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### ► To cite this version:

Matthieu Rolland, Sadia Khan, Sarah Lyon-Caen, Cathrine Thomsen, Amrit Sakhi, et al.. Using Eye Tracking to Evaluate Cognitive and Visual Outcomes of Early Life Phenol Exposure. *Environmental Research*, 2025, 282, pp.122067. <10.1016/j.envres.2025.122067>. <hal-05117375>

**HAL Id: hal-05117375**

**<https://hal.science/hal-05117375v1>**

Submitted on 17 Jun 2025

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# Using Eye Tracking to Evaluate Cognitive and Visual Outcomes of Early Life Phenol Exposure

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27 **Contributors Statement Page**  
28

29 Matthieu Rolland: formal analysis, visualization, writing – original draft

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31 Remy Slama: review and editing, resources, cohort design

32 Sarah Lyon-Caen: review and editing, resources, data collection

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40

41 All authors approved the final manuscript as submitted and agreed to be accountable for all  
42 aspects of the work.

43

44

45 **Abstract**

46 **Introduction:** Studies on behavioral effects of synthetic phenols have often relied on parent-  
47 reported questionnaires and primarily focused on prenatal exposure.

48 **Aims:** We examined associations between prenatal and infancy phenol exposures and  
49 objective measures of child visual behavior and cognitive function at 2 years of age.

50 **Methods:** At age 2, 151 children from the SEPAGES mother-child cohort completed eye-  
51 tracking tasks assessing four indicators: fixation duration (attentional control), novelty  
52 preference (visual recognition memory), time spent looking at eyes (social attention), and  
53 reaction time (processing speed). Phenol concentrations (two bisphenols, three parabens,  
54 benzophenone-3, triclosan) were measured in multiple urine samples collected from mothers  
55 (second and third trimesters; median: 42 samples per woman) and infants (2 and 12 months;  
56 median: 7 samples).

57 **Results :** No associations were found with  $\sum$ parabens. However, individual parabens showed  
58 significant associations: ethylparaben at third trimester (T3) and 12 months (M12) was linked  
59 to shorter reaction time; at 2 months (M2), it was associated with reduced time spent looking  
60 at eyes. Propylparaben at T2 and T3 correlated with increased time spent looking at a novel  
61 face, especially in boys. Bisphenol S at T2 was associated with reduced reaction time; at  
62 M12, infants with detectable bisphenol S was linked to more time spent looking at eyes.

63 **Conclusion:** Several associations observed indicate that increased phenol exposure  
64 sometimes correlated with improved eye-tracking scores. These findings align with prior  
65 literature on phenol exposure and ASD symptoms, which highlight variability by exposure  
66 window and phenol type. Given limited research and typically small sample sizes, further  
67 studies using objective markers and clinical assessments are necessary.



69 **Keywords**

70 Phenol, Parabens, Infancy, Eye-Tracking, Cognition, Neurodevelopment, Exposure

71 **Abbreviations**

72

73	EDCs	-	Endocrine-disrupting chemicals
74	ASD	-	Autism Spectrum Disorders
75	CBCL	-	Child Behavior Checklist
76	SRS	-	Social Responsiveness Scale
77	SDQ	-	Strengths and Difficulties Questionnaire
78	MDI	-	Mental Development Index
79	LOD	-	Limit of detection
80	LOQ	-	Limit of quantification
81	WAIS-IV	-	Wechsler Adult Intelligence Scale – Fourth Edition
82	K-CPT2	-	Conners Kiddie Continuous Performance Test
83	HPLC-MS-MS	-	High-performance liquid chromatography coupled with mass spectrometry
84			
85	SEPAGES	-	Assessment of Air Pollution Exposure during
86	Pregnancy		
87			and Effect on Health

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## 1. Introduction

Despite some synthetic phenols being recognized as endocrine disruptors (Demeneix, 2019); they remain widely present in consumer products, leading to widespread exposure across the general population, including pregnant women and young children (Casas et al., 2013; Dereumeaux et al., 2016; Rolland et al., 2020). This is a public health concern because many health outcomes are closely linked to the endocrine system function. Child neurodevelopment, in particular, is a critical process that depends on hormonal homeostasis during prenatal and early postnatal life and even minor disruptions to this balance can be associated with neurodevelopmental disorders (Gore et al., 2014).

Synthetic phenols can disrupt key hormonal and neurotransmitter pathways—including thyroid hormone signaling, estrogen receptor activity, and dopaminergic systems—essential to neurogenesis, neuronal migration, and synaptogenesis (Diamanti-Kandarakis et al., 2009; Gore et al., 2014; Rice and Barone, 2000). Disruptions during critical periods may impair the maturation of circuits involved in cognition, attention, and social behavior (Stiles and Jernigan, 2010).

Both animal and epidemiological studies have suggested impaired cognitive function and behavior following prenatal exposure to some synthetic phenols. In rodents, prenatal exposure to bisphenol A has been associated with decreased investigation and interaction behaviors (Butler et al., 2020; Kaur et al., 2020; Repouskou et al., 2020) as well as increased repetitive behaviors (Butler et al., 2020).

Several human studies have examined the relationship between prenatal phenol exposure and neurodevelopmental outcomes in early childhood. Most have focused on bisphenol A and reported associations with social impairments and increased behavioral problems (Braun,

119 2017; Evans et al., 2014; Hansen et al., 2021b; Lim et al., 2017; Liu et al., 2021; Maserejian  
120 et al., 2012; Miodovnik et al., 2011; Pan et al., 2019; Philippat et al., 2017; Roen et al., 2015).  
121 Results were mixed for the other phenols, with studies reporting null (Philippat et al., 2017)  
122 or even protective associations (Etzel et al., 2018) depending on exposure timing and sex.  
123 With few exception (Cragoe et al., 2024), most studies used tests done by neuropsychologist  
124 to evaluate cognitive function (i.e. Bayley Scale of Early Learning, Wechsler Scale of  
125 Intelligence) or parent-reported scales such as the CBCL or SRS to evaluate behavior, which  
126 are subjective and may be prone to bias (Rosenman et al., 2011; Ross et al., 1995; Wilson et  
127 al., 2000).

128 To overcome these challenges, eye-tracking offers a non-invasive and objective method to  
129 assess attentional and cognitive processes from early infancy, with implementation possible  
130 as early as 3 months of age. It has demonstrated sensitivity to subtle, subclinical patterns  
131 across domains such as attention, social orientation, memory, and processing speed. Eye-  
132 tracking has been used to detect early atypical visual behaviors in infants who were later  
133 diagnosed with neurodevelopmental disorders such as ASD, including reduced time spent  
134 looking at eyes and altered gaze patterns, both in clinical and at-risk populations (Elsabbagh  
135 et al., 2013; Joseph et al., 2009a; Klin et al., 2002, 2002; Oakes, 2012; Sasson and Elison,  
136 2012a; Telford et al., 2016; Wan et al., 2018; Yurkovic et al., 2021). However, most  
137 epidemiological studies still rely on parent-reported outcomes and often lack postnatal  
138 exposure data, despite infancy being a critical window of rapid brain development, as  
139 highlighted in our previous findings (Mustieles et al., 2023; Rolland et al., 2023).

140 Given the scarcity of studies on early postnatal exposure and objective assessments of child  
141 behavior at a young age, we aim to assess the associations between seven synthetic phenols  
142 measured in repeated urine samples collected during pregnancy and the first year of life, and  
143 behavioral indicators derived from eye-tracking tasks performed at 24 months. To our

144 knowledge, this is one of the first studies in environmental epidemiology to combine repeated  
145 exposure assessment across both prenatal and early postnatal windows with eye-tracking-  
146 based outcomes in early childhood.

147

## 148 **2. Methods**

### 149 **2.1 Study Population**

150 The study sample consisted of mother-child pairs from the French SEPAGES cohort recruited  
151 in the Grenoble area between July 2014 and July 2017 (Lyon-Caen et al., 2019). Eligibility  
152 criteria included: being less than 19 weeks pregnant at enrollment, over 18 years old, fluent in  
153 French, affiliated with the national social security system (i.e., to ensure access to standard  
154 care and reimbursements) and planning to deliver in one of the four area's maternity clinics.  
155 Multiple pregnancies were excluded. Out of the 484 women enrolled in SEPAGES, this  
156 project was restricted to 151 infants whose parent agreed to participate in the eye tracking  
157 sub-study, and for whom both both eye-tracking measurement at 24 months and phenol  
158 exposure data during pregnancy or infancy were available (Figure 1). The relatively limited  
159 sample size for the eye-tracking sub-study can be partly explained by a delayed setup  
160 (starting in September 2017, while SEPAGES children began turning two in January 2017)  
161 and scheduling constraints in the laboratory, which reduced the number of eligible families  
162 who could be tested within the targeted age window. The study received ethical approval  
163 from the Comité de Protection des Personnes (CPP) Sud-Est V (approval number: 13-CHUG-  
164 44), and authorization from the French Data Protection Authority (Commission Nationale de  
165 l'Informatique et des Libertés, CNIL). Written informed consent was obtained from both  
166 parents.

## 167 2.2 Urine Sample Collection and Exposure Assessment

168 Urine samples were collected from the mothers during the second and third trimesters of  
169 pregnancy, and from their infants at 2 and 12 months postnatally. During pregnancy, women  
170 were instructed to collect three spot urine samples per day—morning (first void), midday,  
171 and evening (last void before bedtime)—over seven consecutive days for each collection  
172 period. For infants, one urine sample per day was collected over seven days at each time  
173 point, without constraints on timing, to avoid contamination with stool. Infant urine was  
174 collected using cotton pads placed inside the diaper. These samples were pooled per  
175 participant and per period, resulting in four urine pools per mother–child pair. Aliquotes of  
176 these pooled samples were stored at -80°C in Grenoble University Hospital Biobank (bb-  
177 0033-00069), and shipped on dry ice to the Norwegian Institute of Public Health (NIPH) and  
178 analyzed for phenol concentrations using high-performance liquid chromatography coupled  
179 with mass spectrometry (HPLC-MS-MS) (Sakhi et al., 2018). Total concentrations of 7  
180 phenols were measured including 2 bisphenols, 3 parabens, benzophenone 3 and triclosan.  
181 The phenol analysis method is fully validated, and inter- and intra-assay variabilities were  
182 below 25% for most of the phenols (Sakhi et al. Levels, variability and determinants of  
183 environmental phenols in pairs of Norwegian mothers and children. *Environment*  
184 *International* 114 (2018) 242–251). For quality assurance, two procedural blank samples, two  
185 in-house control samples and one external control sample (standard reference material (SRM  
186 3673) from the National Institute of Standards and Technology (NIST) were analyzed along  
187 with each batch/sequence of 50 samples. Potential contamination through sampling material  
188 was assessed and found negligible (Rolland et al., 2020). However, contamination of infant  
189 urine samples with free bisphenol A and free methylparaben was observed, most likely due to  
190 the use of diapers. To address this, we exclusively used the conjugated (i.e., metabolized)  
191 forms of bisphenol A and methylparaben in all analyses. For the other phenols, total

192 concentrations (sum of free and conjugated forms) were used. Specific gravity was measured  
193 in each pooled sample using a handheld refractometer (Atago PAL 10-S, Atago Co., Japan).

194 To reduce measurement error, concentrations were preprocessed following a two-step  
195 approach: values below LOD were imputed using distribution-based methods (Helsel, 1990),  
196 and concentrations were standardized to account for analytical batch effects and sample  
197 handling conditions (Mortamais et al., 2012; Rolland, 2025).

### 198 **2.3 Eye Tracking Assessment**

199 Eye movements were recorded using an Eyelink 1000 system (SR Research, Ontario) at 250  
200 Hz, or 500 Hz for the saccadic task. Data were captured in head reference mode using a  
201 16mm lens for infant studies and a target sticker for head-free tracking. A 940 nm illuminator  
202 was used for infants. The Eyelink system offers 0.5° accuracy, a tracking range of 32°  
203 (horizontal) x 25° (vertical), and accommodates head movements within a 22x18x20 cm area.  
204 Stimuli were displayed on a monitor (Iiyama Vision Master Pro 514, 40.5 x 30.5 cm, 1024 x  
205 768 pixels). Fixations (pauses at a location for at least 80ms) and saccades (rapid movements  
206 lasting 10-60ms) were identified using the Eyelink parser with predefined parameters  
207 (acceleration  $\geq 8000^\circ/s^2$ , velocity  $\geq 30^\circ/s$ , position change  $>0.15^\circ$ ).

208 During testing, infants sat on their parent's lap at a distance of 520-580 mm from the screen.  
209 The experiments were conducted in low-light, standardized conditions with distractions  
210 minimized by an occluding curtain. A target sticker placed on the infant's forehead served as  
211 a reference point for head tracking. Either the right or left eye was tracked, depending on  
212 signal quality. Calibration was performed using a 5-point procedure with custom audiovisual  
213 targets, ensuring calibration-validation errors were below 1°. Each trial began only after the  
214 infant fixated on an attention grabber (positional error  $< 2^\circ$ ).

215 Infants completed four tasks: (1) scene exploration, (2) visual paired recognition with faces,  
216 (3) saccade-to-target, and (4) smooth pursuit (See Supplementary Material, Table S1 for  
217 details on the tasks).

218

219 The primary outcomes derived from those tasks were:

220 1) the mean fixation durations (in milliseconds, ms) serve as an indicator of attentional  
221 control and were obtained from two tasks: the visual paired recognition task with  
222 faces and the scene exploration task. Shorter mean fixation durations in infancy have  
223 been observed in children with ASD (Al-Haddad et al., 2020; Joseph et al., 2009a;  
224 Sasson and Elison, 2012b; Wan et al., 2019; Wass et al., 2015) and have been linked  
225 to higher scores of hyperactivity-inattention (Papageorgiou et al., 2014)

226 2) novelty preference (%) corresponded to the percentage of time spent looking at a  
227 novel face. It was derived from the visual paired recognition task with faces. This  
228 measure reflects recognition/visual memory rather than processing speed. It has been  
229 shown to predict intellectual quotient scores at 6 and 11 years (Rose et al., 1992; Rose  
230 and Feldman, 1995) as well as the mental development index scores on the Bayley  
231 Scale of Early Learning (BSID) at 3 years (Rose et al., 2009).

232

233 3) percent time spent looking at the eyes (%): the proportion of time spent gazing at the  
234 eyes was obtained from the visual paired recognition task using faces. This metric has  
235 been employed in autism research, with findings indicating that individuals with  
236 autism often exhibit reduced eye contact starting as early as 6 months (Jones and Klin,  
237 2013).

238

239 4) The mean reaction time (ms) was calculated from two tasks: the saccade to target task  
240 and the smooth-pursuit task. This measure reflects the child's ability to shift attention  
241 from one location to another, serving as an indicator of processing speed. Shorter  
242 reaction times during infancy have been associated with higher IQ scores in later  
243 years (Thomas M Dougherty and Haith, 1997). Of interest, infants with ASD have shown  
244 superior performance in visual search tasks, with reaction times that are faster than  
245 those of typically developing children (Joseph et al., 2009b).

246 The sample size slightly varied across scores as a few children did not perform all four tasks  
247 (Table 1).

248

## 249 **2.4 Statistical Analysis**

### 250 *Exposure and outcome data pre-processing*

251 Phenol concentrations below the limit of detection and quantification were singly imputed  
252 using the compound's probability distribution (Helsel, 1990). For compounds with more than  
253 30% of samples below the LOD (butylparaben and bisphenol S), concentrations were  
254 categorized as detected or undetected (Lubin et al., 2004). Concentrations were ln-  
255 transformed for analysis. When needed, urinary concentrations were standardized for  
256 sampling (sample transportation time between the participant's home and the biobank and  
257 sample thawing time during the pooling procedure) and analytical conditions (analytical  
258 batch) (Guilbert et al., 2021; Mortamais et al., 2012), See Supplementary Material for details  
259 on this standardization. Additionally, the molar sum of parabens was calculated and included  
260 in the analysis.

261 With the exception of mean fixation duration, which was ln-transformed to normalize its  
262 distribution, all other eye-tracking scores were used in their original scale in the models.

## 263 **2.5 Covariates**

264 Candidate model covariates included factors that were likely to be associated with both  
265 phenol exposure and eye-tracking scores, without being influenced by them, as well as  
266 potential predictors of eye-tracking scores only. These were selected based on prior literature,  
267 theoretical considerations, and the causal structure outlined in a Directed Acyclic Graph  
268 (Figure S1). Regression models including all candidate covariates and excluding exposure  
269 were performed for each eye-tracking score. A covariate was retained in all final models if its  
270 p-value was less than 0.2 in at least one of the models. This selection criterion was applied  
271 due to the relatively small sample size.

272 The final set of covariates included in all the models was: maternal age (continuous, linear),  
273 maternal tobacco consumption after conception (Yes/No), maternal cognitive function  
274 assessed with the verbal component of the Wechsler Adult Intelligence Scale – Fourth  
275 Edition (WAIS-IV, continuous, linear), parity (1st child/2nd child/3rd child or more),  
276 maternal professional status at sampling time (working, not working and not looking for  
277 work, not working and looking for work), breastfeeding duration (continuous, linear), child  
278 sex (male/female), and experiment time of the day (continuous, 4-degree natural spline). The  
279 considered covariates that were not retained were: maternal education, gestational age at  
280 birth, child age at assessment, and maternal depression (Table S2).

281 Linear regression models were used to study the associations between phenol concentrations  
282 and continuous scores (i.e., fixation duration and reaction time), while beta regression models  
283 were applied to percentage scores (i.e., time spent looking at eyes and novelty preference).

284 Regarding model interpretation, betas are provided for an increase by one in the ln-  
285 transformed concentrations, except for mean fixation duration for which betas represent the  
286 percent change in fixation duration for doubling in biomarker concentration.

## 287 **2.6 Interaction Analysis**

288 Given that previous studies have suggested effects modification by child sex for phenol  
289 exposure (Hansen et al., 2021a; Lim et al., 2017), we performed additional analyses where  
290 we included an interaction term between phenol concentrations and child sex. A p-value for  
291 the interaction term below 0.2 was considered as an indication of potential effect  
292 modification, leading us to perform further analyses stratified by sex.

## 293 **2.7 Interpretation of results**

294 Although we set the significance threshold at a p-value of  $<0.05$ , our interpretation of results  
295 was not based solely on statistical significance. Given our relatively small sample size, and  
296 exploratory setting (among the first study with phenol exposure and eye tracking scores) p-  
297 values between 0.05 and 0.10 were considered suggestive of an association if they aligned  
298 with a consistent pattern of results, rather than being isolated findings.

## 299 **2.8 Sensitivity Analysis**

300 The following sensitivity analysis were performed for the uni-pollutant models

- 301 1. Data points falling below the  $<1$ st and above the  $>99$ th percentiles for the exposures  
302 and outcomes were removed across each model. This was done to rule out artefact  
303 from extreme values.
- 304 2. We also performed the analysis using unstandardised concentrations of the exposures  
305 (i.e. not standardized for sampling and analytical conditions).

306 3. We repeated all models using specific gravity-standardized concentrations, in place of  
307 raw values, to account for urinary dilution.

308 All tasks and eye-tracking data postprocessing were conducted using MatLab (R2007b) and  
309 the Eyelink® toolbox, while statistical analyses were carried out using R version 4.2.0 (R  
310 Core Team, 2021). The R code is available at : [https://gricad-gitlab.univ-grenoble-](https://gricad-gitlab.univ-grenoble-alpes.fr/iab-env-epi)  
311 [alpes.fr/iab-env-epi](https://gricad-gitlab.univ-grenoble-alpes.fr/iab-env-epi).

## 312 **3. Results**

### 313 **3.1. Study Population**

314 Median age of the mothers at enrollment was 32.1 years (IQR: 4.8). Male children were  
315 slightly overrepresented in our study (N = 85, 56%) and majority of the mothers were highly  
316 educated (N=130, 86% had 2 years of studies or more after graduation). No major  
317 differences were observed between included and excluded pairs in maternal or child  
318 characteristics, except for maternal ethnicity (included were 92% European VS 79% for non  
319 included) (Table 1).

### 320 **3.2. Eye Tracking Scores**

321 Eye tracking assessments (81%) were mostly performed in the morning (between 8 AM and  
322 12 PM) and the median age of the children was 24.9 months (IQR: 0.82) (Table 1). Spearman  
323 correlation coefficients for the eye tracking scores were below 0.2 (Supplementary Material,  
324 Table S3).

### 325 **3.3. Exposure**

326 The detection rates for most phenols were generally high, with methylparaben, bisphenol A,  
327 and benzophenone-3 detected in over 90% of samples (Table 2). Exposure levels were

328 notably lower at the 2-month infant sampling period, with detection rates below 90% for  
329 ethylparaben and propylparaben, which may result from over dilution since the median SG  
330 for 2 months samples (M2) was 1.004 whereas median SG for second trimester (T2), third  
331 trimester (T3) and 12 month (M12) was  $> 1.011$  (Table 1). Bisphenol S was detected in only  
332 28% of samples during the second trimester, 30% during the third trimester, 46% at 2  
333 months, and 70% at 12 months (Table 2).

### 334 **3.4. Adjusted Associations between Phenol Exposure and Eye Tracking Scores**

#### 335 *Parabens*

336 While no association was observed with  $\sum$ parabens, several associations were observed with  
337 individual parabens. Ethylparaben concentration at T3 and M12 was associated with  
338 decreased reaction time ( $\beta = -4.4$  ms [-9.4, 0.5] and  $\beta = -2.7$  ms [-6.0, 0.5] respectively). At  
339 M2, this paraben was also associated with reduced time spent looking at the eyes ( $\beta = -7.8\%$   
340 [-14.4,-1.2]) (Figure 2, Supplementary Material, Table S4).

341 Methylparaben concentration at M2 was negatively associated with the percentage of time  
342 spent looking at a novel face ( $\beta = -1.9\%$  [-3.8, -0.1]).

343 Propylparaben concentration at both T2 and T3 was associated with increased time spent  
344 looking at a novel face ( $\beta = 1.9\%$  [-0.0, 3.9] and  $\beta = 1.5\%$  [-0.1, 3.3]). At T3, this trend was  
345 driven by boys ( $\beta = 2.9\%$  [0.7, 5.1] VS  $\beta = -0.4$  [-3.1, 2.3] for girls) (Figure 2 and 3,  
346 Supplementary Material, Table S4-5).

347 Sex stratification also revealed an association between the  $\sum$ parabens and reduced fixation  
348 duration in boys at T3 ( $\beta = -1.8$ ms [-3.4, -0.1]). This association was also observed at the

349 individual compound level for methylparaben and propylparaben ( $\beta = -1.7\text{ms} [-3.3, -0.1]$   
350 and  $-0.9\text{ms} [-1.8, 0.0]$ , respectively) (Figure 2 and 3, Supplementary Material, Table S4-5).

### 351 *Bisphenols*

352 No associations were observed with bisphenol A. Bisphenol S detection at T2 was associated  
353 with reduced reaction time ( $\beta = -16.0 \text{ ms} [-31.9, -0.1]$ ) (Figure 2, Supplementary Material,  
354 Table S4).

355

### 356 *Benzophenone-3*

357 Benzophenone-3 concentrations at M2 and M12 were associated with increased time looking  
358 at a novel face ( $\beta = 5.6\% [1.5, 9.8]$  at M2 and  $\beta = 5.5\% [-1.0, 12.0]$  at M12). These  
359 associations were mainly seen in boys (Figure 2 and 3, Supplementary Material, Table S4-5).

### 360 *Triclosan*

361 An isolated association was observed between triclosan exposure at M12 and reduced  
362 reaction time ( $\beta = -7.1\text{ms} [-13.8, -0.4]$ ) (Figure 2, Supplementary Material, Table S4).

## 363 **3.5. Sensitivity analyses**

364 The results of our primary analysis persisted across the sensitivity analyses (Supplementary  
365 Material, Figure S2-4).

## 366 **4. Discussion**

367 Several phenols and parabens (bisphenol S, benzophenone-3, methyl and ethyl parabens)  
368 showed associations with eye-tracking measures. Some of these associations seem to differ

369 between child sex; however, given our limited sample size, such results require cautious  
370 interpretation. To our knowledge, this study is one of the first relying on eye-tracking  
371 measures to investigate neurodevelopmental effect of synthetic phenols. Since some  
372 indicators such as shorter fixation duration (associated with methylparaben, propylparaben),  
373 shorter reaction times (associated with bisphenol S, ethylparaben and triclosan) and decrease  
374 time looking at eyes (associated with ethylparaben) have been previously associated with  
375 diagnosis of ASD (Al-Haddad et al., 2020; Joseph et al., 2009a; Sasson and Elison, 2012b;  
376 Wan et al., 2019; Wass et al., 2015), we reported in the discussion section results of  
377 epidemiological studies investigating effect of phenols exposure on ASD or ASD like  
378 symptoms.

379

### 380 *Parabens*

381 We identified associations between several parabens and eye-tracking scores, including ethylparaben  
382 in the main analysis and all parabens in the sex-stratified analysis. At T3 and M12, ethylparaben was  
383 associated with shorter reaction times, while at M2, it was linked to less time spent looking at eyes.  
384 M2 methylparaben concentration was negatively associated with the percentage of time spent looking  
385 at novel faces. In the sex-stratified analysis, methylparaben at T3 was associated with reduced fixation  
386 duration in boys. Although the windows of exposure differ, these findings suggest that methyl- and  
387 ethylparaben may influence traits commonly observed in children with ASD (Al-Haddad et al.,  
388 2020; Joseph et al., 2009a; Sasson and Elison, 2012b; Wan et al., 2019). In contrast, several  
389 borderline associations were observed for propylparaben (p-values between 0.05 and 0.1), which  
390 tended to indicate potentially beneficial effects on eye-tracking scores, such as longer time spent  
391 looking at novel faces and eyes.

392 Few studies have investigated the associations between early paraben exposure and ASD-like  
393 behaviors. In the SEPAGES cohort, no clear associations were observed between  $\sum$ parabens (prenatal  
394 and infancy urinary concentrations) and SRS scores (Mustieles et al., 2023). Another French study,

395 restricted to boys, found that prenatal exposure to  $\Sigma$ parabens was associated with improved prosocial  
396 behavior scores at age 3 (Philippat et al., 2017). Similarly, in a high-risk cohort, increased urinary  
397 concentration of methyl- or propyl- parabens was associated with decreased ASD risk (Sotelo-  
398 Orozco et al., 2024) , aligning with our findings for propylparaben. Conversely, the only study  
399 reporting an increased ASD risk with methylparaben exposure was cross-sectional in design (Bennett  
400 et al., 2022). Overall, these studies do not support a strong association between parabens and ASD  
401 risk. However, the limited sample sizes emphasize the need for further well-designed research.

402

### 403 *Bisphenols*

404 Bisphenol S detection at T2 was negatively associated with reaction time, a measure predictive of  
405 higher IQ scores (Thomas M. Dougherty and Haith, 1997) shown to be shorter in children with  
406 ASD (Joseph et al., 2009a). At 12 months (M12), infants with detectable bisphenol S levels showed  
407 a positive association with time spent looking at eyes. In the SEPAGES cohort, previous findings for  
408 bisphenol S were mixed: SRS scores at 2 years increased with T3 concentration (indicating worse  
409 behavior) but decreased with M2 concentration (Mustieles et al., 2023). Other studies found no  
410 association between urinary bisphenol S concentrations (pre- or postnatally) and socioemotional  
411 scores at 2 years (Liu et al., 2021) or ASD diagnosis (Sotelo-Orozco et al., 2024).

412 Given the limited number of studies and the typically low detection frequency of bisphenol S (Liu et  
413 al., 2021; Mustieles et al., 2023), the current literature is insufficient to draw firm conclusions  
414 regarding the potential effects of bisphenol S on ASD-like behaviors.

415

### 416 *Benzophenone-3*

417 In our study, postnatal - but not prenatal - benzophenone-3 concentrations were associated with  
418 improved eye-tracking scores, particularly in boys, who showed increased time spent looking at a  
419 novel face (Dzwilewski et al., 2020; Fagan and Detterman, 1992; Sterling et al., 2008). These findings

420 are partially consistent with those from a high-risk cohort, which reported decreased ASD risk with  
421 higher benzophenone-3 urinary concentrations at 3–6 months of age (Sotelo-Orozco et al., 2024).  
422 However, a recent study using eye-tracking methods found that prenatal exposure to BP-3 was  
423 associated with slower processing speed in infants (Cragoe et al., 2024), suggesting potential adverse  
424 effects during the prenatal period. Additionally, in the SEPAGES cohort, increased BP-3 exposure at  
425 age 1 was associated with worse social behavior scores based on parent-reported SRS assessments  
426 (Mustieles et al., 2023). Together, these mixed findings may reflect differences in exposure timing,  
427 assessment methods, or population characteristics.

428

### 429 **Strengths and limitations**

430 Our study is among the first to use eye-tracking scores to evaluate the potential impact of  
431 environmental exposures on child neurodevelopment. These scores are less prone to measurement  
432 errors and can be applied at earlier ages compared to the questionnaires traditionally used in  
433 population-based studies to assess ASD-like symptoms (Rosenman et al., 2011). Our findings  
434 underscore their potential sensitivity to environmental influences.

435 However, limitations include the lack of a standardized procedure for eye-tracking, which may  
436 introduce variability in parameter definitions across studies (Mastergeorge et al., 2021). This  
437 variability could affect the consistency and comparability of findings, although some indicators, such  
438 as time spent looking at eyes and novel faces, are relatively common.

439 Importantly, while some of the eye-tracking indicators used here (e.g., fixation duration, time spent  
440 looking at eyes, reaction time) have been studied in clinical populations — including children with  
441 ASD — they should not be interpreted as diagnostic markers. In our study, these outcomes are used as  
442 early, objective markers of attentional and social-cognitive functioning in the general population.  
443 Comparisons with ASD literature was intended to provide functional context but does not imply  
444 clinical interpretation or elevated risk.

445 Additionally, due to the innovative nature of these outcomes, direct comparisons with previous studies  
446 was limited, highlighting the need for further research to better understand these associations.

447 A key strength of our study is the exposure assessment, which utilized pooled urine samples collected  
448 repeatedly across different sensitivity windows, spanning both pregnancy and infancy. Unlike studies  
449 relying on spot samples, this approach minimizes exposure misclassification and improves the  
450 reliability of our estimates (Perrier et al., 2016). Furthermore, few studies have successfully  
451 collected biospecimens during infancy, a critical period marked by rapid brain development and  
452 heightened sensitivity to environmental exposures. Exposure levels to phenols in the SEPAGES  
453 cohort were generally lower than those reported in earlier French cohorts (EDEN, 2003–2006).  
454 Median bisphenol A and paraben concentrations in SEPAGES infants were comparable to or lower  
455 than those reported among infants in other countries, such as the United States and Germany  
456 (Mendonca et al., 2014; Stacy et al., 2016; Völkel et al., 2011).  
457 However, our relatively small sample size limits the power to detect associations, particularly in  
458 stratified analyses or for exposures with low detection frequencies, such as bisphenol S. This  
459 necessitates cautious interpretation of our findings.  
460 Additionally, although we examined multiple exposure windows, our study design does not allow us  
461 to fully explore the temporal mechanisms by which exposures may influence outcomes. Approaches  
462 such as mediation analysis or life-course models could help address this in future research.

## 463 **Conclusion**

464 Using enhanced exposure assessment and novel eye-tracking measures, we identified associations  
465 between prenatal and postnatal phenol exposure and several early markers known to be affected in  
466 individuals with neurodevelopmental disorders. Our findings add to the growing evidence of the  
467 adverse effects of phenol exposure on neurodevelopment. However, the limited sample size,  
468 combined with the scarcity of studies employing eye-tracking in environmental epidemiology, calls  
469 for cautious interpretation. Further research with larger sample sizes is needed to validate our  
470 findings.

471

472 **Declaration of generative AI and AI-assisted technologies in the writing process**

473

474 During the preparation of this work the author(s) used ChatGPT in order to enhance text grammar and  
475 readability. After using this tool/service, the author(s) reviewed and edited the content as needed and  
476 take(s) full responsibility for the content of the publication.  
477

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718  
 719

720 **Funding**

721 This project was funded by INSERM - INRAE Grant (THYREX), ANSES (HyPaxE project EST-  
 722 2019/1/039) and Fondation de France (ELEMENTUM - 00124527). The SEPAGES cohort was  
 723 supported by the **European Research Council** (N°311765-E-DOHaD), the **European Community’s**  
 724 **Seventh Framework Programme** (FP7/2007-206 - N°308333-892 HELIX), the **European Union’s**  
 725 **Horizon 2020** research and innovation programme (N° 874583 ATHLETE Project, N°825712  
 726 OBERON Project), the **French Research Agency - ANR** (PAPER project ANR-12-PDOC-0029-01,  
 727 SHALCOH project ANR-14-CE21-0007, ANR-15-IDEX-02 and ANR-15-IDEX5, GUMME project  
 728 ANR-17-CE34-0013, ETAPE project ANR-18-CE36-0005 - EDen project ANR-19-CE36-0003-01 –  
 729 MEMORI project ANR 21-CE34-0022, ORANDANI project ANR-22-CE36-0018), the **French**  
 730 **Agency for Food, Environmental and Occupational Health & Safety - ANSES** (CNAP project  
 731 EST-2016-121, PENDORE project EST-2018-1-264, HyPaxE project EST-2019/1/039,  
 732 PENDALIRE project EST-2022-169), the **Plan Cancer** (Canc’Air project), the **French Cancer**  
 733 **Research Foundation Association de Recherche sur le Cancer – ARC**, the **French Endowment**  
 734 **Fund AGIR for chronic diseases – APMC** (projects PRENAPAR, LCI-FOT, DysCard), the **French**  
 735 **Endowment Fund for Respiratory Health**, the **French Fund – Fondation de France**  
 736 (CLIMATHES – 00081169, SEPAGES 5 – 00099903, ELEMENTUM - 00124527).

737

738 Acknowledgment

739

740 SEPAGES biospecimens are stored at Grenoble University Hospital biobank (bb-0033-00069). We  
741 would like to thank the whole CRB team, led by Pr. P. Mossuz (until 2021), by Pr S. Valmary-Degano  
742 (since 2021) and Mr. P. Lorimier, and in particular the technicians for the huge work of biospecimens  
743 processing and pooling: Mrs. W. Jayar, Mrs. L. Than, Mrs J. Lafond, Mrs C. Chalazon, Mr T.  
744 Caffaratti, Mr N. Francini and as well as Mr. G. Schummer.

745

746 We thank the Sepages study group: A. Licinia (Groupe Hospitalier Mutualiste, Grenoble), S. Bayat ,  
747 P. Hoffmann, E. Hullo, (Grenoble Alpes University Hospital, La Tronche), X. Morin (Clinique des  
748 Cèdres, Echirolles), A. Morlot (Clinique Belledonne, Saint-Martin d'Hères), J. Lepeule, S. Lyon-  
749 Caen, M.Ouidir, C. Philippat, I. Pin, J. Quentin, V. Siroux, R. Slama (Grenoble Alpes University,  
750 Inserm, CNRS, IAB).

751 We thank the research team of the Grenoble Laboratoire de Psychologie et Neurocognition (LPNC),  
752 for the eye tracking assessments done in its Babylab.

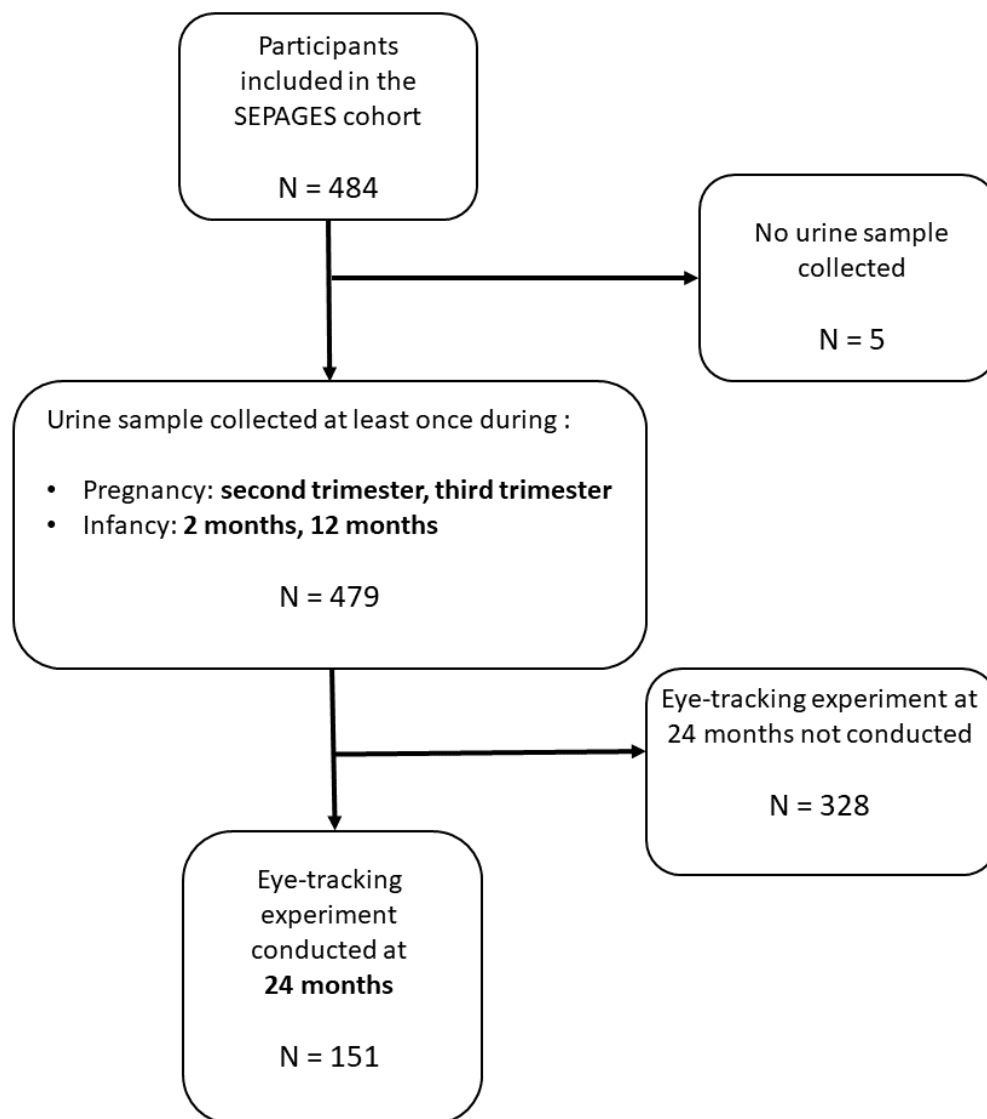
753 Many thanks to Dr I. Pin who was the Sepages PI from 2012 until 2022. We thank also Mr. Y. Gioria,  
754 Mrs. A. Guerrache-Siebert, clinical research assistants; Mrs. M. Marceau, nurses; Mrs. E. Charvet ,  
755 midwives; Mrs. M. Graca, Mrs. K.Gridel, Mrs. C. Pelini, Mrs M.Barbagallo fieldworkers; Mrs.  
756 A.Bossant, K. Guichardet, J-T Iltis, C.Martel, E. Quinteiro, neuropsychologists; Mrs K.Supernant,  
757 A.Boudier the Sepages data managers; the staff from Grenoble Center for Clinical Investigation  
758 (CIC): Prof. J.-L. Cracowski, Dr. C. Cracowski, Dr. E. Hodaj, Mrs. D. Abry, Mr. N. Gonnet and Mrs.  
759 A. Tournier. A warm thank you also Dr. M. Althuser, , Dr. F. Camus-Chauvet, Mr. P. Dusonchet,  
760 Mrs. S. Dusonchet, Mrs. A. Royannais, Dr. D. Tournadre, Mr. P. Viossat, and clinicians from  
761 Grenoble University Hospital for their support in the recruitment of the study volunteers. We also  
762 thank Mrs. SF. Caraby, Mrs. J. Dujourdil, and all midwives from the four maternity wards of  
763 Grenoble urban areas. SEPAGES data are stored thanks to Inserm RE-CO-NAI platform funded by  
764 Commissariat Général à l'Investissement, with the implication of Sophiede Visme (Inserm DSI).  
765 Many thanks to Dr. M.A. Charles, RE-CO-NAI coordinator, for her support. Finally, and importantly,  
766 we would like to express our sincere thanks to participants of the Sepages study.

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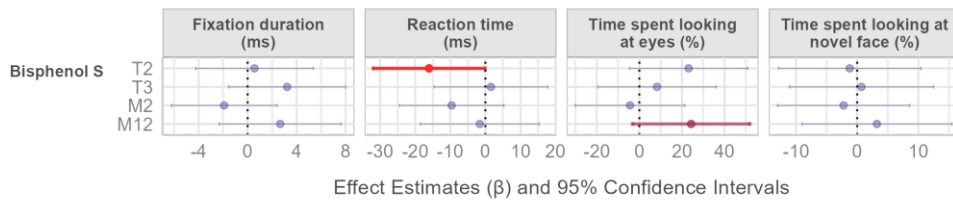
# Figures

**Figure 1:** Participant Flow and Timing of Urinary Phenol Exposure Assessments (T2, T3, 2 and 12 Months) and Eye-Tracking Outcomes at 24 Months in the SEPAGES Cohort

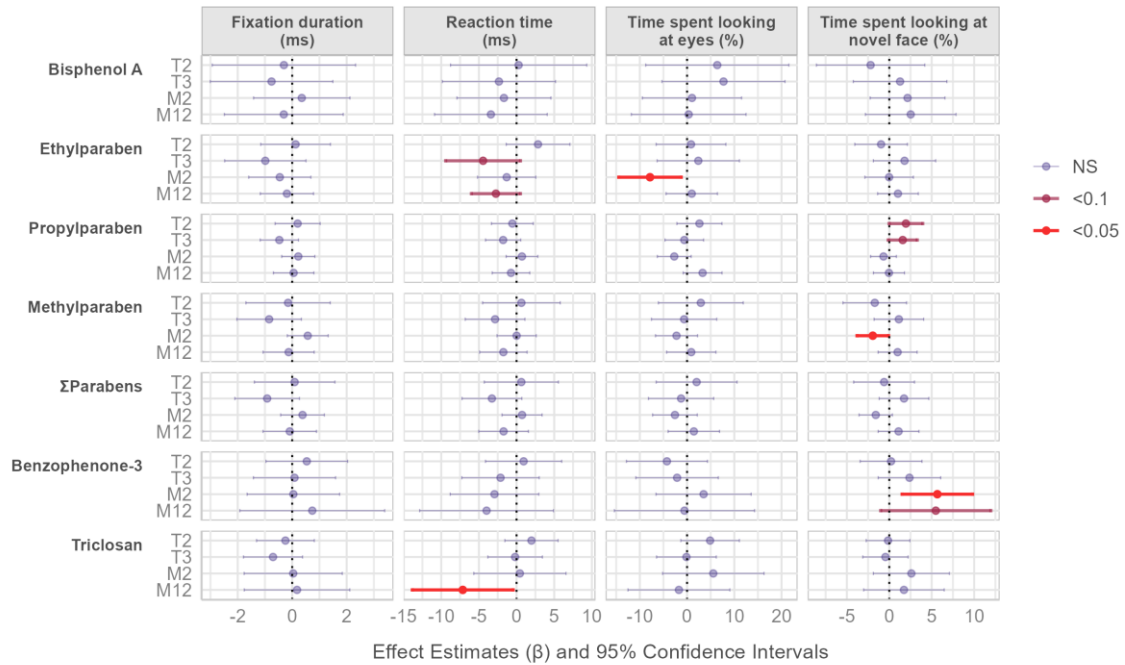


**Figure 2: Adjusted associations between urinary concentrations of phenol metabolites and eye tracking scores for each exposure period in the SEPAGES mother-child cohort**

a. Effect Estimates for Categorical Compounds (Detected/Undetected)



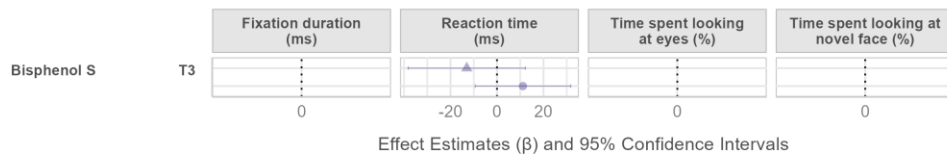
b. Effect Estimates for Continuous Compounds



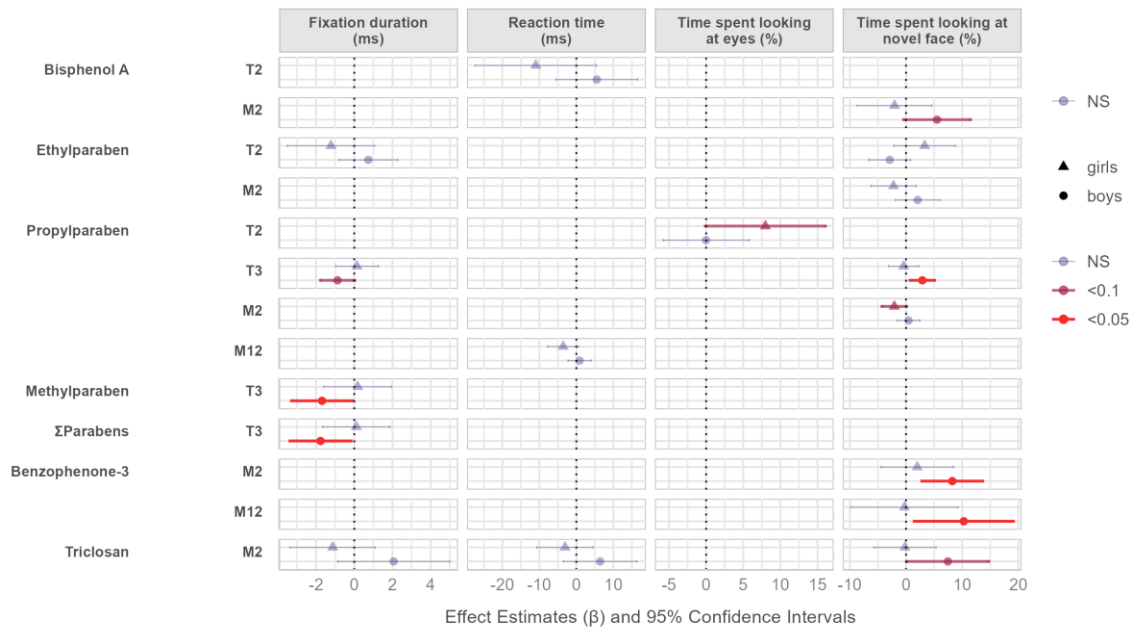
Abbreviations:  $\Sigma$  molar sum. T2, Second trimester of pregnancy; T3, Third trimester of pregnancy; M2, 2 month infancy; M12, 12 month infancy. Values are presented in Supplementary Material Table S4.. Models are adjusted for maternal age, maternal tobacco consumption, maternal cognitive function (WAIS-IV verbal component), parity, maternal professional status, breastfeeding duration, child sex, experiment time of the day.

**Figure 3: Adjusted associations between urinary concentrations of phenol metabolites and eye tracking scores for each exposure period in the SEPAGES mother-child cohort according to child sex**

a. Effect Estimates for Categorical Compounds (Detected/Undetected)



b. Effect Estimates for Continuous Compounds



Abbreviations  $\Sigma$  molar sum. T2, Second trimester of pregnancy; T3, Third trimester of pregnancy; M2, 2 month infancy; M12, 12 month infancy. Values are presented in Supplementary Material Table S5. Models are adjusted for maternal age, maternal tobacco consumption, maternal cognitive function (WAIS-IV verbal component), parity, maternal professional status, breastfeeding duration, child sex, experiment time of the day.

# Tables

**Table 1. Description of the study population**

Characteristic	N	Included N = 151 <sup>1</sup>	Not Included N = 333 <sup>1</sup>	p-value <sup>2</sup>
Maternal tobacco consumption during pregnancy	435	17 (12%)	38 (13%)	0.7
Maternal age (years)	484	32.1 (30.0, 35.0)	32.2 (29.9, 35.4)	0.7
Child sex	479			0.4
Male		85 (56%)	171 (52%)	
Female		66 (44%)	157 (48%)	
Maternal depression during pregnancy	438			0.2
HAD <11		103 (69%)	180 (62%)	
HAD > 11		46 (31%)	109 (38%)	
Maternal education	484			0.2
Highschool + 2 years or less		21 (14%)	62 (19%)	
Highschool + 3 years or more		130 (86%)	271 (81%)	
Parity	484			0.2
First child		76 (50%)	146 (44%)	
Second child		65 (43%)	149 (45%)	
Third child or more		10 (6.6%)	38 (11%)	
Professional status at inclusion	444			>0.9
Working		127 (87%)	257 (86%)	
Not working, not looking for work		13 (8.9%)	26 (8.7%)	
Not working, looking for work		6 (4.1%)	15 (5.0%)	
Breastfeeding duration (weeks)	445	31 (17, 48)	30 (17, 47)	0.4
Maternal WAIS- verbal score	322	12.00 (10.00, 14.00)	12.00 (10.00, 15.00)	0.5
Ethnicity	484			<0.001
European		139 (92%)	262 (79%)	
Missing		9 (6.0%)	64 (19%)	
Other <sup>a</sup>		3 (2.0%)	7 (2.1%)	
Gestation age at T2 sample (weeks)	477	18.00 (16.57, 18.86)	17.57 (16.29, 18.86)	0.13
Gestation age at T3 sample (weeks)	456	34.21 (32.14, 35.29)	34.00 (32.14, 35.14)	0.8
Age at M2 sample (months)	427	1.55 (1.42, 1.78)	1.68 (1.48, 2.44)	<0.001
Age at M12 sample (months)	386	12.13 (11.87, 12.56)	12.26 (11.93, 12.73)	0.009
N samples in M12 pool	387	7.00 (6.00, 7.00)	6.00 (5.00, 7.00)	0.016
N samples in M2 pool	427	7.00 (6.00, 7.00)	7.00 (6.00, 7.00)	0.5
N samples in T2 pool	477	21.00 (20.00, 21.00)	21.00 (20.00, 21.00)	0.13
N samples in T3 pool	455	21.00 (20.00, 21.00)	21.00 (20.00, 21.00)	0.009
Sample specific gravity in T2 pool	477	1.018 (1.014, 1.020)	1.018 (1.015, 1.021)	0.5
Sample specific gravity in T3 pool	456	1.017 (1.013, 1.020)	1.017 (1.014, 1.020)	0.2
Sample specific gravity in M2 pool	427	1.0040 (1.0040, 1.0050)	1.004 (1.004, 1.005)	0.8
Sample specific gravity in M12 pool	387	1.011 (1.009, 1.014)	1.011 (1.009, 1.015)	0.3
Reaction time (ms)	145	282 (252, 316)		
Fixation duration (ms)	150	5.86 (5.78, 5.97)		
Time spent looking at novel face (%)	150	0.55 (0.50, 0.60)		
Time spent looking at eyes (%)	150	0.73 (0.58, 0.81)		
Age at eye tracking experiment in months	151	24.87 (24.51, 25.33)		
Eye tracking experiment hour	151			
8AM - 12PM		122 (81%)		
12PM - 14PM		7 (4.6%)		
14PM - 16PM		22 (15%)		

<sup>1</sup> n (%); Median (Q1, Q3)<sup>2</sup> Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Abbreviations: HAD, Hospital Anxiety and Depression scale score. <sup>a</sup> Includes Africa, America, Oriental Mediterranean countries, South East Asia and Other.

**Table 2: Detection rates of phenols urinary concentrations by sampling period**

Compound	2nd trimester (N = 151)						3rd trimester (N = 150)				2 months (N = 144)				12 months (N = 145)			
	LOD	LOQ	%>LOD	p5	p50	p95	%>LOD	p5	p50	p95	%>LOD	p5	p50	p95	%>LOD	p5	p50	p95
<b>Bisphenol A</b>	0.04	0.1	99%	0.64	1.72	7.80	98%	0.43	1.45	9.53	100%	0.21	0.74	3.03	100%	0.88	2.74	14.02
<b>Bisphenol A (conj.)</b>	0.04	0.1	-	-	-	-	-	-	-	-	-	0.05	0.48	2.60	-	0.47	2.13	11.33
<b>Bisphenol S</b>	0.1	0.4	28%	-	-	1.00	30%	-	-	1.00	46%	-	-	1.00	70%	-	1.00	1.0
<b>Ethylparaben</b>	0.04	0.1	99%	0.25	0.84	43.01	99%	0.24	0.76	26.96	88%	0.03	0.10	21.03	99%	0.21	4.34	397.20
<b>Propylparaben</b>	0.04	0.1	78%	0.00	0.32	20.08	73%	0.00	0.26	91.08	60%	0.00	0.07	92.59	92%	0.03	2.93	431.81
<b>Methylparaben</b>	0.04	0.1	100%	2.29	11.33	180.83	100%	2.03	9.56	1,452.64	100%	0.17	0.85	1,224.60	100%	1.78	86.04	2,395.23
<b>Methylparaben (conj.)</b>	0.04	0.1	-	-	-	-	-	-	-	-	-	0.13	0.64	808.20	-	1.22	81.29	2,383.80
<b>∑Parabens</b>	-	-	-	0.02	0.10	1.78	-	0.02	0.08	9.97	-	0.00	0.01	8.73	-	0.02	0.74	21.49
<b>∑Parabens (conj.)<sup>a</sup></b>	-	-	-	-	-	-	-	-	-	-	-	0.00	0.01	5.99	-	0.01	0.67	21.24
<b>Benzophenone-3</b>	0.04	0.1	100%	0.18	0.90	33.50	100%	0.14	0.77	20.20	97%	0.04	0.34	4.84	99%	0.13	0.39	1.56
<b>Triclosan</b>	0.04	0.1	99%	0.21	0.93	153.64	97%	0.13	0.86	125.94	92%	0.02	0.30	1.59	93%	0.03	0.25	1.64

Abbreviations: LOD: Limit of detection, LOQ: Limit of quantification, ∑: molar sum

For bisphenol A and methylparaben, both total and conjugated concentrations are presented for infancy samples, due to suspected contamination of free forms from diaper materials. For other compounds, only total concentrations (free + conjugated) are reported.

<sup>a</sup>∑Parabens (conj.) corresponds to the sum of methylparaben (conjugated), ethylparaben (total), and propylparaben (total).