁵⁹.

114 Given the antimicrobial properties of certain compounds of the phenol family (e.g.,
115 parabens and triclosan) and the results of these previous studies on triclosan^{41,42} (with a
116 limited number of subjects) and on the most common PFAS⁵⁷⁻⁵⁹, perturbations of one year
117 child gut microbiota diversity and composition might be expected in relation with exposure
118 to parabens, triclosan and certain PFAS. The objective of this study was to investigate the
119 sensitivity of the gut microbiota at one year of age to specific phenols and PFAS.

120 **Materials and Methods**

121 **Design of SEPAGES couple-child cohort and data collection**

122 **Study population**

123 We relied on SEPAGES cohort (Suivi de l'Exposition à la Pollution Atmosphérique
124 durant la Grossesse et Effet sur la Santé), a French couple-child cohort with detailed
125 monitoring of environmental exposures⁶⁰. The SEPAGES study population lives
126 approximately in a buffer of 80 km around the center of Grenoble, and includes urban,
127 peri-urban and rural zones. The SEPAGES cohort participants were pregnant women, their
128 partner and future child. Pregnant women had to fulfil the following eligibility criteria:
129 being pregnant by less than 19 gestational weeks at inclusion, being older than 18 years,
130 having a singleton pregnancy, to be living in the study area and to plan to give birth in one
131 of the four maternity clinics from Grenoble area. Recruitment took place between July
132 2014 and July 2017 in eight obstetrical ultrasonography practices located in the Grenoble
133 area. From the 484 families included in SEPAGES cohort, our study is restricted to 360
134 families with full outcome data. All required ethical and data privacy agreements
135 (including from CPP and CNIL) were obtained; all enrolled families signed an informed
136 consent form.

137

138 **Biospecimens collection**

139 Women collected samples from three micturitions per day during each follow-up
140 week around 18 and 34 gestational weeks (median (25th–75th centiles) gestational age at
141 urine collection: 18 weeks (16, 19) and 34 weeks (32, 35)), and around 2 months and 12
142 months (median (25th–75th centiles) child age at urine collection: 7 weeks (6, 9)) and 53
143 weeks (52, 55)), in plastic vials which composition did not include bisphenols. From the
144 population of SEPAGES feasibility study, it was demonstrated that, when it comes to

145 estimating the effects of exposures averaged over windows of a week or more, collecting
146 three urine samples per day was not expected to entail bias, compared to a collection of all
147 daily urine samples, which is more cumbersome⁶¹. Women were asked to fill in a diary
148 indicating the hours of all collected micturitions and delay before putting the urine sample
149 in the freezer. After collection, samples were stored at -20°C at the house of the
150 participants. At the end of the follow-up week, samples were picked up by a study
151 fieldworker and brought to the certified biobank of Grenoble University hospital (bb-0033-
152 00069), stored at -20°C until they were thawed at 4°C and pooled within-subject, within-
153 period (pools of the same volume of each of the samples collected over a follow-up week).
154 These weekly pools were aliquoted and stored at -80°C. Maternal blood was collected at
155 home around the 18th gestational week (median (25th–75th centiles) gestational age at blood
156 collection: 18 weeks (16, 19)).

157 Parents from SEPAGES cohort were asked to collect fecal samples of their
158 offspring in a sealed container (median (25th–75th centiles) child age at stool collection: 54
159 weeks (52, 55)). We focused on one year of age, a sensitive period when the microbiota
160 undergoes rapid development^{62–64}. To ensure proper frozen conservation, samples were
161 immediately stored at -20°C at the volunteer's home (for 1 to 7 days), transported on ice
162 from the volunteer's home to the biobank where they were separated in three aliquots and
163 stored at -80°C.

164

165 **Assessment of chemical exposures**

166 All chemical analyses were performed at the Norwegian Institute of Public Health
167 in Oslo (NIPH). Our focus here was on compounds of the chemical families of phenols and
168 PFAS (Table S1). Because of their short half-life and the fact that they are mainly excreted
169 in urine, phenols were assessed in urine samples of both SEPAGES mothers and children

170 collected during the second and third trimester of pregnancy, and post-natally at 2 and 12
171 months of age. Phenols were assessed in weekly pools after thawing by on-line solid phase
172 extraction with ultra-high-performance liquid chromatography and mass spectrometry⁶⁵.
173 While not formally accounting for urine dilution of individual samples, biomarker
174 concentrations assessed in such equal volume pools have shown to correlate well with
175 those assessed in a pool of all urine samples collected over 24h or a week⁶⁶. PFAS were
176 determined in the serum samples collected around 18 gestational by high performance
177 liquid chromatography coupled with tandem mass spectrometry^{67,68}. PFAS have a strong
178 affinity for binding to serum proteins, such as albumin, which results in their distribution
179 mainly in serum, and less in milk⁶⁹ and urine⁷⁰, with urinary concentrations being less than
180 1% of those found in serum⁷¹. The choice of serum was justified by the reasons mentioned
181 above and by the fact that not all women breastfed.

182 Measurements below the limit of detection (LOD) and the limit of quantification
183 (LOQ) were singly imputed using the compound's probability distribution⁷². We applied a
184 Neperian logarithmic transformation to the pollutant variables (ng/mL) to limit the
185 impact of high concentrations on our effect estimations. Compounds with more than
186 70% of observations below the limit of detection were categorized (2 categories: <LOD
187 and >LOD; or 3 categories <LOD, LOD-LOQ, >LOQ depending on the sample size in
188 each category). Compounds with more than 95% of observations below the limit of
189 detection were not considered in our analyses (these were the following phenols:
190 bisphenols AF, B, F and triclocarban; and the following PFASs: perfluorotetradecanoic
191 acid (PFTeDa), perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA),
192 perfluorohexanoic acid (PFHxA), perfluorodecane sulfonic acid (PFDS), n-
193 methylperfluorooctane sulfonamide (MeFOSA), n-ethylperfluorooctane sulfonamide
194 (EtFOSA), 6:2 fluorotelomer phosphate monoester (6:2 PAP), 8:2 fluorotelomer phosphate

195 monoester (8:2 PAP), perfluorooctyl phosphonic acid (PFOPA), perfluorodecyl
196 phosphonic acid (PFDPA)).

197 Total and free forms of phenol concentrations were measured to evaluate potential
198 external contamination in a subset of 100 prenatal samples and in all the postnatal samples,
199 since these samples were at higher risk of contamination (as urine was collected from
200 diapers). Contamination testing of phenol assays (by regressing the free against conjugated
201 forms of each compound) suggested no contamination for prenatal samples, while for
202 postnatal samples contamination was suspected for bisphenol A at 2 and 12 months, and
203 methylparaben at 12 months⁷³. For these specific chemicals and exposure windows,
204 conjugated concentrations (obtained by subtracting the free form from the total) were used
205 for associations reported in the main analyses.

206

207 **Assessment of adjustment factors**

208 From SEPAGES questionnaires, information on sociodemographic factors
209 (including parental occupation), medical history, medical treatments, health events, active
210 smoking during pregnancy, passive smoking exposure during pregnancy and postnatally,
211 characteristics of the home (pet ownership) was collected. Mode of delivery, weight and
212 height measurements performed by health care practitioners were copied from the child
213 health booklet. Information on diet and food frequency were asked at 3, 6, 12, 18 and 36
214 months.

215

216 **Assessment of the gut microbiota**

217 **Sequencing and data processing**

218 Fecal samples (~150 mg) were aliquoted from 360 children at one year of age, a
219 critical period for the development of the gut microbiota, particularly with the introduction

220 of solid food^{1,2}. Total DNA was extracted from all samples with the PowerFecal DNA
221 Isolation Kit (Qiagen), with a prior homogenization including chemical (incubation for 1h
222 at 70°C with guanidine thiocyanate and N-lauroyl-sarcosine 5%) and mechanical
223 (beadbeating for 10 minutes) lysis steps. DNA quality and quantity were evaluated using a
224 spectrophotometer (Nanodrop 1000, ThermoScientific). The V3-V4 hypervariable region
225 of the 16S ribosomal RiboNucleic Acid (rRNA) gene was amplified with the following
226 primers: 341F-CCTACGGGNGGCWGCAG and 805R-
227 GACTACHVGGGTATCTAATCC⁷⁴. Following quality control and sequencing library
228 construction, high-throughput sequencing was performed (MiSeq Illumina), the remaining
229 adapter/primer sequences were trimmed, and reads were checked for quality (≥ 20) and
230 length (≥ 200 bases) using cutadapt⁷⁵. Reads were further corrected for known sequencing
231 errors using SPAdes⁷⁶ and then merged using PEAR⁷⁷. Amplicons sequencing variants
232 (ASV) were identified using a Vsearch pipeline⁷⁸ set up to dereplicate, cluster and chimera
233 check the merged reads. ASV taxonomical classification was performed using a classifier
234 from the RDPTools suit⁷⁹. From the 360 stool samples collected at one year, we removed 4
235 samples which had a low DNA or sequencing quality (samples with number of reads below
236 2500). To control for variation in sequencing depth for diversity analyses, ASV matrix was
237 rarefied to 5,000 sequences, which led to the removal of 6 additional samples (n=350). To
238 see if our estimated richness matched the actual richness of the gut microbiota samples, we
239 looked at rarefaction curves and counted the number of ASVs for a set of subsamples at
240 different sequencing depth thresholds. The number of ASVs detected increased and then
241 stabilized as the number of extracted sequences increased. The sequencing depth chosen
242 for our analyses (5,000) was appropriate to observe a large number of ASVs excluding
243 only 6 samples (Figure S1). Taxa counts were converted to relative abundances (n=356).

244 350 and 356 children were available for the diversity analyses (see below), and taxonomy
245 analyses, respectively.

246

247 **Gut microbiota composition: α -diversity, β -diversity and taxonomy**

248 α -diversity (i.e. diversity within a sample) was estimated using the specific
249 richness, Shannon diversity⁸⁰ and Faith's phylogenetic diversity indices⁸¹, on the rarefied
250 ASVs table (5,000 sequences) with R program version 4.2.2, package Phyloseq version
251 1.27.6⁸². β -diversity between each given pair of gut microbiota samples was calculated
252 using the Bray-Curtis dissimilarity metric⁸³, defined on the rarefied ASVs table (5,000
253 sequences).

254 Taxonomic affiliation was described at all taxa levels. Taxonomy analyses were
255 conducted for the most abundant phyla and genera in our population. 16S rRNA gene
256 sequencing is unable to differentiate *Shigella* species from *Escherichia coli* because of
257 their nucleotide similarity. For this reason, genera *Escherichia* and *Shigella* were studied as
258 a single taxon in all our analyses⁸⁴.

259

260 **Statistical analyses**

261 We imputed missing values of adjustment covariates using simple imputation by
262 predictive mean matching^{85,86}. Correlations between exposures, between exposures and
263 covariates, and between gut microbiota parameters were assessed using Spearman's rank
264 correlation coefficient. The directed acyclic graph presenting the assumed causal relations
265 between covariates is given in Figure S2.

266 The parameters of gut microbiota considered in relation to exposures were the three
267 above-mentioned indices of α -diversity, the Bray-Curtis β -diversity metric, the 4 most
268 abundant phyla and the 46 genera detected in at least 30% of the children.

269 Regarding specifically α -diversity analyses, we relied first on single-pollutant
270 approaches using multiple linear regression (one model per exposure and outcome)
271 adjusted for *a priori* identified covariates: analytic batch effect (MiSeq 16S rRNA gene
272 sequencing run), child age at feces collection, delivery mode, gestational age,
273 interpregnancy interval, child characteristics (sex, weight and length at birth and at one
274 year), period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics
275 use during the first year of life, presence of pets at home, passive smoking during the first
276 year of life, and maternal characteristics (parity, age and body mass index (BMI) before
277 pregnancy, education, and smoking status during pregnancy).

278 Regarding β -diversity analyses, we investigated group differences in Bray-Curtis β -
279 diversity for low (1st tertile or <LOD), medium (2nd tertile or LOD-LOQ), and high (3rd
280 tertile or >LOQ) levels of exposure considered separately at each time window (one model
281 per exposure) by testing significance of pairwise groups of exposure with Permutational
282 Multivariate Analysis of Variance Using Distance Matrices (PERMANOVA), using R
283 program version 4.2.2, package Vegan version 2.6-4, Adonis2 function⁸⁷. For a sub-group
284 of pollutants for which within-group β -diversity was significantly different from the inter-
285 group diversity, we performed further analyses to identify if the observed difference was
286 between the low and medium exposure groups, between the low and high exposure groups,
287 or between the medium and high exposure groups, using R program version 4.2.2, package
288 pairwiseAdonis, pairwise.adonis2 function⁸⁸. β -diversity analyses were adjusted for the
289 same covariates as the α -diversity analyses.

290 To limit associations due to multiple comparisons, a family-wise error rate (FWER)
291 correction to the p-value significance threshold was applied for the single-pollutants
292 models (α - and β -diversity) for pollutants without *a priori* known antimicrobial properties
293 (i.e., bisphenols A and S, benzophenone 3 and the PFAS). The correction used a

294 Bonferroni procedure extended to handle correlated tests: the actual number of associations
295 being tested (T) is replaced by a smaller value, the effective number of independent tests
296 (Te). Te was estimated by the effective number of independent exposures $\sum_{i=1}^M [I(\lambda_i >$
297 $1)(\lambda_i - 1)]$ multiplied by the effective number of independent outcomes $\sum_{i=1}^N [I(\lambda_i >$
298 $1)(\lambda_i - 1)]$, where I(x) is an indicator function and λ_i are the eigenvalues of the matrix of
299 correlations between M exposures and the eigenvalues of the matrix of correlations
300 between N outcomes. The p-value threshold to control FWER to α (in our case, 5%), using
301 Te in a Bonferroni procedure, is then α / Te (adapted from⁸⁹). For the main diversity
302 analysis, the 27 time window-specific exposure corresponded to 17 independent predictors
303 and the 4 α - and β -diversity indices to 3 independent outcomes. The corrected significance
304 level was thus $0.05/(17 \times 3) = 0.001$. No such correction was applied to the regression
305 models corresponding to compounds with *a priori* known antimicrobial properties (i.e.
306 parabens and triclosan).

307 To identify any mixture effect of multiple pollutant exposures on α -diversity
308 indices, we first used multiple linear regressions models including all exposures assessed at
309 the same time window. Then, for continuous exposure variables only, we implemented
310 BKMR, a statistical approach for analyzing multipollutant mixtures⁹⁰, adjusted for the
311 same covariates as for the single-pollutant regression models, and using R program version
312 4.2.2, package bkmr version 0.2.2. The cumulative effects of the mixtures were assessed
313 by estimating the expected change in indices of α -diversity associated with concurrent
314 changes in all of the components of the mixture from their 25th percentile levels. The
315 estimated effect of an increase from the 25th to 75th percentile in a single pollutant level on
316 α -diversity indices when all other pollutant levels are fixed at either the 25th, 50th, or 75th
317 percentiles were also investigated, with the aim to identify the most important contributors
318 of the mixture.

319 Then, we investigated associations between exposures and the gut microbiota
320 taxonomy at one year. We performed independent linear regression models using the 4
321 most abundant phyla and the 46 genera detected in at least 30% of the children as
322 explained variables, and each of the exposure as explanatory log-transformed continuous
323 variables. These taxonomy analyses were adjusted for the same covariates as the diversity
324 analysis. Null values in genera variables were replaced by the value 1/5000 before the
325 variables were log-transformed. We applied a FWER multiple comparison correction for
326 all associations between bacterial genera and pollutants (with and without known
327 antimicrobial properties). The 47 time window-specific exposure corresponded to 29
328 independent predictors and the 46 genera detected in at least 30% of the children to 31
329 independent outcomes. The corrected significance level was thus $0.05/(29 \times 31) = 5.6 \times 10^{-5}$.

330 As sensitivity analyses, we repeated the α -diversity analyses using two different
331 thresholds of rarefaction (5,000 and 10,000 reads). Postnatal samples contamination was
332 suspected for bisphenol A at 2 and 12 months, and methylparaben at 12 months⁷³; for
333 these specific chemicals and exposure windows, conjugated concentrations were used for
334 associations reported in the main analyses, while associations with total and free
335 concentrations were reported in the sensitivity analyses. Finally, we repeated our analyses
336 for perfluoroheptanesulfonic acid (PFHpS), PFHxS and PFOS exposures during the second
337 trimester of pregnancy excluding one mother with very high concentrations.

338 All statistical analyses were performed with R program version 4.2.2.

339

340 **Results**

341 **Study population**

342 Out of 484 families participating in SEPAGES cohort, 356 had available
343 exposure and microbiota data, on which we focused. These women were highly

344 educated (95% had an undergraduate or graduate degree) and 94% of them did not
345 smoke during pregnancy. Most of them (76%) had a body mass index (BMI) between
346 18.5 and 25 kg/m² ⁶⁰. No significant difference existed between SEPAGES pregnant
347 women included in the microbiota analyses and those excluded (Table S2). The
348 proportion of SEPAGES children with a weight at birth under 2.5 kg was 4.2%; 8.4% of
349 children were not breastfed at birth, while 23% were still breastfed at 48 weeks.
350 SEPAGES children were more often full-term deliveries compared to children from
351 France and tended to have a higher birth weight and height. No significant difference in
352 the considered characteristics was observed between SEPAGES children included in the
353 microbiota analyses and those excluded (Table S3).

354 Comparisons of exposures between the 356 mothers and children included and
355 those excluded are given Table S4. Compared to excluded mothers, mothers who were
356 included in this study had lower concentrations of second and third trimester
357 propylparaben and butylparaben and second trimester PFOA, and higher
358 perfluorotridecanoic acid (PFTrDa) and perfluorobutanesulfonic acid (PFBS) ($p < 0.05$).
359 Pearson correlations between exposures at various exposure windows are given Figure S3.
360 Exposures to certain PFAS during the second trimester of pregnancy were correlated.
361 Perfluorononanoic acid (PFNA) was correlated with perfluorodecanoic acid (PFDA)
362 ($r = 0.8$, $p < 0.001$) and PFOA ($r = 0.8$, $p < 0.001$), and PFOS was correlated with PFHxS
363 ($r = 0.8$, $p < 0.001$) and perfluoroheptane sulfonic acid (PFHpS) ($r = 0.9$, $p < 0.001$). Child
364 exposures to methyl- and propylparaben at one year of age were also strongly correlated
365 ($r = 0.9$, $p < 0.001$). Correlations of exposures across exposure windows were generally very
366 low. Perinatal exposures to phenols and PFAS were not strongly associated with most
367 covariates, with the exception of PFAS levels that tended to decrease with parity (Figure
368 S4).

369 The distribution of α -diversity indices and of the most abundant phyla and genera
370 in the gut microbiota is given Table S5 and Figures 1a and 1b.

371

372 **Relations between maternal and child characteristics and gut microbiota**

373 Associations of maternal and child characteristics with the gut microbiota α -
374 diversity are presented in Table S6. Child passive smoking during the first year of life was
375 associated with a lower specific richness index and a lower Faith's phylogenetic index.
376 Birth length was positively associated with all three α -diversity indices. Antibiotics use
377 during the first year of life tended to be associated with a decreased specific richness. None
378 of the other characteristics were associated with α -diversity at the (uncorrected) 5% level.

379 Associations of maternal and child characteristics with the 4 main phyla are given
380 in Table S7. Boys tended to have fewer Actinobacteria, compared to girls. Maternal active
381 smoking during pregnancy was associated with fewer Bacteroidetes. A longer gestational
382 duration was associated with fewer Actinobacteria and more Bacteroidetes.

383

384 **Relations between chemical exposures and gut microbiota diversity**

385 **α -diversity**

386 The number of children included in the single-pollutant analysis varied between
387 334 and 356, depending on the availability of the exposure data. When we considered
388 associations with the strongest *a priori* hypothesis (corresponding to pollutants with *a*
389 *priori* known antimicrobial properties, i.e., triclosan and parabens), which were therefore
390 not corrected for multiple testing, child butylparaben concentration at two months was
391 associated with increased specific richness, Shannon diversity index and Faith
392 phylogenetic diversity (p-values: 0.03, 0.04 and 0.04 respectively, Table 1 and Figure 2)
393 and there were suggestive associations with ethylparaben concentration during the third

394 pregnancy trimester and propylparaben concentration at 12 months. The point estimates of
395 these associations with butylparaben concentrations at two months were only weakly
396 attenuated in multiple linear regression models simultaneously adjusted for co-exposures
397 (Table S10; see also Table S8, Table S9 and Table S11 for analyses co-adjusted for all
398 exposures at the other exposure windows).

399 Regarding compounds without *a priori* known antimicrobial properties (i.e., other
400 phenols and PFAS), for which a multiple comparison correction was applied, there was no
401 clear evidence in favor of associations (Table 2 and Figure S5). The strongest associations
402 (in terms of p-value) were observed with bisphenol S levels assessed in 2-month children.

403 When we investigated a possible mixture effect on the α -diversity indices using
404 Bayesian kernel machine regression (BKMR) model (313 children with full exposure and
405 α -diversity data assessment, Figure 3 and Figure S6), Shannon diversity index tended to
406 increase with increased exposure to the mixture. The estimated effects of an increase from
407 the 25th to 75th percentile in a single biomarker concentration on α -diversity indices when
408 all other biomarkers' concentrations were fixed did not permit to identify one or several
409 important contributors to the mixture effect (Figure S6). No clear associations were
410 observed for the specific richness and the Faith phylogenetic diversity (Figure 3).

411

412 **β -diversity**

413 For each pollutant, we tested whether children gut microbiota exposed to “low” (1st
414 tertile or <LOD), “medium” (2nd tertile or between LOD and LOQ) or relatively “high” (3rd
415 tertile or >LOQ) concentrations were more or less similar based on β -diversity distance
416 (Bray-Curtis dissimilarity index), using permutational multivariate analysis of variance
417 (PERMANOVA) to test significance, with FWER correction for multiple testing in the
418 case of compounds without strong *a priori* evidence of antimicrobial properties. For

419 pollutants with *a priori* known antimicrobial properties, there were significant differences
420 in community composition in association with methylparaben and propylparaben levels at
421 12 months (p-values: 0.03 and 0.008 respectively, Table 3), with greater dissimilarity
422 between the low and high exposure tertiles (p-values: 0.03 and 0.002 respectively, Figure
423 4). For pollutants without *a priori* known antimicrobial properties, no association passed
424 the threshold corrected for multiple testing (p-value<0.001). Analyses not corrected for
425 multiple testing suggested differences in community composition in relation with
426 benzophenone 3 exposure levels at 2 months (p-value: 0.03, Table 4).

427

428 **Relations between phenols and gut microbiota taxonomy**

429 **Phylum level**

430 Spearman correlations between the relative abundances of the 4 most abundant
431 phyla are given Figure S7.

432 In an attempt to explain the above-mentioned associations of parabens with
433 diversity, we studied associations between pollutants associated with α - and β -diversity
434 and the four most abundant phyla (Table 5). Child concentrations of methylparaben and
435 propylparaben at 12 months were associated with decreased relative abundance of phylum
436 Proteobacteria (p-values: 0.01 and 0.02, respectively). Maternal exposure to ethylparaben
437 during the third pregnancy trimester was associated with increased abundance of phylum
438 Firmicutes (p-value: 0.04). Child exposure to butylparaben at 2 months was not associated
439 with any disturbance of the phyla studied. Regarding the pollutants not associated with
440 perturbations in α - or β -diversity, associations with the 4 most abundant phyla are given
441 for exploratory purposes in Table S12.

442

443 **Genus level**

444 46 of the 192 genera present in the children gut microbiota at one year of age were
445 detected in at least 30% of children. None of the associations between these 46 genera and
446 the 47 exposure variables passed the threshold corrected for multiple testing (p-
447 value $<5.6 \times 10^{-5}$). Among the strongest associations (p-value <0.0035), exposure to
448 methylparaben at 12 months tended to be associated with an increase in *Lachnospiracea*
449 *incertae sedis* (p-value: 0.003); exposure to ethylparaben during the second trimester of
450 pregnancy tended to be associated with an increase in *Enterococcus* (p-value: 0.002) while
451 ethylparaben at 12 months tended to be associated with a decrease in *Enterobacter* and
452 *Klebsiella* (p-values: 0.0004 and 0.0006, respectively); exposure to propylparaben during
453 the second trimester of pregnancy tended to be associated with a decrease in *Anaerostipes*
454 (p-value: 0.002); exposure to butylparaben at 12 months tended to be associated with an
455 increase in *Lachnospiracea incertae sedis* and *Anaerotruncus* (p-values: 0.0002 and 0.001,
456 respectively) and a decrease in *Enterococcus* genus (p-value: 0.0008); exposure to
457 bisphenol A at 12 months tended to be associated with an increase in *Clostridium XVIII*
458 and *Coproccocus* (p-values: 0.003 and 0.002, respectively); bisphenol S exposure at 2
459 months tended to be associated with an increase in *Collinsella* and a decrease in
460 *Romboutsia* (p-values: 0.0002 and 0.002, respectively); finally, exposure to benzophenone
461 3 during the second trimester of pregnancy tended to be associated with a decrease in
462 *Romboutsia* and *Clostridium XIVa* (p-values: 0.002 and 0.003, respectively), while
463 exposure to benzophenone 3 at 2 months tended to be associated with a decrease in the
464 taxon grouping genera *Escherichia* and *Shigella* (p-value: 0.001). The p-values and the
465 direction of the associations according to bacterial genus and exposure are shown Figure 5.
466 Beta values of the strongest associations (p-value <0.0035) with their confidence intervals
467 are given Figure 6, while all associations with the genera analyses are shown in Table S13.
468

Sensitivity analyses

469 Using two different thresholds (5,000 and 10,000) of rarefaction to define α -
470 diversity did not strongly influence our results (Table S14). We tested different qualitative
471 and quantitative α -diversity indices, with results qualitatively similar to those obtained
472 with specific richness, Shannon α -diversity, and Faith's phylogenetic diversity indices.
473 Associations using 12 months total and free methylparaben concentrations and 2- and 12-
474 month total and free bisphenol A concentrations are reported in Table S15. Estimated
475 effects of PFHpS, PFHxS and PFOS exposures during the second trimester of pregnancy
476 excluding one mother with very high concentrations of these three compounds are given in
477 Table S16. The exclusion of this subject resulted in stronger associations between exposure
478 to PFHxS during the second trimester of pregnancy and Shannon diversity index, and
479 between exposure to each of these three PFAS and the abundance of phylum
480 Proteobacteria (Table S16). Finally, adjusting associations between phenols exposures and
481 the gut microbiota composition for specific gravity measured in urine samples did not
482 strongly influence our results (Table S17).
483

484 **Discussion**

485 In our couple-child cohort of 356 families, perinatal exposure to certain parabens,
486 which have *a priori* known antimicrobial properties, tended to be associated with
487 perturbations in α - and β -diversity in one year child gut microbiota. These parabens were
488 also associated with changes in the abundances of specific phyla and genera.

489

490 In our study, most of the associations observed between maternal and child
491 characteristics (leaving chemical factors aside) with child gut microbiota were in
492 agreement with the literature. As expected, vaginal delivery was associated with increased
493 Shannon diversity⁹¹. Maternal and infant exposure to tobacco, and antibiotic use during the
494 first year of life are known to alter the gut microbiota^{92,93} and they were associated with
495 decreases of specific α -diversity measures or alteration of certain phyla abundances.
496 Longer gestation duration was associated with increased abundance of Bacteroidetes, and
497 with decreased abundance of Actinobacteria. As reviewed by Kumbhare et al., preterm
498 infants show high levels of facultative anaerobes and lower levels of strict anaerobes like
499 *Bacteroides* when compared with term infants⁹⁴.

500 Maternal distant exposure to a compound with antimicrobial properties
501 (ethylparaben in the third trimester of pregnancy) tended to be associated with a decrease
502 in α -diversity at one year (specific richness and Faith phylogenetic diversity), whereas
503 more recent exposure of the newborn to these antimicrobial compounds (propylparaben at
504 12 months, butylparaben at 2 months) was associated with an increase in α -diversity
505 indices (Shannon diversity and the three diversity indices, respectively). Parabens are
506 postulated to exert their antimicrobial properties by disrupting membrane transport
507 processes or by inhibiting synthesis of DNA and RNA or of some key enzymes, such as
508 ATPases and phosphotransferases, in some bacterial species⁹⁵. Perinatal exposure to

509 triclosan, for which we expected an effect because of its antimicrobial properties⁹⁶⁻⁹⁸,
510 showed no evidence of association with gut microbiota α -diversity, and this was also the
511 case for the other pollutants of the phenol and PFAS families considered (after correction
512 for multiple comparisons). A few of the exposures studied were highly correlated,
513 including child exposures to certain parabens at one year of age, and certain PFAS
514 exposures during the second trimester of pregnancy (Figure S3). The BKMR mixture
515 analysis showed that increased exposure to the mixture of chemicals considered tended to
516 increase Shannon diversity but did not permit to identify the most important contributors of
517 the mixture. A higher α -diversity in infancy indicates a more mature, adult-like
518 community. It has been hypothesized that functional redundancy provided by a highly
519 diverse microbiota may allow better responses to environmental fluctuations, promoting
520 intestinal homeostasis and maintaining human health⁹³. However, the idea that a high α -
521 diversity is always beneficial for health in children has been questioned⁹⁹, especially
522 considering that certain diseases, such as autism spectrum disorders, have been associated
523 with increased α -diversity^{100,101}.

524 To our knowledge, there is no previous study on the effects of ethyl-, propyl- and
525 butyl-parabens on the diversity of the human gut microbiota. Two toxicological studies
526 have investigated the effects of methylparaben on the diversity of the gut microbiota in
527 animal models: Hu et *al.* described that oral methylparaben exposure (0.105 mg/kg/day)
528 did not change the α -diversity at any time point but resulted in significant changes in the
529 overall bacterial composition (β -diversity) and in taxonomy in adolescent rats at postnatal
530 day 62⁴⁰ coherently with our results. In another study, methylparaben exposure at
531 environmentally realistic concentrations (1 and 10 μ g/L) was capable of driving gut
532 microbiota of zebrafish to dysbiosis. Particularly in female intestine, methylparaben

533 exposure led to a significant increase in diversity of gut microbiota measured directly after
534 exposure¹⁰².

535 In a second tier, we investigated if the compounds associated with changes in α - or
536 β -diversity were associated with perturbations in the gut microbiota phyla at one year. In
537 the study of Hu et al., relative abundance of phylum Proteobacteria was increased in
538 methylparaben-treated rats compared to controls⁴⁰, contrary to our results. Then, to provide
539 a broader vision, we extended the phyla analyses to all pollutants whatever their
540 associations with α - or β -diversity (Table S12). Many of the compounds tested were
541 associated with a decrease in the abundance of Proteobacteria.

542 Finally, as an exploratory analysis, we investigated the relation between each of the
543 exposures and the relative abundance of the 46 most abundant genera (detected in at least
544 30% of the children). None of the associations passed the threshold corrected for multiple
545 comparison (p -value $<5.6 \times 10^{-5}$), in a context of a large number of associations tested. The
546 strongest associations (p -value <0.0035) may be worth discussing. These associations were
547 between genera belonging to 3 phyla, which were Firmicutes, Actinobacteria, and
548 Proteobacteria, and mainly postnatal exposures from the phenol family. None of the
549 exposures to PFAS or triclosan were strongly associated with bacterial genera. Perinatal
550 exposures (bisphenol A, methyl-, ethyl- and butyl-parabens at 12 months, propylparaben
551 and benzophenone 3 during the second trimester of pregnancy, benzophenone 3 at 2
552 months) showed effects on genera belonging to the family *Lachnospiraceae* (increases of
553 genera *Clostridium XVIII*, *Coprococcus* and *Lachnospiraceae incertae sedis* and decreases
554 of genera *Anaerostipes* and *Clostridium XIVa*) and the *Enterobacteriaceae* (decreases in
555 the taxon grouping genera *Escherichia* and *Shigella*, and of genera *Enterobacter* and
556 *Klebsiella*). Some toxicological studies on animal models also suggested an association
557 between bisphenol A exposure and an increase in *Lachnospiraceae* taxa^{46,103,104} similarly

558 to the trend observed in our study, while another found the opposite association¹⁰⁵.
559 *Coprococcus comes* was increased in bisphenol A exposed mice compared with control
560 mice in the study by Lai et al.⁴⁷, similarly to the trend observed in our study at the genus
561 level. To our knowledge, no other study investigated the effects of phenol exposures on the
562 gut microbiota, either in toxicology or epidemiology.

563 The clinical features associated with early life gut dysbiosis may include, among
564 others, the emergence of antimicrobial resistance¹⁰⁶, autoimmunity^{107,108} and
565 neurocognitive developmental problems^{109,110}. Members of *Lachnospiraceae* family are
566 among the main producers of short-chain fatty acids, and therefore play an important role
567 in host physiology¹¹¹, but different taxa from this family were also associated with
568 different intra- and extraintestinal diseases. For example, *Lachnospiraceae incertae sedis*
569 was higher in children with autism spectrum disorders and attention deficit hyperactivity
570 disorders compared to neurotypical children in 2 case-control studies^{112,113}. In an
571 prospective study, Laue et al. found that higher relative abundance of *Coprococcus* in the
572 gut microbiota of children at 2 years was associated with poorer social behaviors at 3 years
573 of age¹¹⁴.

574 Previous studies have shown that the gut microbiota develops intensively in the first
575 years of life in relation to the development of the central nervous system¹¹⁵⁻¹¹⁷ and that it is
576 needed to prime the innate immune system in both the periphery and central nervous
577 system¹¹⁸. Clarke et al. showed that peptidoglycan from commensal bacteria primes the
578 innate immune system. The pattern recognition receptor Nod1, which recognizes meso-
579 diaminopimelic acid containing peptidoglycan found predominantly in gram-negative
580 bacteria, was identified as the homeostatic regulator mediating the systemic effects of
581 peptidoglycan¹¹⁹. As confirmed by our study, gram-negative bacteria from the
582 Proteobacteria phylum, such as *Escherichia* and *Shigella*, are among the most abundant

583 microbes during the first year of life¹. *Escherichia* and/or *Shigella* genera were decreased
584 in the gut microbiota of autistic children compared to neurotypical children in 3 case-
585 control studies^{112,120,121}, but increased in another one¹²². Together, these results suggest that
586 the components found in bacteria from *Escherichia* and *Shigella* genera may play a role in
587 priming the host immune system during infancy, and in the long-term programming of
588 central nervous system and behavior, and that an early decrease in these bacteria in
589 childhood could have consequences on the development of the child.

590

591 Our study is the first to present results on the impact of perinatal exposure to
592 widespread chemicals on the gut microbiota of one-year children. It is based on a
593 prospective couple child cohort including 360 families with child microbiota assessment,
594 with rich questionnaire data to assess potential confounders and extensive exposure
595 assessment of two families of pollutants (phenols and PFAS) measured in urine and serum.
596 The assessment of chemical exposures during four perinatal time windows enabled a
597 unique and precise evaluation of exposures during critical developmental periods. DNA
598 was extracted from fecal samples using a technique that has been proven to allow an
599 accurate representation of the overall microbial community (validated by the
600 Metagenomics of the Human Intestinal Tract project and International Human Microbiome
601 Standards^{123–125}). For short half-life chemicals with high intra-individual variability, such
602 as the synthetic phenols studied in this work, the four urine collection weeks we relied on
603 has shown, for a given sample size, to strongly decrease bias in the effect estimates and
604 increase power, compared with studies relying on one urine sample per subject^{61,126}.

605 In spite of the relatively large sample size compared to the existing literature, our
606 power was probably low, in particular for the compounds with low *a priori* likelihood of
607 an effect, for which we applied a multiple testing correction procedure. Also, despite the

608 fact that the analyses were adjusted for potential confounders, residual confounding factors
609 cannot be excluded. Exposure to toxicants other than phenols and PFAS, has not been
610 considered in this study. However, other studies suggested that biomarkers of exposure to
611 phenols are not or weakly correlated with pollutants from other chemical families^{127,128},
612 limiting the potential for residual confounding by co-exposures. Finally, cross-sectional
613 associations with 1 year chemical exposures and 1 year child gut microbiota should be
614 interpreted with caution, as gut microbiota may influence xenobiotic metabolism¹²⁹, hence
615 to a risk of reverse causality.

616

617 Perinatal exposure to certain parabens possibly influences the diversity of the gut
618 microbiota in early childhood. Methyl-, ethyl- and propyl-paraben exposures were also
619 associated with the abundance of phyla Firmicutes and Proteobacteria. Perinatal exposures
620 to certain parabens were also associated with the taxonomy at the genus level, particularly
621 genera belonging to the families *Lachnospiraceae* and *Enterobacteriaceae*, but these
622 associations were not maintained after correction for multiple testing. Studies on even
623 larger sample sizes should be conducted to confirm these results and assess whether
624 associations are maintained in childhood.

625 **Abbreviations**

- 626 ASVs: Amplicon Sequence Variants
- 627 BMI: Body Mass Index
- 628 BKMR: Bayesian kernel machine regression
- 629 CNIL: Commission Nationale de l'Informatique et des Libertés
- 630 CPP: Comité de Protection des Personnes
- 631 DNA: DeoxyriboNucleic Acid
- 632 EtFOSA: n-ethylperfluorooctane sulfonamide
- 633 FOSAs: fluorooctane sulfonamides
- 634 FWER: family-wise error rate
- 635 GUMME: Gut Microbiota in early childhood and Maternal Environmental exposures
- 636 MeFOSA: n-methylperfluorooctane sulfonamide
- 637 NIPH: Norwegian Institute of Public Health
- 638 PFAS: poly- and perfluoroalkyl substances
- 639 PFBA: perfluorobutanoic acid
- 640 PFBS: perfluorobutanesulfonic acid
- 641 PFCAs: perfluoroalkyl carboxylates
- 642 PFDA: perfluorodecanoic acid
- 643 PFDoDa: perfluorododecanoic acid
- 644 PFDPA: perfluorodecyl phosphonic acid
- 645 PFDS: perfluorodecane sulfonic acid
- 646 PFHpA: perfluoroheptanoic acid
- 647 PFHpS: perfluoroheptanesulfonic acid
- 648 PFHxA: perfluorohexanoic acid
- 649 PFHxPA: perfluorohexylphosphonic acid

- 650 PFHxS: perfluorohexanesulfonic acid
- 651 PFNA: perfluorononanoic acid
- 652 PFOA: perfluorooctanoic acid
- 653 PFOPA: perfluorooctyl phosphonic acid
- 654 PFOS: perfluorooctane sulfonic acid
- 655 PFOSA: perfluorooctane sulfonamide
- 656 PFPeA: perfluoropentanoate
- 657 PFSA: perfluoroalkyl sulfonates
- 658 PFUnDA: perfluoroundecanoic acid
- 659 PFTeDa: perfluorotetradecanoic acid
- 660 PFTrDa: perfluorotridecanoic acid
- 661 rRNA: ribosomal RiboNucleic Acid
- 662 SEPAGES cohort: Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse
663 et Effet sur la Santé
- 664 6:2 diPAP: 6:2 fluorotelomer phosphate diester
- 665 6:2 PAP: 6:2 fluorotelomer phosphate monoester
- 666 8:2 diPAP: 8:2 fluorotelomer phosphate diester
- 667 8:2 PAP: 8:2 fluorotelomer phosphate monoester

668 **Supporting Information**

669 Table S1: Assessment of exposure to phenols and perfluoroalkyl substances in SEPAGES cohort.

670 Table S2: Description of pregnant women from SEPAGES cohort and comparison with women
671 from Grenoble and France.

672 Table S3: Description of children from SEPAGES cohort, and comparison with children from
673 Grenoble and France.

674 Table S4: Distribution and comparison of chemical exposures in SEPAGES cohort (484 mother-
675 child pairs).

676 Table S5: Distribution of α -diversity and major taxa in one year child gut microbiota from
677 SEPAGES cohort.

678 Table S6: Influence of maternal and child characteristics on the gut microbiota diversity in one-
679 year SEPAGES children.

680 Table S7: Influence of the maternal and child characteristics on the gut microbiota most abundant
681 phyla in one-year SEPAGES children.

682 Table S8: Associations between concentrations of pollutants during the second trimester of
683 pregnancy and the α -diversity of the child gut microbiota at one year (single-pollutant models and
684 multiple linear regression models adjusted for all mentioned exposures assessed during the second
685 trimester of pregnancy, n = 333 mother-child pairs in all models).

686 Table S9: Associations between concentrations of pollutants during the third trimester of pregnancy
687 and the α -diversity of the child gut microbiota at one year (single-pollutant models and multiple
688 linear regression models adjusted for all mentioned exposures assessed during the third trimester of
689 pregnancy, n = 344 mother-child pairs in all models).

690 Table S10: Associations between concentrations of pollutants at two months and the α -diversity of
691 the child gut microbiota at one year (single-pollutant models and multiple linear regression models
692 adjusted for all mentioned exposures assessed in two-month old children, n = 338 mother-child
693 pairs in all models).

694 Table S11: Associations between concentrations of pollutants at twelve months and the α -diversity
695 of the child gut microbiota at one year (single-pollutant models and multiple linear regression

696 models adjusted for all mentioned exposures assessed in one-year old children, n = 345 mother-
697 child pairs in all models).

698 Table S12: Adjusted associations between concentrations of pollutants without identified effects on
699 α -diversity or β -diversity and the 4 most abundant phyla in one-year children gut microbiota (n
700 between 340 and 355 mother-child pairs).

701 Table S13: Adjusted associations between concentrations of pollutants and the 46 most abundant
702 genera in one-year children gut microbiota (n between 340 and 355 mother-child pairs).

703 Table S14: Adjusted associations between chemical exposures and the gut microbiota α -diversity at
704 different sequencing depths.

705 Table S15: Adjusted associations between phenol assays suspected of contamination and one year
706 child gut microbiota composition.

707 Table S16: Adjusted associations between PFHpS, PFHxS and PFOS and gut microbiota
708 composition, before and after exclusion of one outlier.

709 Table S17: Adjusted associations between phenols exposures and the gut microbiota composition
710 before and after adjustment for specific gravity.

711

712 Figure S1: Observed ASVs regarding the depth of sequencing in one-year child gut microbiota
713 from SEPAGES cohort.

714 Figure S2: Direct acyclic graph of the relation between chemical exposures and one year child gut
715 microbiota.

716 Figure S3: Pearson correlations between chemicals assessed during various exposure windows.

717 Figure S4: Spearman correlations between chemicals and covariates.

718 Figure S5: Associations between concentrations of pollutants without a priori known antimicrobial
719 properties and the α -diversity of the child gut microbiota at one year (adjusted single-pollutant
720 models, n between 334 and 349 mother-child pairs).

721 Figure S6: Estimated effect of an increase from the 25th to 75th percentile in a single biomarker
722 concentration on α -diversity indices when all other biomarkers are fixed at either the 25th, 50th, or
723 75th percentiles (mixture models, n = 313 mother-child pairs).

724 Figure S7: Spearman correlations between the most abundant taxa in the gut microbiota of
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- 1238

1239 **Tables**

1240 *Table 1: Adjusted associations between concentrations of pollutants with a priori known antimicrobial properties (parabens, triclosan) and the*
 1241 *α -diversity of the child gut microbiota at one year (n between 334 and 349 mother-child pairs).*

Chemical and exposure window	N ¹	Specific richness			Shannon diversity			Faith's phylogenetic diversity		
		Beta ²	95% CI ³	p-value	Beta ²	95% CI ³	p-value	Beta ²	95% CI ³	p-value
Methylparaben										
Mother, pregnancy trim. 2	349	-0.5	-3, 2	0.50	0.02	-0.02, 0.07	0.26	-1	-7, 4	0.63
Mother, pregnancy trim. 3	344	-0.7	-2, 0.8	0.32	0.02	-0.01, 0.05	0.15	-2	-7, 2	0.27
Child, 2 months	338	0.6	-0.4, 2	0.21	0	-0.02, 0.02	0.99	1	-2, 4	0.39
Child, 12 months	345	0.7	-0.6, 2	0.26	0.02	-0.01, 0.05	0.14	2	-2, 6	0.25
Ethylparaben										
Mother, pregnancy trim. 2	349	-1	-3, 0.5	0.13	0	-0.04, 0.04	0.92	-4	-10, 2	0.18
Mother, pregnancy trim. 3	344	-2	-4, 0.1	0.06	0.02	-0.03, 0.06	0.42	-6	-12, 0.5	0.07
Child, 2 months				0.18			0.14			0.24
<LOQ	115 (34%)	—	—		—	—		—	—	
>LOQ	223 (66%)	4	-2, 11		0.1	-0.03, 0.23		11	-7, 29	
Child, 12 months	345	0.3	-1, 2	0.52	0.01	-0.02, 0.03	0.61	0.9	-3, 5	0.62
Propylparaben										
Mother, pregnancy trim. 2	349	-0.3	-1, 0.8	0.47	0	-0.02, 0.02	0.97	-2	-5, 2	0.34
Mother, pregnancy trim. 3	344	-0.5	-1, 0.5	0.27	0.01	-0.01, 0.02	0.59	-2	-5, 0.9	0.19
Child, 2 months				0.26			0.35			0.49
<LOD	125 (37%)	—	—		—	—		—	—	
>LOD	213 (63%)	3	-3, 10		0.06	-0.07, 0.19		6	-12, 24	
Child, 12 months	345	0.5	-0.6, 1	0.32	0.02	0.00, 0.04	0.06	1	-1, 4	0.34
Butylparaben										
Mother, pregnancy trim. 2				0.15			0.41			0.12
<LOD	274 (79%)	—	—		—	—		—	—	
LOD-LOQ	44 (13%)	-7	-16, 2	0.13	-0.06	-0.25, 0.13	0.51	-23	-49, 2	0.07
>LOQ	31 (8.9%)	-7	-17, 3	0.18	-0.14	-0.35, 0.08	0.21	-19	-48, 10	0.19
Mother, pregnancy trim. 3				0.11			0.98			0.10
<LOD	277 (81%)	—	—		—	—		—	—	
LOD-LOQ	37 (11%)	-8	-17, 2	0.10	-0.01	-0.20, 0.18	0.91	-23	-50, 3	0.09
>LOQ	30 (8.7%)	-7	-18, 3	0.16	-0.02	-0.23, 0.19	0.86	-21	-50, 8	0.15
Child, 2 months				0.03			0.04			0.04
<LOD	265 (78%)	—	—		—	—		—	—	

>LOD	73 (22%)	8	0.6, 15		0.15	0.00, 0.30		22	1, 42	
Child, 12 months				0.20			0.29			0.25
<LOD	221 (64%)	—	—		—	—		—	—	
LOD-LOQ	35 (10%)	4	-6, 14	0.46	0.03	-0.18, 0.24	0.76	11	-17, 39	0.44
>LOQ	89 (26%)	6	-1, 13	0.10	0.12	-0.03, 0.26	0.12	16	-4, 36	0.11
Triclosan										
Mother, pregnancy trim. 2	349	0	-1, 1	0.63	-0.01	-0.04, 0.03	0.74	0.1	-4, 4	0.97
Mother, pregnancy trim. 3	344	0.1	-1, 2	0.62	0.01	-0.01, 0.04	0.33	0.5	-4, 5	0.82
Child, 2 months	338	2	-1, 4	0.20	0.03	-0.02, 0.08	0.27	5	-2, 12	0.19
Child, 12 months	345	0.8	-2, 3	0.42	0.02	-0.04, 0.07	0.52	2	-5, 10	0.53

¹Number of observations (%).

²Average changes in α -diversity indices when the level of exposure to the biomarker is multiplied by Euler number e or compared to the reference category; adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode, gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year), period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics (parity, age and body mass index (BMI) before pregnancy, education, and smoking status during pregnancy).

³CI: Confidence Interval.

1243 Table 2: Adjusted associations between concentrations of pollutants without a priori known antimicrobial properties and the α -diversity of the child gut
 1244 microbiota at one year (n between 334 and 349 mother-child pairs).

Chemical and exposure window	N ¹	Specific richness			Shannon diversity			Faith's phylogenetic diversity		
		Beta ²	95% CI ³	p-value ⁴	Beta ²	95% CI ³	p-value ⁴	Beta ²	95% CI ³	p-value ⁴
Bisphenol A										
Mother, pregnancy trim. 2	349	-0.6	-4, 3	0.55	0.02	-0.05, 0.09	0.59	-1	-11, 8	0.77
Mother, pregnancy trim. 3	344	1	-2, 4	0.34	0.06	0.00, 0.12	0.07	4	-4, 13	0.33
Child, 2 months	338	0.6	-1, 3	0.45	0.03	-0.01, 0.07	0.15	2	-4, 8	0.51
Child, 12 months	345	1	-2, 4	0.42	0.04	-0.02, 0.10	0.24	3	-5, 12	0.43
Bisphenol S										
Mother, pregnancy trim. 2				0.39						0.57
<LOD	255 (73%)	—	—		—	—		—	—	
>LOD	94 (27%)	-2	-9, 4		-0.05	-0.19, 0.09		-6	-25, 14	
Mother, pregnancy trim. 3				0.57						0.91
<LOD	252 (73%)	—	—		—	—		—	—	
>LOD	92 (27%)	-0.9	-7, 6		0	-0.13, 0.14		1	-17, 20	
Child, 2 months				0.06						0.08
<LOD	182 (54%)	—	—		—	—		—	—	
>LOD	156 (46%)	6	-0.5, 12		0.11	-0.01, 0.24		16	-2, 33	
Child, 12 months				0.57						0.63
<LOD	102 (30%)	—	—		—	—		—	—	
LOD-LOQ	82 (24%)	-3	-11, 5	0.49	-0.16	-0.33, 0.02	0.08	-11	-34, 13	0.38
>LOQ	161 (47%)	-3	-11, 4	0.36	-0.06	-0.21, 0.09	0.42	-9	-29, 12	0.41
Benzophenone 3										
Mother, pregnancy trim. 2	349	-2	-4, 0.4	0.10	-0.01	-0.05, 0.03	0.67	-5	-11, 0.4	0.07
Mother, pregnancy trim. 3	344	-0.6	-3, 1	0.46	0.03	-0.01, 0.07	0.20	-2	-8, 4	0.55
Child, 2 months	338	0.9	-1, 3	0.37	0.04	-0.01, 0.08	0.12	2	-4, 9	0.46
Child, 12 months	345	2	-1, 6	0.15	0.05	-0.02, 0.12	0.16	6	-3, 15	0.18
PFOA , Mother, pregnancy trim. 2	334	0.7	-6, 7	0.59	0	-0.14, 0.14	>0.99	2	-17, 21	0.82
PFNA , Mother, pregnancy trim. 2	334	-2	-10, 6	0.48	0.01	-0.16, 0.17	0.95	-7	-29, 15	0.52
PFHxS , Mother, pregnancy trim. 2	334	3	-3, 8	0.30	0.07	-0.04, 0.18	0.22	6	-9, 22	0.42
PFOS , Mother, pregnancy trim. 2	334	1	-5, 7	0.54	0.03	-0.09, 0.15	0.65	2	-14, 18	0.78
PFDA , Mother, pregnancy trim. 2	334	0.8	-5, 7	0.58	0.01	-0.12, 0.14	0.88	2	-16, 20	0.84
PFUnDA , Mother, pregnancy trim. 2	334	-1	-8, 5	0.54	0	-0.14, 0.15	0.95	-5	-24, 14	0.62
PFHpS , Mother, pregnancy trim. 2	334	2	-4, 7	0.45	0.03	-0.08, 0.14	0.60	2	-13, 17	0.77
PFDoDa , Mother, pregnancy trim. 2				0.51			0.87			0.70
<LOD	34 (10%)	—	—		—	—		—	—	
LOD-LOQ	245 (73%)	5	-5, 15	0.32	0.04	-0.17, 0.25	0.69	12	-16, 40	0.40
>LOQ	55 (16%)	3	-9, 15	0.60	0.07	-0.19, 0.32	0.60	10	-25, 44	0.58
PFHxPA , Mother, pregnancy trim. 2				0.88			0.76			0.98
<LOD	51 (15%)	—	—		—	—		—	—	
LOD-LOQ	105 (31%)	0.5	-9, 10	0.91	-0.05	-0.24, 0.14	0.61	0.8	-25, 27	0.95
>LOQ	178 (53%)	0.7	-8, 9	0.87	0	-0.18, 0.18	>0.99	2	-22, 26	0.87
PFHpA , Mother, pregnancy trim. 2				0.62			0.45			0.98

<LOD	262 (78%)	—	—		—	—		—	—	
>LOD	72 (22%)	0	-7, 7		0.06	-0.09, 0.21		0.2	-20, 21	
PFTrDa , Mother, pregnancy trim. 2				0.31			0.40			0.51
<LOD	110 (33%)	—	—		—	—		—	—	
LOD-LOQ	155 (46%)	4	-2, 11	0.21	0.03	-0.12, 0.17	0.70	11	-9, 30	0.28
>LOQ	69 (21%)	-0.1	-8, 8	0.99	-0.09	-0.26, 0.09	0.35	2	-22, 26	0.86
PFBS , Mother, pregnancy trim. 2				0.13			0.88			0.14
<LOD	206 (62%)	—	—		—	—		—	—	
>LOD	128 (38%)	4	-2, 11		-0.01	-0.14, 0.12		13	-4, 30	
PFOSA , Mother, pregnancy trim. 2				0.60			0.30			0.75
<LOD	227 (68%)	—	—		—	—		—	—	
>LOD	107 (32%)	-0.5	-7, 6		-0.07	-0.21, 0.06		-3	-21, 15	
6:2 diPAP , Mother, pregnancy trim. 2				0.31			0.96			0.48
<LOD	263 (79%)	—	—		—	—		—	—	
>LOD	71 (21%)	-3	-10, 4		0	-0.16, 0.15		-7	-28, 13	
8:2 diPAP , Mother, pregnancy trim. 2				0.53			0.60			0.60
<LOD	293 (88%)	—	—		—	—		—	—	
>LOD	41 (12%)	-2	-11, 7		-0.05	-0.24, 0.14		-7	-33, 19	

¹Number of observations (%).

²Average changes in α -diversity indices when the level of exposure to the biomarker is multiplied by Euler number e or compared to the reference category; adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode, gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year), period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics (parity, age and body mass index (BMI) before pregnancy, education, and smoking status during pregnancy).

³CI: Confidence Interval.

⁴After correction for multiple testing, the significance threshold is 0.001.

1246 *Table 3: Adjusted associations between levels of pollutants with a priori known*
 1247 *antimicrobial properties (parabens, triclosan) and Bray-Curtis gut microbiota β -diversity*
 1248 *in one-year children (n between 334 and 349 mother-child pairs).*

Chemical and exposure window ¹	N ²	Bray-Curtis dissimilarity		
		Sum of squares ³	F-statistic ⁴	p-value
Methylparaben				
Mother, pregnancy trim. 2	349	0.76	1.11	0.27
Mother, pregnancy trim. 3	344	0.55	0.80	0.87
Child, 2 months	338	0.79	1.15	0.23
Child, 12 months	345	0.97	1.42	0.03
Ethylparaben				
Mother, pregnancy trim. 2	349	0.69	1.01	0.45
Mother, pregnancy trim. 3	344	0.89	1.31	0.08
Child, 2 months	338	0.28	0.81	0.72
Child, 12 months	345	0.88	1.28	0.08
Propylparaben				
Mother, pregnancy trim. 2	349	0.58	0.85	0.79
Mother, pregnancy trim. 3	344	0.62	0.90	0.68
Child, 2 months	338	0.34	0.98	0.45
Child, 12 months	345	1.13	1.66	0.008
Butylparaben				
Mother, pregnancy trim. 2	349	0.82	1.20	0.14
Mother, pregnancy trim. 3	344	0.81	1.18	0.17
Child, 2 months	338	0.38	1.13	0.29
Child, 12 months	345	0.68	1.00	0.46
Triclosan				
Mother, pregnancy trim. 2	349	0.61	0.89	0.69
Mother, pregnancy trim. 3	344	0.76	1.11	0.23
Child, 2 months	338	0.69	1.01	0.44
Child, 12 months	345	0.59	0.85	0.78

¹Most pollutants were coded as categorical variables (1st tertile, 2nd tertile and 3rd tertile) except ethylparaben at 2 months (<LOQ vs >LOQ), propylparaben and butylparaben at 2 months (<LOD vs >LOD) and butylparaben during 2nd and 3rd trimester of pregnancy and at 12 months (<LOD, LOD-LOQ, >LOQ).

²Number of observations.

³Variance in β -diversity that can be explained by differences in pollutant exposure between the different exposure groups; adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode, gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year), period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics (parity, age and body mass index (BMI) before pregnancy, education, and smoking status during pregnancy).

⁴Ratio of the mean square between exposure level groups due to the pollutant exposure to the mean square within exposure level groups (error mean square).

1249

1250 *Table 4: Adjusted associations between levels of pollutants without a priori known*
 1251 *antimicrobial properties and Bray-Curtis β -diversity in one-year children gut microbiota*
 1252 *(n between 334 and 349 mother-child pairs).*

Chemical and exposure window ¹	N ²	Bray-Curtis dissimilarity		
		Sum of squares ³	F-statistic ⁴	p-value ⁵
Bisphenol A				
Mother, pregnancy trim. 2	349	0.53	0.78	0.89
Mother, pregnancy trim. 3	344	0.88	1.29	0.08
Child, 2 months	338	0.72	1.06	0.36
Child, 12 months	345	0.67	0.98	0.50
Bisphenol S				
Mother, pregnancy trim. 2	349	0.27	0.79	0.78
Mother, pregnancy trim. 3	344	0.34	1.01	0.42
Child, 2 months	338	0.43	1.25	0.16
Child, 12 months	345	0.77	1.13	0.24
Benzophenone 3				
Mother, pregnancy trim. 2	349	0.89	1.30	0.07
Mother, pregnancy trim. 3	344	0.78	1.14	0.24
Child, 2 months	338	0.96	1.42	0.029
Child, 12 months	345	0.63	0.92	0.63
PFOA , Mother, pregnancy trim. 2	334	0.66	0.96	0.54
PFNA , Mother, pregnancy trim. 2	334	0.70	1.03	0.41
PFHxS , Mother, pregnancy trim. 2	334	0.79	1.16	0.17
PFOS , Mother, pregnancy trim. 2	334	0.90	1.31	0.06
PFDA , Mother, pregnancy trim. 2	334	0.59	0.87	0.74
PFUnDA , Mother, pregnancy trim. 2	334	0.84	1.23	0.12
PFHpS , Mother, pregnancy trim. 2	334	0.63	0.93	0.62
PFDoDa , Mother, pregnancy trim. 2	334	0.62	0.90	0.63
PFHxPA , Mother, pregnancy trim. 2	334	0.59	0.87	0.74
PFHpA , Mother, pregnancy trim. 2	334	0.32	0.95	0.54
PFTTrDa , Mother, pregnancy trim. 2	334	0.87	1.28	0.08
PFBS , Mother, pregnancy trim. 2	334	0.20	0.59	0.97
PFOSA , Mother, pregnancy trim. 2	334	0.28	0.81	0.72
6:2diPAP , Mother, pregnancy trim. 2	334	0.37	1.09	0.33
8:2diPAP , Mother, pregnancy trim. 2	334	0.36	1.06	0.37

¹Most pollutants were coded as categorical variables (1st tertile, 2nd tertile and 3rd tertile) except bisphenol S during the 2nd and 3rd trimester and at 2 months, and PFHpA, PFBS, PFOSA, 6: 2 diPAP and 8:2 diPAP during 2nd trimester of pregnancy (<LOD vs >LOD) and bisphenol S at 12 months and PFDoDa, PFHxPA, PFTTrDa during 2nd trimester of pregnancy (<LOD, LOD-LOQ, >LOQ).

²Number of observations.

³Variance in β -diversity that can be explained by differences in pollutant exposure between the different exposure groups; adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode, gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year), period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics (parity, age and body mass index (BMI) before pregnancy, education, and smoking status during pregnancy).

⁴Ratio of the mean square between exposure level groups due to the pollutant exposure to the mean square within exposure level groups (error mean square).

⁵After correction for multiple testing, the significance threshold was 0.003.

1253

1254 *Table 5: Associations between concentrations of pollutants with identified effects on α -diversity or β -diversity and the 4 most abundant phyla in*
 1255 *one-year children gut microbiota (n between 342 and 351 mother-child pairs).*

Chemical and exposure window	N ¹	Phylum Firmicutes			Phylum Actinobacteria			Phylum Bacteroidetes			Phylum Proteobacteria		
		Beta ²	95% CI ³	p-value	Beta ²	95% CI ³	p-value	Beta ²	95% CI ³	p-value	Beta	95% CI ²	p-value
Methylparaben													
Child, 12 months	351	-0.1	-1, 0.9	0.91	-0.3	-1, 0.8	0.59	0.4	-0.5, 1	0.35	-1	-2, -0.2	0.01
Ethylparaben													
Mother, pregnancy trim. 3	350	2	0.1, 3	0.04	0.8	-0.9, 3	0.34	-0.9	-2, 0.5	0.2	-0.6	-2, 0.6	0.34
Propylparaben													
Child, 12 months	351	0.3	-0.4, 1	0.42	-0.4	-1, 0.4	0.31	0.5	-0.1, 1	0.13	-0.7	-1, -0.1	0.02
Butylparaben													
Child, 2 months				0.26			0.58			0.91			0.82
<LOD	267 (78%)	—	—		—	—		—	—		—	—	
>LOD	75 (22%)	3	-2, 8		-2	-8, 4		-0.3	-5, 5		0.5	-4, 5	

¹Number of observations (%).

²Average changes in relative abundances of major phyla when the level of exposure to the biomarker is multiplied by Euler number e or compared to the reference category; adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode, gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year), period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics (parity, age and body mass index (BMI) before pregnancy, education, and smoking status during pregnancy).

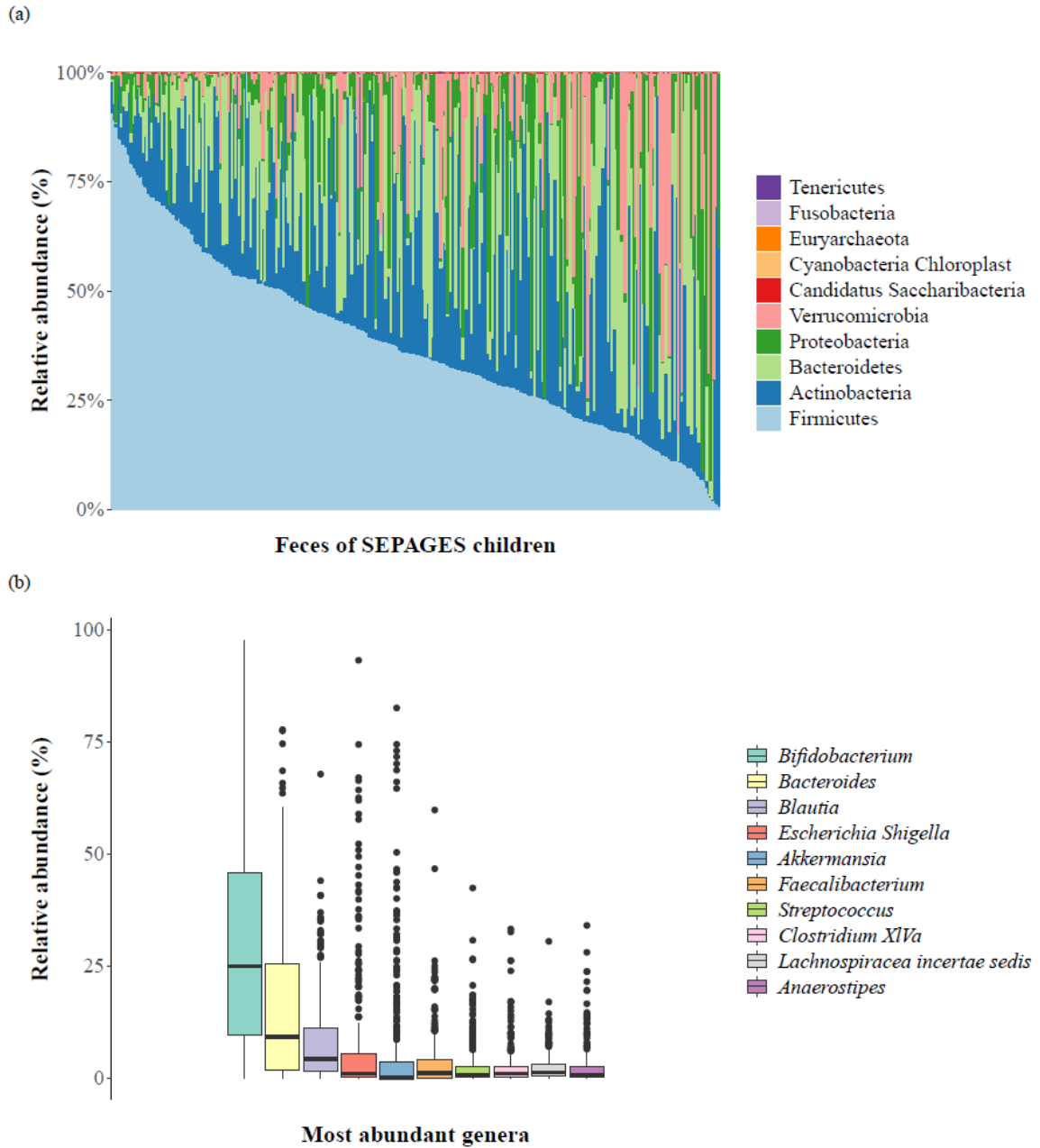
³CI: Confidence Interval.

1256

1257 **Figures**

1258 *Figure 1: Distribution of the most abundant taxa in gut microbiota in one-year children*

1259 *from SEPAGES cohort (n =356).*

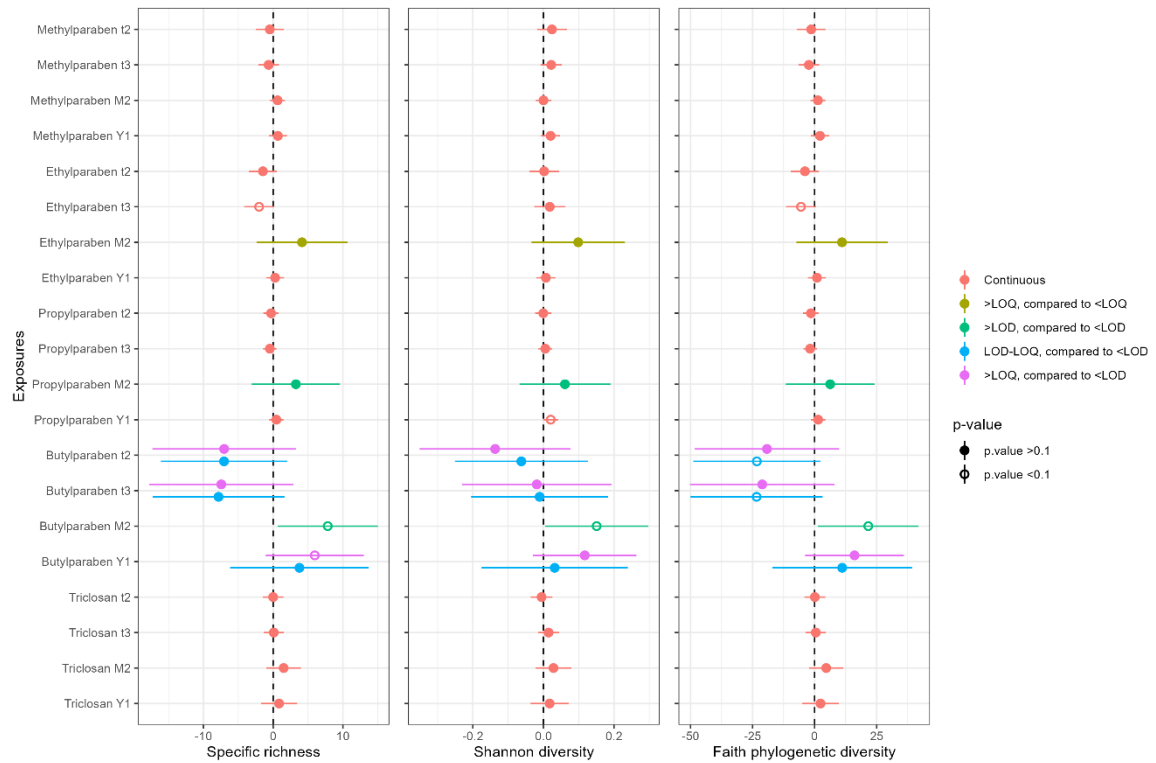


1260

1261 (a) Relative abundance of the phyla in one year child gut microbiota.

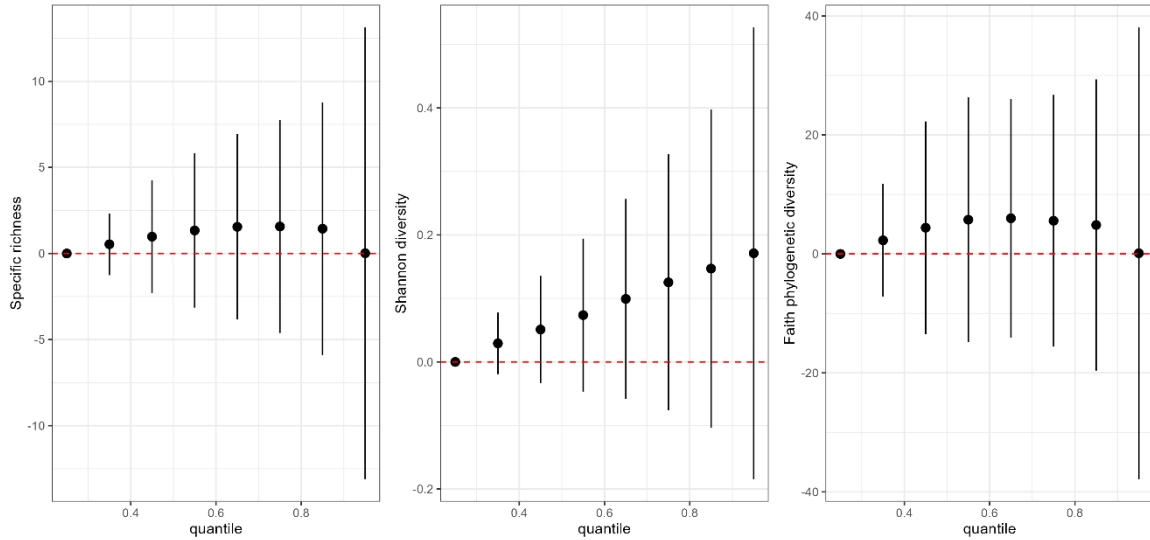
1262 (b) Relative abundance of the 10 most abundant genera in one year child gut microbiota.

1263 *Figure 2: Adjusted associations between concentrations of pollutants with a priori known*
 1264 *antimicrobial properties and the α -diversity of the child gut microbiota at one year*
 1265 *(adjusted single-pollutant models, n between 334 and 349 mother-child pairs).*



1266
 1267 Average changes in α -diversity indices when the level of exposure to the biomarker is multiplied by Euler
 1268 number e or compared to the reference category; adjusted for MiSeq analytic batch effect, child age at feces
 1269 collection, delivery mode, gestational age, interpregnancy interval, child characteristics (sex, weight and
 1270 length at birth and at one year), period of introduction of solid food, breast-feeding status up to 48 weeks,
 1271 antibiotics use during the first year of life, presence of pets at home, passive smoking during the first year of
 1272 life, and maternal characteristics (parity, age and body mass index (BMI) before pregnancy, education, and
 1273 smoking status during pregnancy).
 1274 t2: second trimester exposure, t3: third trimester exposure, M2: 2-month exposure, Y1: 12-month exposure.
 1275 Details on the calculation of the α -diversity indices are given in the methods section.

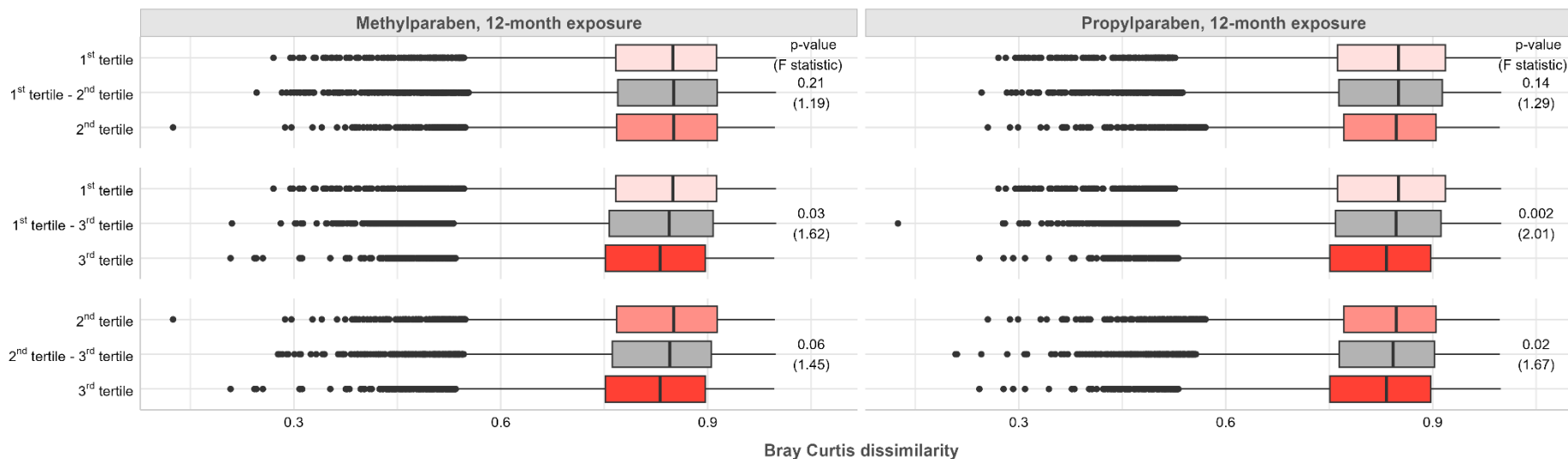
1276 *Figure 3: Expected changes in α -diversity indices associated with concurrently increasing*
1277 *quantiles of all chemicals (continuous variables), relative to when all concentrations were*
1278 *fixed at their 25th percentile (adjusted mixture models, $n = 313$ mother-child pairs).*



1279

1280 Mixture models are adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode,
1281 gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year),
1282 period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year
1283 of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics
1284 (parity, age and body mass index (BMI) before pregnancy, education, and smoking status during pregnancy).
1285 Details on the calculation of the α -diversity indices are given in the methods section.

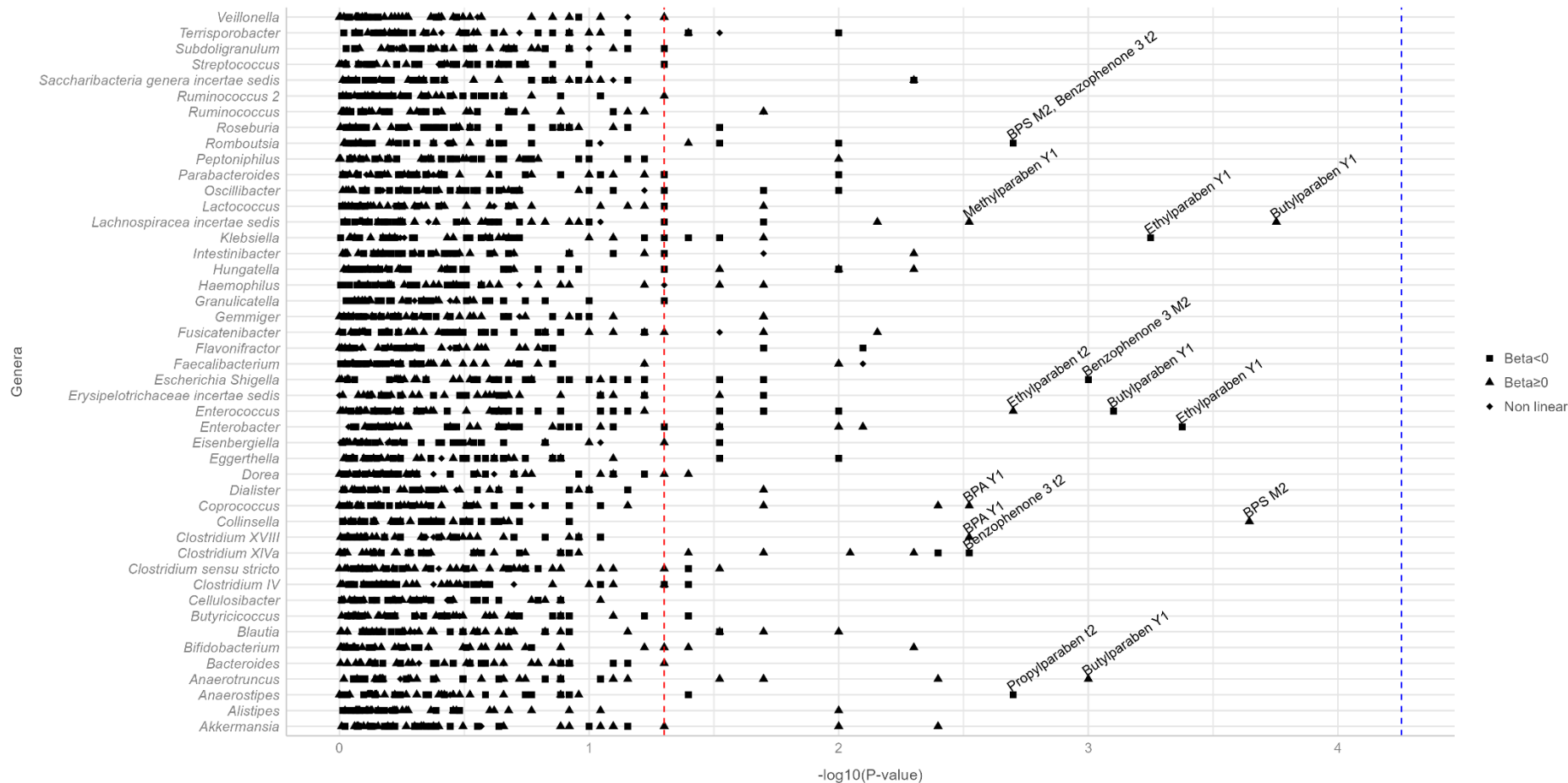
1286 *Figure 4: Adjusted associations between chemicals and children gut microbiota β -diversity at one year according to exposure levels in tertiles (n*
 1287 *= 345 mother-child pairs).*



1288
1289

1290 PERMANOVA models were adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode, gestational age, interpregnancy interval, child
 1291 characteristics (sex, weight and length at birth and at one year), period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year
 1292 of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics (parity, age and body mass index (BMI) before pregnancy,
 1293 education, and smoking status during pregnancy).

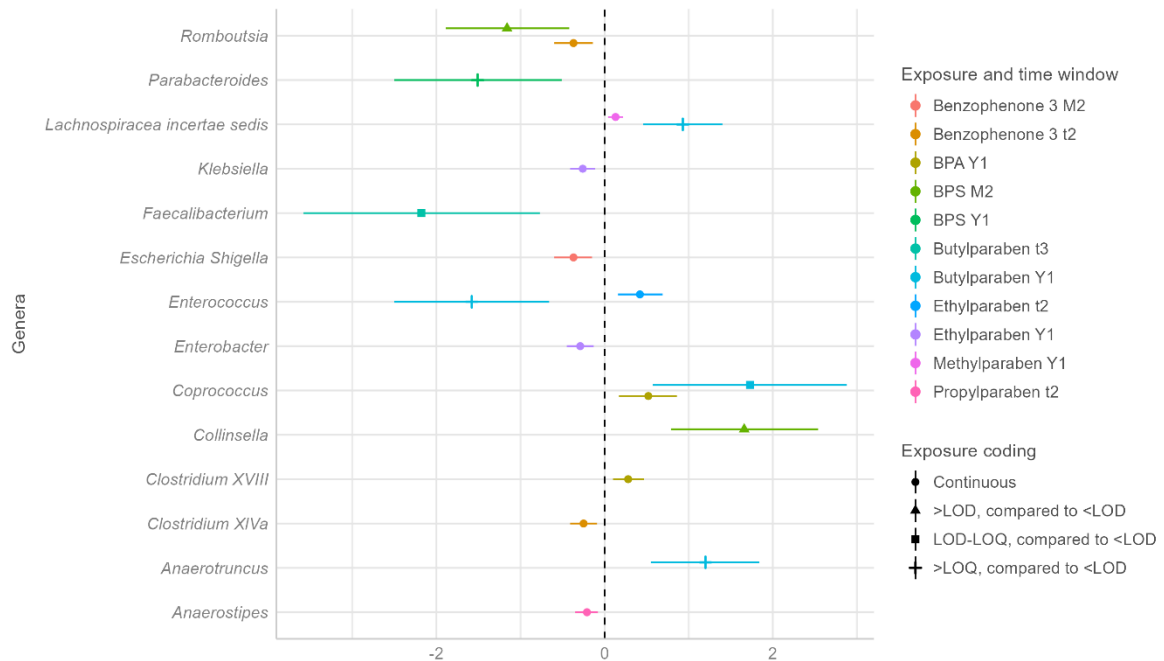
1294 Figure 5: Adjusted associations between concentrations of pollutants and the 46 most abundant genera in the child gut microbiota at one year
 1295 (adjusted single-pollutant models, n between 340 and 355 mother-child pairs).



1296

1297 -log₁₀(p-value) of the associations between the pollutants and the 46 most abundant genera (detected in at least 30% of the children) when the level of exposure to the
1298 biomarker is multiplied by Euler number e or compared to the reference category, adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode,
1299 gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year), period of introduction of solid food, breast-feeding status up to
1300 48 weeks, antibiotics use during the first year of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics (parity, age and body
1301 mass index (BMI) before pregnancy, education, and smoking status during pregnancy).
1302 The vertical red dotted line represents a p-value equal to 0.05. The vertical blue dotted line represented the threshold for the multiple testing corrected p-value (5.6×10^{-5}).
1303 t2: second trimester exposure, t3: third trimester exposure, M2: 2-month exposure, Y1: 12-month exposure, BPA: bisphenol A, BPS: bisphenol S.
1304 Complete results of the associations between pollutant exposures and the 46 most abundant genera are given Table S13.

1305 *Figure 6: Strongest adjusted associations between concentrations of pollutants and the 46*
 1306 *most abundant genera in the child gut microbiota at one year (adjusted single-pollutant*
 1307 *models, n between 340 and 355 mother-child pairs).*



1308
 1309 Average changes in the relative abundance of the most abundant genera (detected in at least 30% of the
 1310 children) when the level of exposure to the biomarker is multiplied by Euler number e or compared to the
 1311 reference category; adjusted for MiSeq analytic batch effect, child age at feces collection, delivery mode,
 1312 gestational age, interpregnancy interval, child characteristics (sex, weight and length at birth and at one year),
 1313 period of introduction of solid food, breast-feeding status up to 48 weeks, antibiotics use during the first year
 1314 of life, presence of pets at home, passive smoking during the first year of life, and maternal characteristics
 1315 (parity, age and body mass index (BMI) before pregnancy, education, and smoking status during pregnancy).
 1316 t2: second trimester exposure, t3: third trimester exposure, M2: 2-month exposure, Y1: 12-month exposure,
 1317 BPA: bisphenol A, BPS: bisphenol S.
 1318 Complete results of the associations between pollutant exposures and the 46 most abundant genera are given
 1319 Figure 5 and Table S13.