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Associations between a mixture of phenols and phthalates and child behaviour in a French mother–child cohort with repeated assessment of exposure

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ABSTRACT

Background: Synthetic phenols and phthalates can interfere with biological pathways involved in brain development. Despite the high within-subject temporal variability of urinary concentrations observed for their metabolites, studies investigating effects of phenols and phthalates on child behaviour often relied on a limited number of spot biospecimens to assess exposure. Besides, the majority did not consider mixture effects.
Objectives: To study the combined effect of prenatal exposure to synthetic phenols and phthalates on child behaviour using repeated exposure measurements.
Methods: We assessed concentrations of 12 phenols, 13 phthalate and 2 non-phthalate plasticizer metabolites in within-subject pools of multiple urine samples (median = 21 samples per individual pool) collected at two distinct time points during pregnancy in 416 mother–child pairs from the French SEPAGES cohort. Child behaviour was evaluated at two years using the Child Behaviour Checklist 1.5–5 (CBCL). Associations between a mixture of biomarkers of exposure and externalizing and internalizing behaviour scores were studied using adjusted Weighted Quantile Sum (WQS) regressions with a repeated holdout validation (100 repetitions).
Results: The positive WQS indexes were associated with both the externalizing and internalizing behaviour scores in the whole population, indicating greater risk of behavioural problems. Stratification for child sex suggested stronger associations in girls than boys. On average, girls externalizing and internalizing scores increased by 3.67 points (95% CI: 1.24, 6.10) and 2.47 points (95 %CI: 0.60, 4.33) respectively, for an increase of one tertile in the WQS index, compared with 1.70 points (95 %CI: −0.42, 3.81) and 1.17 points (95 %CI: −0.50, 2.84) in boys. Main contributors for the associations observed in girls were bisphenol A (weight of 18%), triclosan (17%) and monoethyl phthalate (MEP, 15%) for the externalizing score and MEP (19%), mono-benzyl phthalate (MBzP, 19%) and mono-n-butyl phthalate (MnBP, 16%) for the internalizing score.

Abbreviations: CBCL, child behaviour checklist; CI, confidence interval; cx-MiNP, mono(4-methyl-7-carboxy-heptyl) phthalate; DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DiBP, diisobutyl phthalate; DiNCH, di(isononyl)cyclohexane-1,2-dicarboxylate; DiNP, diisononyl phthalate; DPHP, di(2-propylheptyl) phthalate; FWER, family-wise error rate; IQR, interquartile range; MBzP, mono-benzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MMCHP, mono(2-methylcarboxyhexyl) phthalate; MnBP, mono-n-butyl phthalate; LOD, limit of detection; LOQ, limit of quantification; ohMiNCH, 2-(((hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic acid; OH-MiNP, mono(4-methyl-7-hydroxy-octyl) phthalate; ohMPHP, 6-hydroxy-mono-propyl-heptyl phthalate; oxoMiNCH, 2-(((4-methyl-7-oxyooctyl)oxy)carbonyl)cyclohexanecarboxylic acid; oxo-MiNP, mono(4-methyl-7-oxo-octyl) phthalate; SD, standard deviation; SE, standard error; WQS, weighted quantile sum; ΣDEHP, molar sum of di(2-ethylhexyl) phthalate; ΣDiNP, molar sum of diisononyl phthalate; ΣDiNCH, molar sum of di(isononyl)cyclohexane-1,2-dicarboxylate.

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Discussion: Our results suggest adverse associations between in utero exposure to a mixture of phenols and phthalates and child behaviour, mainly in girls. Public health consequences may be substantial due to the widespread exposure of the population to these compounds.

1. Introduction

Human brain development starts in the first weeks after conception and is controlled by many factors including genes and hormones (Stiles and Jernigan, 2010; Williams, 2008). Neural structures evolve fast and are extremely receptive to external influences during the prenatal period (Grandjean and Landrigan, 2014; Rice and Barone, 2000). Exposure to some environmental chemicals over this period can interfere with these processes, affect acquisition of sensory, motor, cognitive or socio-emotional skills (Grandjean and Landrigan, 2014; Scott et al., 2016) and significantly impact children's future social, academic or professional lives (Lyons-Ruth et al., 2017; Scott et al., 2016).

Among environmental chemicals, synthetic phenols and phthalates can cross the placental barrier (Mose et al., 2007; Pycke et al., 2015; Vandenberg et al., 2007). They are suspected to interfere with hormonal (Schug et al., 2015) and epigenetic (Ponsonby et al., 2016) pathways involved in brain development (Miodovnik et al., 2014; Mustieles et al., 2015). These chemicals are commonly used as preservatives in food, cosmetics and pharmaceuticals (parabens), as biocides in personal care products, clothing and toys (triclosan, triclocarban), as anti-UV agent in sun creams and food packaging (benzophenone-3) or as fixatives in fragrances and plasticizers in hygiene products, food packaging and building materials (phthalates, bisphenols (Hauser and Calafat, 2005; Morais et al., 2016; Soni et al., 2005; Vandenberg et al., 2007; Wang et al., 2019)). The general population, including pregnant women, is widely exposed to these chemicals (Casas et al., 2013; Haug et al., 2018; Montazeri et al., 2019; Woodruff et al., 2011).

Several epidemiological studies have suggested detrimental associations between prenatal exposure to bisphenol A and both children externalizing behaviour (defined by hyperactivity, aggressiveness, etc. (Braun et al., 2017; 2011; 2009; Evans et al., 2014; Harley et al., 2013; Jedynak et al., 2021; Perera et al., 2012; Philippat et al., 2017; Roen et al., 2015; Stacy et al., 2017)) and internalizing behaviour (characterised by anxiety, depression, withdrawal, etc. (Braun et al., 2011; 2009; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015)). When studies explored effect modification by child sex, associations were more frequently observed for boys (Evans et al., 2014; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015), except in the HOME cohort in which associations were observed for girls (Braun et al., 2017; 2011; 2009; Stacy et al., 2017). Sex specific effects are consistent with the endocrine disrupting properties of this phenol and have also been observed in rodents (Rochester et al., 2018). Among the four studies looking at triclosan exposure (Etzel et al., 2018; Guo et al., 2020; Jackson-Browne et al., 2019; Philippat et al., 2017), two suggested adverse associations with boys behaviour (Jackson-Browne et al., 2019; Philippat et al., 2017) while the two others did not report any association (Etzel et al., 2018; Guo et al., 2020). To our knowledge, only two studies (including one restricted to boys (Guo et al., 2020; Philippat et al., 2017)), assessed other phenols such as parabens and benzophenone-3 among which one concluded on deleterious effect of the latter on child behaviour (Guo et al., 2020).

Regarding phthalates, di(2-ethylhexyl) phthalate (DEHP) has been associated with more externalizing (Engel et al., 2018; Huang et al., 2019; Lien et al., 2015) and internalizing (Huang et al., 2019; Kobrosly et al., 2014) behaviours in American and Asian cohorts. Several studies also suggested increasing child behaviour problems with increasing prenatal exposure to diisobutyl phthalate (DiBP (Daniel et al., 2020; England-Mason et al., 2020; Kobrosly et al., 2014; Whyatt et al., 2012)) and dibutyl phthalate (DBP (Daniel et al., 2020; England-Mason et al., 2020; Jedynak et al., 2021; Kobrosly et al., 2014; Lien et al., 2015; Philippat et al., 2017; Whyatt et al., 2012)), with a trend for boys to be more affected than girls (Daniel et al., 2020; England-Mason et al., 2020; Kobrosly et al., 2014). Studies reporting no association between prenatal exposure to some of these phthalates and child behaviour also exist (Gascon et al., 2015; Huang et al., 2019; Jankowska et al., 2019; Li et al., 2020).

Although phenols and phthalate metabolites have shown moderate to high within-subject temporal variability (Casas et al., 2018; Shin et al., 2019; Vernet et al., 2018), most previous studies measured them in only one to three spot urine samples per individual. Such design only reflects short-term exposure and is expected to bias the effect estimation towards the null (Perrier et al., 2016). In addition, most of the previous studies relied on single-pollutant statistical models that do not account for mixture effects (Lazarevic et al., 2019). Finally, data are scarce for compounds possibly used as substitutes of high molecular weight phthalates, such as diisononyl phthalate (DiNP), di(2-propylheptyl) phthalate (DPHP) or the non-phthalate plasticizer di(isononyl) cyclohexane-1,2-dicarboxylate (DiNCH).

To overcome these limitations, we relied on a mother–child cohort with within-subject pools of repeated urine samples collected during early and late pregnancy (Lyon-Caen et al., 2019; Rolland et al., 2020). We used this novel sampling design to explore the effects of a mixture of phenols, phthalates and non-phthalate plasticizers on child behaviour at 2 years of age.

2. Materials and methods

2.1. Study population

This work relied on a subsample of the French prospective mother–child cohort SEPAGES that recruited 484 pregnant women from eight obstetrical ultrasonography practices of the Grenoble metropolitan area between 2014 and 2017 (Lyon-Caen et al., 2019). Main eligibility criteria were being pregnant by less than 19 gestational weeks at inclusion, older than 18 years old, having a singleton pregnancy, being affiliated to the French national security system, planning to deliver in one of the four maternity clinics of Grenoble and living in the study area. The present analyses were restricted to the 416 mother–child pairs with both urine samples during pregnancy and behavioural assessments at 2 years.

The SEPAGES cohort received approval from the Ethics Committee (CPP) Sud-Est V and the National Commission on Informatics and Liberty (CNIL). Both the mother and the father of the expected child gave written informed consent prior to inclusion.

2.2. Exposure assessment

Enrolled women were asked to collect three urine samples per day, over seven consecutive days, at two time points during early and late pregnancy. Median gestational age was 17 weeks (interquartile range (IQR) = 16-18) at the first collection week and 34 weeks (IQR = 32-35) at the second collection week. Most women (98%) provided urine at the two collection weeks (N = 414 urine pools in the first collection week and N = 408 urine pools in the second collection week). Observance to the protocol was high, median number of samples collected per participant at each collection week was 21 (IQR = 20–21). Women stored the samples in their freezer until the SEPAGES field workers picked them up at the end of each collection week and transported them to a certified biobank (ISO 9001 standard, Grenoble University Hospital, bb-0033-00069). Within-subject weekly pools were then made by combining

equal volumes of all the samples gathered over a collection week. While not formally accounting for spot urine volume or dilution, this pooling approach has shown to be a good proxy of the urine concentrations that would have been obtained in the pool of the whole volume of all individual spot samples collected (Philippat and Calafat, 2020).

Specific gravity was assessed in each weekly pool using a handheld Atago PAL 10-S refractometer (Atago). Aliquots of weekly pools were then stored at −80 °C before being sent on dry ice with a temperature sensor to the Norwegian Institute of Public Health (Oslo, Norway) where the concentrations of 12 phenols (total concentrations), 13 phthalate and 2 DiNCH metabolites were measured (Table S1 (Rolland et al., 2020; Philippat et al., 2021)). Phenols were analysed and quantified using ultra high performance liquid chromatography coupled to mass spectrometry (UPLC-MS-MS (Sakhi et al., 2018)). Phthalate and DiNCH biomarkers were analysed and quantified using high performance liquid chromatography coupled to mass spectrometry (HPLC-MS-MS (Sabaredzovic et al., 2015)).

2.3. Behaviour assessment

The Child Behaviour Checklist (CBCL 1.5-5 (Achenbach and Rescorla, 2000)) was administered to one of the parents, mostly mothers (98%), blinded to the maternal exposure, when their child was two years old (standard deviation [SD]: 0.05 years). We focused on the externalizing (addition of the attention and aggressive sub-scores) and internalizing (addition of the emotionally reactive, anxious/depressed, somatic complaints and withdrawn sub-scores) raw scores. These two broad-band scales present a higher test-retest fidelity and a better ability to detect children at risk of developing behavioural disorders than individual sub-scores (Crawford and Lee, 1991; Konold et al., 2004; Petty et al., 2008). In addition, focusing on these two summary scores rather than on the seven specific sub-scores allowed to limit the number of statistical tests performed. Higher CBCL scores indicate more behavioural problems.

2.4. Statistical analysis

2.4.1. Exposure

Bisphenols F-B-AF and triclocarban were detected in less than 2% of the pooled urine samples and were not considered in statistical analyses. Butylparaben and bisphenol S were detected in 22.1% and 26.4% of the pooled samples respectively and were included as categorical variables (not detected in urine collection week 1 and 2; detected in collection week 1 or 2; detected in both urine collection weeks) in the single-pollutant analyses. For the other biomarkers, detection levels exceeded 70% and concentrations below the limit of detection (LOD) and between the LOD and the limit of quantification (LOQ) were singly imputed by values randomly selected between 0 and LOD and between LOD and LOQ respectively, based on the estimated underlying distribution and using the "fill-in" method (see Supplemental material for further details on the method (Helsel, 1990; Lubin et al., 2004)).

To limit the impact of between-sample variations related to urine processing and assay, we standardized the measured biomarker concentrations using a two-step approach (Mortamais et al., 2012; Philippat et al., 2014). Three conditions were considered: sample transport time from participant's home to the biobank, time during which the individual samples were thawed at 4 °C during the pooling procedure and analytical batches. First, we estimated the associations between each biomarker concentration assessed in pools (natural log-transformed) and the three conditions above-mentioned using linear regression further adjusted for maternal age, education, pre-pregnancy body mass index (BMI), parity, date, season and pregnancy trimester of sample collection and specific gravity. We then used the measured biomarker concentrations and the estimated effects of processing/assay conditions associated with the biomarker urine concentrations (p-value < 0.20) to predict standardized concentrations, that is, concentrations that would have been observed if all samples had been processed under the same conditions and assayed in the same batch (see Supplemental material for further details on the method).

Molar sums were computed for the DEHP (ΣDEHP), DiNP (ΣDiNP) and DiNCH (ΣDiNCH) metabolites.

For each biomarker and participant, we computed the mean of naturally log transformed concentrations measured in urine sample pools collected in the first and second collection weeks. We used these average concentrations in statistical analyses.

2.4.2. Covariates

Adjustment variables were selected a priori and included variables possibly related to both exposure and child behaviour without being possible consequences thereof. A directed acyclic graph (DAG) is presented in the Supplemental Material (Figure S1). All models were adjusted for maternal age at conception (continuous coding), level of education (below vs. Master's degree or above), pre-pregnancy BMI (continuous coding), maternal psychological difficulties during the third trimester (assessed using the "Hospital Anxiety and Depression scale" (Zigmond and Snaith, 1983), continuous coding), parity (0 vs. 1 child or more), child sex and specific gravity (continuous coding). Except for specific gravity, data on covariates were collected by self-administrated questionnaires using an online platform and administrated questionnaires by a fieldworker during study visits.

Missing values for covariates were handled using multiple imputation ("mice" R package (Van Buuren, 2019; 2018)). Imputed datasets ($N = 20$) were generated using the predictive mean matching method (initial percentages of missing data are described in Table 1). All variables considered in the final analyses (outcomes, exposures and covariates) as well as auxiliary variables (maternal employment in the first trimester of pregnancy, maternal alcohol, vitamins consumption during pregnancy and breastfeeding duration) were included in the imputation model.

Table 1
Characteristics of the study population (N = 416 mother–child pairs from the SEPAGES cohort, 2014–2017).

Characteristics	N (%)	NA
Highest level of education achieved by the mother		3
Less than a Master's degree	176 (42.6)	
Master's degree or more	237 (57.4)	
Mother's employment situation during the first trimester of pregnancy		21
Works	345 (87.3)	
Unemployed and not looking for a job	34 (8.6)	
Unemployed and looking for a job	16 (4.0)	
Mother's vitamins consumption during pregnancy (n, % consumers)	378 (93.1)	10
Mother's tobacco consumption during pregnancy (n, % consumers)	23 (6.0)	35
Child's sex (n, % boys)	227 (54.6)	0
Parity		0
0 child	194 (46.6)	
1 child or more	222 (53.4)	
Breastfeeding (in tertiles)		61
0 to 3 months	111 (31.3)	
4 to 6 months	125 (35.2)	
7 months or more	119 (33.5)	
	Mean ± SD	**NA**
Mother's age at conception (years)	32.6 ± 3.9	0
Mother's body mass index before pregnancy (kg/m2)	22.3 ± 3.9	3
Mother's anxiety during the third trimester[a]	6.2 ± 2.9	25
Mother's depressive symptoms during the third trimester[a]	4.1 ± 2.9	26
Child's age at CBCL assessment (years)	2.0 ± 0.05	0
Externalizing CBCL raw score	13.2 ± 6.5	0
Internalizing CBCL raw score	6.9 ± 4.9	0

Abbreviations: NA: Number of missing observations; SD: Standard deviation.
[a] Hospital Anxiety and Depression scale score on a scale of 21.

2.4.3. Associations between phenols, phthalates and child behaviour

Associations between the average biomarker concentrations and raw CBCL scores were investigated using adjusted linear Weighted Quantile Sum (WQS) regression ("miWQS" R package (Hargarten and Wheeler, 2018)). This analysis was restricted to the compounds detected in more than 70% of the samples.

WQS regression consists in grouping chemicals into an empirically weighted additive index, constructed based on exposure quantiles and bootstrapping. When this WQS index is incorporated into a multivariable regression model, the associated effect estimate represents the overall mixture effect while weights represent the relative contribution of each biomarker in this overall effect.

WQS regression assumes that all exposures included in the index are associated with the outcome in the same direction. Therefore, we first relied on adjusted single-pollutant linear regressions to assess the sign of the associations between each biomarker and each CBCL score. Since we hypothesized that exposure to a mixture of phenols, phthalates and non-phthalate plasticizers can be deleterious for child neurodevelopment, we only considered positive WQS indexes and only included in the indexes biomarkers that were positively associated with CBCL scores (that is, likely to have a deleterious effect on behaviour), based on the sign of the effect estimates, with no consideration of the corresponding p-values. WQS models were adjusted for the above-mentioned covariates and for the biomarkers not included in the index (i.e. those with a negative parameter in single-pollutant regressions of the CBCL scores). Such approach has already been implemented in a similar context (Romano et al., 2018).

Theory recommends to randomly partition the data into a training and validation datasets, used to estimate the chemical weights and test the statistical significance of the WQS index respectively. Such splitting reduces statistical power and may lead to distorted partitions and unstable results (Tanner et al., 2019). Therefore, we implemented an extension of WQS named repeated holdout validation, designed to overcome this issue (Tanner et al., 2019). This approach consists in repeating "n" times the random partitioning and WQS analyses, taking the mean of the "n" estimates and calculating their variability. Thus, we repeated WQS regressions 100 times, for each of the 20 imputed datasets. For each WQS run, biomarker concentrations were categorized into tertiles; study population was split into training (40%) and validation (60%) sets; weights were computed based on 100 bootstraps. Results from the 20 imputed datasets were then pooled using the Barnard-Rubin method (Hargarten and Wheeler, 2018). Mean effect estimates are provided with 95% Confidence Interval (CI) and mean biomarker weights with standard error (SE). These analyses were applied for the whole population sample. Given previous results suggesting sex specific effect for some of the biomarkers included in the WQS indexes, we also ran analyses stratified by child sex.

2.5. Additional analyses

We ran additional WQS analyses using not standardized biomarker concentrations.

To allow comparison with previous studies and possible future meta-analyses (which require beta coefficients), we reported results of the adjusted single-pollutant linear regressions (with same adjustment as the WQS analyses). Bisphenol S and butylparaben were included as categorical variables in these analyses.

In addition, in order to investigate the shape of the exposure-outcome relationships, we carried out adjusted single-pollutant linear regressions with standardized biomarker concentrations coded as restricted cubic splines (Perperoglou et al., 2019) with 3 degrees of freedom. We performed likelihood ratio tests for departure from linearity.

Finally, we explored the effects of adjustment for maternal employment, tobacco or vitamins consumption during pregnancy in the single-pollutant linear models. These three variables, which showed low variability, did not allow the models to converge when considered in the WQS analyses.

We relied on the following thresholds for results interpretation: p-values below 0.05 were considered statistically significant and p-values below 0.10 suggestive of an association. In the WQS analyses, we identified as important contributors the biomarkers showing the heaviest weights and the sum of which explained at least 50% of the observed associations.

Analyses were carried out using the Stata ® (version 14) and R © (version 3.6.0) software.

3. Results

3.1. Population characteristics

Mothers included in our study were highly educated (57.4% had at least a Master's degree) and their mean age at conception was 32 years (SD: 3.9 years; Table 1). There was a slightly larger number of boys (54.6%) than girls born in the study population.

Mothers excluded from our analyses breastfed their children for a shorter time (p-value for Chi-square test = 0.01) and showed higher anxiety and depression scores (p-value for Wilcoxon test $\leq$ 0.05) than our study population (Table S2).

Children were on average 2 years old (SD: 0.05) when one of their parents completed the CBCL. Average externalizing and internalizing scores were 13.2 (SD: 6.5) and 6.9 (SD: 4.9) respectively. Boys and girls did not significantly differ with regard to CBCL scores, exposure and covariates (p-values for Wilcoxon and Chi-square tests $>$ 0.05) except for maternal psychological difficulties: mothers of boys showed significant higher anxiety and depression scores than mothers of girls (p-values for Wilcoxon test $\leq$ 0.05).

Bisphenols F-B-AF and triclocarban were detected in less than 2% of the pooled urine samples and were excluded from the statistical analyses (Table 2). Butylparaben and bisphenol S were detected in 22.1% and 26.4% of the samples and were only considered in the single-pollutant model. Other phenols, as well as phthalates and DiNCH metabolites were detected in most of the samples (detection rates ranged from 79.3% to 98.8%). Among phenols, methylparaben showed the highest geometric mean concentration, while among phthalate metabolites, the highest geometric mean concentrations were observed for the metabolites of phthalates with the lower molecular weight (monoethyl phthalate [MEP], mono-isobutyl phthalate [MiBP] and mono-n-butyl phthalate [MnBP]). Mothers excluded from our analyses did not differ with regard to exposure levels compared with our study population (Table S2).

Correlations between standardized and measured concentrations exceeded 0.84 for all compounds indicating little influence of conditions related to urine processing and assay batch on measured concentrations. Moderate positive Spearman correlations were observed between methylparaben and ethylparaben (ρ = 0.51), methylparaben and propylparaben (ρ = 0.62), MnBP and MiBP (ρ = 0.58), mono-benzyl phthalate (MBzP) and MnBP (ρ = 0.57), ΣDEHP and MnBP (ρ = 0.53), ΣDEHP and 6-hydroxy-mono-propyl-heptyl phthalate (ohMPHP) (ρ = 0.51) (Table S3).

3.2. Phenols and phthalates exposure and child behaviour

The positive WQS indexes were associated with both the externalizing and internalizing CBCL scores in the whole population (meaning worse behaviour, Table 3). After stratification for child sex, magnitude of the associations tended to be stronger in girls than boys, although 95 %CI overlapped. None of the positive WQS indexes were significantly associated with CBCL scores in boys (β = 1.70, 95 %CI: −0.42, 3.81 for the externalizing score and β = 1.17, 95 %CI: −0.50, 2.84 for the internalizing score, for an increase of one tertile in the WQS index). In girls, we observed significant positive associations with both CBCL scores. On

Table 2
Phenol, phthalate and non-phthalate plasticizer metabolite concentrations in maternal urine (average concentrations assessed in weekly pools collected in the first and second urine collection weeks, 822 pooled urine samples; N = 416 mother–child pairs from the SEPAGES cohort, 2014–2017).

Biomarkers	LOD	% >LOD[a]	Standardized[b] concentrations				Measured concentrations				Spearman rank correlation between standardized and measured concentrations
			Geometric mean	Percentiles			Geometric mean	Percentiles			
				33th	50th	66th		33th	50th	66th	
Phenols											
Methylparaben	0.04	98.8	27.45	9.50	17.94	35.34	26.03	9.05	15.04	33.73	0.97
Ethylparaben	0.04	98.4	1.74	0.77	1.07	1.99	1.35	0.58	0.81	1.39	0.96
Propylparaben	0.04	79.3	1.25	0.27	0.94	3.73	1.10	0.24	0.92	3.13	0.97
Butylparaben	0.07	22.1	/	/	/	/	/	<LOD	<LOD	<LOD	/
Bisphenol A	0.04	97.6	1.83	1.31	1.69	2.31	2.31	1.69	2.20	2.89	0.95
Bisphenol S	0.10	26.4	/	/	/	/	/	<LOD	<LOD	<LOD	/
Bisphenol F	0.07	1.3	/	/	/	/	/	<LOD	<LOD	<LOD	/
Bisphenol B	0.03	0.0	/	/	/	/	/	<LOD	<LOD	<LOD	/
Bisphenol AF	0.02	0.1	/	/	/	/	/	<LOD	<LOD	<LOD	/
Benzophenone-3	0.04	98.6	1.17	0.54	0.85	1.60	1.70	0.77	1.14	2.24	0.97
Triclosan	0.04	97.0	1.92	0.61	1.03	1.84	1.92	0.61	1.03	1.84	1.00
Triclocarban	0.04	1.0	/	/	/	/	/	<LOD	<LOD	<LOD	/
Phthalate metabolites											
MEP	0.20	98.8	25.25	15.82	23.95	34.86	26.51	16.74	24.11	37.27	0.99
MiBP	0.20	98.8	16.92	13.28	16.52	20.13	19.60	14.90	18.99	24.71	0.88
MnBP	0.20	98.8	12.13	9.71	11.98	14.41	13.91	11.07	13.36	16.61	0.98
MBzP	0.07	98.8	5.31	3.92	4.97	6.57	5.20	3.74	4.81	6.31	0.98
ohMPHP	0.07	98.8	0.98	0.77	0.86	1.01	0.92	0.70	0.85	1.05	0.84
ΣDEHP[c]	–	–	0.12	0.09	0.11	0.13	0.13	0.10	0.12	0.15	0.98
ΣDiNP[d]	–	–	0.05	0.03	0.04	0.06	0.05	0.04	0.05	0.06	0.99
Non-phthalate plasticizer metabolites											
ΣDiNCH[e]	–	–	0.013	0.008	0.011	0.014	0.011	0.007	0.009	0.012	0.90
Marker of urine dilution											
Specific gravity	–	–	–	–	–	–	1.018	1.015	1.018	1.019	–

Abbreviations: LOD: Limit of detection; MEP: Monoethyl phthalate; MiBP: Mono-isobutyl phthalate; MnBP: Mono-n-butyl phthalate; MBzP: Mono-benzyl phthalate; ohMPHP: 6-hydroxy-mono-propyl-heptyl phthalate; ΣDEHP: Molar sum of di(2-ethylhexyl) phthalate; ΣDiNP: Molar sum of diisononyl phthalate; ΣDiNCH Molar sum of di(isononyl)cyclohexane-1,2-dicarboxylate.
Concentrations expressed in μg/L, except molar sums (ΣDEHP, ΣDiNP and ΣDiNCH) expressed in μmol/L.
/: Concentrations not computed, not available due to low detection frequencies.
[a] Frequency of detection computed using concentrations assessed in each pool of urine samples collected in the first and second collection weeks.
[b] Biomarker concentrations standardized for sample transport time, defreeze time, measurement batch.
[c] Molar sum of mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono (2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-methylcarboxyhexyl) phthalate (MMCHP).
[d] Molar sum of mono(4-methyl-7-hydroxy-octyl) phthalate (OH-MiNP), mono(4-methyl-7-oxo-octyl) phthalate (oxo-MiNP), mono(4-methyl-7-carboxy-heptyl) phthalate (cx-MiNP).
[e] Molar sum of 2-(((hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic acid (ohMiNCH), 2-(((4-methyl-7-oxyooctyl)oxy)carbonyl)cyclohexanecarboxylic acid (oxoMiNCH).

average, the externalizing and internalizing scores were 3.67 points (95 % CI: 1.24, 6.10) and 2.47 points (95 %CI: 0.60, 4.33) higher for an increase of one tertile in the WQS index. In girls, among the eight biomarkers incorporated into the WQS index, three, including bisphenol A (weight of 18%), triclosan (17%) and MEP (15%), were responsible for more than 50% of the observed association with the externalizing score. For the internalizing score, the highest weights were observed for MEP (19%), MBzP (19%) and MnBP (16%). These weights should be interpreted with caution considering the associated standard errors were relatively large (Table 3).

3.3. Additional analyses

Relying on biomarker concentrations not standardized for the urine processing/assay conditions led to similar conclusions than those obtained with standardized concentrations (Table S4). Associations with the mixture were mainly observed for girls. For girls and the externalizing score, the order of the main WQS index contributors was slightly modified. The first four biomarkers with the heaviest weights were bisphenol A (18%), MnBP (15%), triclosan (15%) and MEP (14%) when using unstandardized concentrations compared with bisphenol A (18%), triclosan (17%), MEP (15%) and MnBP (13%) in the main analysis.

Results of the single-pollutant adjusted linear regressions were also suggestive of sex specific effect for some biomarkers (p-values for interaction ≤ 0.20, Tables S5 and S6) and, after stratification, most of the associations were observed in girls. Consistently with the main contributors identified by the WQS approach, bisphenol A ($\beta = 1.17$, 95 %CI: −0.11, 2.46, p-value = 0.07), triclosan ($\beta = 0.47$, 95 %CI: −0.06, 1.01, p-value = 0.08) and MEP ($\beta = 1.20$, 95 %CI: 0.05, 2.35, p-value = 0.04) were associated with increased externalizing scores in girls (Table S5). Regarding internalizing scores (Table S6), we observed positive associations with methylparaben ($\beta = 0.49$, 95 %CI: 0.00, 0.98, p-value = 0.05) and MEP ($\beta = 0.74$, 95 %CI: −0.12, 1.60, p-value = 0.09) in girls. MEP, but not methylparaben, had also been identified as one of the main contributors of the WQS index for internalizing score in girls. The few associations observed in boys were all suggestive of improved behaviour. In this group, bisphenol A was negatively associated with the externalizing score ($\beta = -1.35$, 95 %CI: −2.66, −0.04, p-value = 0.04) while increased detection of bisphenol S in urine was associated with a decreased internalizing score.

Adjustment of the single-pollutant analyses for maternal employment, tobacco or vitamins consumption during pregnancy did not

Table 3
Effect estimates and weights from adjusted linear WQS regression of maternal urinary phenol, phthalate, non-phthalate plasticizer standardized concentrations index and CBCL raw scores (N = 227 mother-boy and 189 mother-girl pairs from the SEPAGES cohort, 2014–2017).

CBCL score	Child sex	Effect estimate (95 %CI)[a, b]	Biomarkers included in the WQS index[c, d]	Average weight ± SE
Externalizing score	Boys and girls together	1.95 (0.20, 3.70)**	Benzophenone-3	0.17 ± 0.09
			ΣDiNP	0.15 ± 0.08
			Triclosan	0.14 ± 0.08
			Ethylparaben	0.12 ± 0.08
			MBzP	0.12 ± 0.08
			Methylparaben	0.11 ± 0.07
			ΣDiNCH	0.10 ± 0.07
			MEP	0.10 ± 0.07
	Boys	1.70 (-0.42, 3.81)	Benzophenone-3	0.22 ± 0.11
			ΣDiNP	0.19 ± 0.10
			Methylparaben	0.12 ± 0.09
			ΣDiNCH	0.11 ± 0.09
			Triclosan	0.11 ± 0.08
			Ethylparaben	0.10 ± 0.08
			Propylparaben	0.08 ± 0.08
			ohMPHP	0.07 ± 0.06
	Girls	3.67 (1.24, 6.10)**	Bisphenol A	0.18 ± 0.09
			Triclosan	0.17 ± 0.09
			MEP	0.15 ± 0.09
			MnBP	0.13 ± 0.09
			Ethylparaben	0.10 ± 0.07
			MBzP	0.10 ± 0.07
			Methylparaben	0.09 ± 0.07
			Benzophenone-3	0.08 ± 0.07
Internalizing score	Boys and girls together	1.31 (0.05, 2.58)**	Methylparaben	0.20 ± 0.10
			MEP	0.15 ± 0.09
			Triclosan	0.13 ± 0.08
			MBzP	0.12 ± 0.08
			ΣDEHP	0.10 ± 0.08
			ΣDiNCH	0.09 ± 0.07
			MnBP	0.08 ± 0.07
			Propylparaben	0.08 ± 0.07
			Bisphenol A	0.06 ± 0.06
	Boys	1.17 (-0.50, 2.84)	Methylparaben	0.42 ± 0.15
			Triclosan	0.22 ± 0.13
			ΣDiNP	0.17 ± 0.10
			MnBP	0.10 ± 0.08
			ΣDiNCH	0.10 ± 0.08
	Girls	2.47 (0.60, 4.33)**	MEP	0.19 ± 0.10
			MBzP	0.19 ± 0.10
			MnBP	0.16 ± 0.09
			Bisphenol A	0.11 ± 0.08
			Ethylparaben	0.09 ± 0.08
			Methylparaben	0.09 ± 0.07
			Propylparaben	0.09 ± 0.07
			ΣDEHP	0.07 ± 0.06

Abbreviations: WQS: Weighted Quantile Sum; CI: Confidence Interval; SE: Standard Error; MEP: Monoethyl phthalate; MiBP: Mono-isobutyl phthalate; MnBP: Mono-n-butyl phthalate; MBzP: Mono-benzyl phthalate; ohMPHP: 6-hydroxy-mono-propyl-heptyl phthalate; ΣDEHP: Molar sum of di(2-ethylhexyl) phthalate; ΣDiNP: Molar sum of diisononyl phthalate; ΣDiNCH Molar sum of di(isononyl)cyclohexane-1,2-dicarboxylate.

[a] Models adjusted on maternal age at conception, level of education, body mass index before pregnancy, psychological difficulties during the third trimester, parity(, child sex) and specific gravity.

[b] Change in CBCL raw scores for an increase of one tertile in the WQS index.

[c] Biomarker concentrations standardized for sample transport time, defreeze time, measurement batch.

[d] Since our hypothesis was that exposure to phenols, phthalates and non-phthalate plasticizers can be deleterious for child neurodevelopment, we only included in the WQS indexes biomarkers positively associated with CBCL scores in single-pollutant models (based on the sign of the effect estimates with no consideration for the p-values).

** p-value $\leq$ 0.05.

meaningfully change the results (Tables S7 and S8).

Curves modelling the predicted CBCL scores using biomarker concentrations coded as restricted cubic splines were suggestive of potential nonlinear relationships between ΣDiNP and externalizing score as well as between ΣDiNP, ΣDiNCH and internalizing score (p-values for likelihood ratio tests $\leq$ 0.05; Figures S2 and S3). These trends seemed to be driven by few extreme concentrations and should be considered with caution.

4. Discussion

We assessed 27 biomarkers of exposure to synthetic phenols, phthalates and DiNCH in within-subject pools of repeated urine samples collected during pregnancy and investigated their combined effects on child behaviour at 2 years of age. Both WQS regressions and single-pollutant models showed deleterious associations which tended to be more pronounced among girls. In girls, main contributors of the WQS

indexes were bisphenol A, triclosan and MEP (metabolite of diethyl phthalate [DEP]) for the externalizing score (in agreement with single-pollutant analyses) and MEP, MBzP (metabolite of butyl-benzyl phthalate [BBzP]) and MnBP (metabolite of dibutyl phthalate [DBP]) for the internalizing score (only MEP in agreement with single-pollutant analyses). WQS estimates were not significant for boys but confidence intervals overlapped those observed for girls. Considering, the relatively low sample size of our study, a possible milder effect among boys can not be ruled out.

Strengths of this study included the collection of multiple urine samples at two time points during pregnancy (median = 21 samples per individual at each collection week with IQR = 20–21). Although, for short half-life chemicals with high intra-individual variability such as phenols and phthalates, the two urine collection weeks we relied on cannot be claimed as representative of the exposure over the nine months of pregnancy, such study design has shown, for a given sample size, to decrease bias in the effect estimates and increase power compared with studies relying on fewer samples (Perrier et al., 2016; Vernet et al., 2019). Measurements below LOD and LOQ were treated using the "fill-in" approach, a method which proved to limit bias compared with simpler single imputation (such as $LOD/\sqrt{2}$ (Lubin et al., 2004)). Besides, our study is one of the first to implement a multi-pollutant approach to explore the associations between exposure to a mixture of phenols, phthalates, non-phthalate plasticizers and child behaviour (Daniel et al., 2020; Li et al., 2020). Compared with classical single-pollutant models, WQS regressions allow to estimate the joint effects of these compounds on child behaviour, to account for co-exposure effects and to reduce multiple testing (Carrico et al., 2015). Here, we combined WQS regressions with repeated holdout validation to improve results stability and assess estimates uncertainty (Tanner et al., 2019). WQS method showed improved accuracy compared with other multi-pollutant approaches such as lasso, adaptive lasso and elastic net (Carrico et al., 2015). WQS approach assumes directional homogeneity (all exposures included in the index should be associated with the outcome in the same direction) (Carrico et al., 2015). To overcome these constraints, we first ensured that all biomarkers included in the WQS index were associated with the outcome in the same direction and adjusted for exposures acting on the opposite direction (Romano et al., 2018). WQS regression also assumes linear relationships between the studied exposures and the outcome (Carrico et al., 2015). In our single-pollutant models, spline modelling did not highlight major deviation from linearity.

Limitations should be acknowledged too. First, we focused on exposure during the prenatal period with no information on the pre-conception and early pregnancy periods. The earliest urine samplings occurred between the 12th and 22th gestational weeks. Cohorts investigating earlier periods are rather rare due to complex participant recruitment. To our knowledge, only one study explored the preconception period, highlighting deleterious associations between maternal and paternal exposure to several phthalates before pregnancy and child behaviour (Messerlian et al., 2017). Also, no adjustment for postnatal exposure, another period of vulnerability for child neurodevelopment, was made. Second, we assessed child behaviour only once, at an early age (2 years). While such early preschool assessments have shown to predict behaviour latter in childhood (Mesman and Koot, 2001), measurement error are likely to occur and having repeated assessments at different ages, completed by different informants would have been preferable (Zentner et al., 2014). Third, despite the analyses were adjusted for potential confounders, residual confounding cannot be discarded. Notably, exposure to other toxicants than phenols and phthalates has not been taken into account in this study. However, biomarkers of exposure to phenols and phthalates seem weakly correlated with other pollutants (Robinson et al., 2015; Tamayo-Uria et al., 2019). Besides, women of the SEPAGES cohort tended to have a higher education level, to be older and to smoke less than the average French pregnant women (Lyon-Caen et al., 2019). Tertiles defined in the WQS analyses were also specific of our population. This does not call into question the observed associations but restricts results generalizability/transportability. Lastly, interactions between chemicals could not be tested with WQS regression that only considers additive effects among chemicals included in the index. This may lead to bias (Keil Alexander P. et al., 2020). In practice, further investigation of the topic appears complicated in an exposome context: interactions may involve multiple compounds, act in various directions and require very large sample size to be analysed (Lazarevic et al., 2019).

Bisphenol A, an additive used in polycarbonate plastics and epoxy, was one of the most important contributors to the WQS index for the externalizing score in girls. This compound was also positively associated with this score among girls in the single-pollutant model while negative association was observed among boys. Several studies rather reported adverse associations for boys (Evans et al., 2014; Harley et al., 2013; Perera et al., 2012; Philippat et al., 2017; Roen et al., 2015) or for internalizing behaviour in girls and/or boys (Braun et al., 2011, 2009; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015). Exposure levels in these cohorts were similar (HOME: median = 2.0 μg/L (Braun et al., 2009); EDEN: median = 2.37 μg/L (Philippat et al., 2017); CCCEH: geometric mean = 1.96 μg/L (Perera et al., 2012)) or lower (CHAMACOS, SFFII,: median = 1.1 μg/L (Harley et al., 2013; Evans et al., 2014)) than those observed in SEPAGES (median = 2.20 μg/L). Most of these studies assessed behaviour at older ages (3–12 years) than us. Only one study, relying on the HOME cohort, assessed behaviour at early age (2 years) and, as us, reported deleterious association between BPA and externalizing behaviour in girls (Braun et al., 2009). This association was also observed at latter age in this cohort (Braun et al., 2017, 2011, 2009; Stacy et al., 2017).

Regarding other bisphenols, only bisphenol S was sufficiently detected to be included in our single-pollutant analyses. It tended to be associated with a decrease of the internalizing score among boys. This result should be interpreted with caution considering the low number of urine samples with detectable concentrations (26.4%). As far as we know, no study investigated the relationship between prenatal exposure to bisphenol S and child behaviour, limiting results comparison. Nevertheless, studies looking at other aspects of child neurodevelopment suggested that prenatal exposure to bisphenol S was related to a lower psychomotor developmental index (Jiang et al., 2020) or did not identify this compound as an important contributor to decreased IQ among seven-year old children (Tanner et al., 2020).

Triclosan, a broad-spectrum biocide found in hygiene products and textiles (Morais et al., 2016), made the second largest contribution to the positive WQS index for the externalizing score among girls and also tended to be positively associated with this score in the single-pollutant model. A study based on the HOME cohort also reported positive associations between pre- and postnatal exposure to triclosan and externalizing behaviour scores at 8 years (Jackson-Browne et al., 2019) while another suggested positive associations with both externalizing and internalizing behaviour subscales at 3 years in the EDEN cohort (Philippat et al., 2017). Contrary to the present work, these associations were observed in boys only. Measured concentrations in these populations (EDEN: median = 28.2 μg/L (Philippat et al., 2017); HOME: median > 13 μg/L (Jackson-Browne et al., 2019)) were much higher than those quantified in the SEPAGES cohort (median = 1.03 μg/L). Reports of improved behaviour (Etzel et al., 2018) or no association (Guo et al., 2020) also exist for this phenol.

Several phthalate metabolites substantially contributed to the positive WQS index for both the externalizing and internalizing scores in girls. That included MEP for the externalizing score and MEP, MBzP, MnBP for the internalizing score. Positive associations between MEP and both scores in girls were also observed in the single-pollutant models. Parent compounds of MEP, MBzP and MnBP (DEP, BBzP and DBP, respectively) are used as additives in various hygiene products, drugs or building materials. In line with our results, two previous studies based on the CCCEH cohort have reported positive associations between maternal MnBP and internalizing behaviour scores in girls at different

ages (3 and 7 years (Daniel et al., 2020; Whyatt et al., 2012)). However, others have highlighted such associations in boys (Philippat et al., 2017; Whyatt et al., 2012) or for externalizing behaviour in girls and/or boys (Kobrosly et al., 2014; Lien et al., 2015). Exposure levels in these populations tended to be similar (SFF: geometric mean = 13.61 μg/L (Kobrosly et al., 2014)) or higher (CCCEH: geometric mean = 38.0 μg/L (Whyatt et al., 2012); EDEN: median = 44.2 μg/L (Philippat et al., 2017)) than the ones measured in SEPAGES (median = 13.36 μg/L). For this metabolite, reports of null associations also exist in young (1–2 years (Kim et al., 2018)) and older (7 or more years (Gascon et al., 2015; Huang et al., 2019; Jankowska et al., 2019; Li et al., 2020)) children. Similar to our analysis, two other studies showed an increase of internalizing behaviour in relation with increased maternal MBzP urinary concentrations among girls (Daniel et al., 2020; Whyatt et al., 2012). However, several studies also observed associations among boys (England-Mason et al., 2020; Philippat et al., 2017; Whyatt et al., 2012) or for externalizing score in girls and/or boys (England-Mason et al., 2020; Hyland et al., 2019; Kobrosly et al., 2014) or did not highlight detrimental relationship (Daniel et al., 2020; Gascon et al., 2015; Huang et al., 2019; Jankowska et al., 2019; Li et al., 2020; Lien et al., 2015). Measured concentrations were often higher (APrON: median = 8.56 μg/L (England-Mason et al., 2020); CCCEH: geometric mean = 19.0 μg/L (Whyatt et al., 2012); EDEN: median = 18.4 μg/L (Philippat et al., 2017); SFF: geometric mean = 6.59 μg/L (Kobrosly et al., 2014)) than those quantified in SEPAGE (median = 4.81 μg/L). Regarding MEP, a few studies highlighted a deleterious effect of this compound on behaviour at 1–2-years (Kim et al., 2018) and 7 years or more (Hyland et al., 2019; Jankowska et al., 2019) among girls but also boys. Many others concluded on the absence of association (Daniel et al., 2020; England-Mason et al., 2020; Gascon et al., 2015; Huang et al., 2019; Kobrosly et al., 2014; Lien et al., 2015; Philippat et al., 2017), despite exposure levels often higher (APrON: median = 46 μg/L (England-Mason et al., 2020); SFF: geometric mean = 81.01 μg/L (Kobrosly et al., 2014); EDEN: median = 97.0 μg/L (Philippat et al., 2017)) than the one observed in this study (median = 24.11 μg/L).

While several studies reported some associations between the biomarkers highlighted in this work and child behaviour, the gender and type of behaviour affected often diverge. Variations in study designs (population characteristics, frequency and timing of sample collection, age at behavioural assessment, instrument used to assess behaviour, etc.) and exposure levels could explain part of the discrepancies noted across studies (England-Mason et al., 2020). In addition, most of the works relied on single-pollutant models with no correction for multiple comparisons, which, given the high number of chemicals and sometimes behavioural scores considered, are likely to result in a high family-wise error rate (FWER; probability of making one or more false discoveries (Agier et al., 2016)). As highlighted by our analysis, single-pollutant models can also sometimes lead to different conclusions than multi-pollutant models. As an example, in our study, methylparaben was positively associated with internalizing scores in girls, while this compound was not identified as an important contributor by WQS regressions.

Regarding potential mechanisms of action, some phenols may notably act on thyroid hormone homeostasis which influences neurogenesis, neuron differentiation, migration and communication (Ghassabian and Trasande, 2018; Prezioso et al., 2018). In particular, bisphenol A and triclosan, the two phenols identified as important contributors of the WQS index for externalizing score in girls, have been identified as *in vitro* inhibitors of the thyroid peroxidase, a crucial enzyme for thyroid hormones production and of the sodium-iodide symporter in charge of active iodine intake into the thyroid follicular cells (US EPA, n.d.). In Humans, studies based on the HOME cohort concluded that exposure to these two phenols may influence thyroid hormone levels in newborns (Braun et al., 2018; Romano et al., 2015). Bisphenol A has also been shown to act on steroid, oestrogen, androgen receptors and to be a disruptor of the brain aromatase activity (Wolstenholme et al., 2011). Other potential mechanisms may include oxidative stress (Steffensen et al., 2020) and epigenetic modifications (Ling et al., 2020; Mileva et al., 2014; Wolstenholme et al., 2011). A recent study coupling diffusion magnetic resonance imaging scan and behavioural assessment suggested that white matter microstructure changes may mediate the associations between prenatal exposure to bisphenol A and the internalizing CBCL score among preschool children (Grohs et al., 2019). Exposure to parent compounds of MEP, MBzP and MnBP has also been associated with thyroid homeostasis, calcium signalling disruption (involved in neurogenesis, cell proliferation and differentiation (Miodovnik et al., 2014; Romano et al., 2018)). Studies suggesting an impact of phthalates on oxidative stress (Ponsonby et al., 2020) and epigenetics (Dutta et al., 2020) exist too.

5. Conclusions

This work reports associations of exposure to a mixture of selected phenols and phthalates with child behaviour, especially in girls. Two phenols (bisphenol A and triclosan) and three phthalate metabolites (MEP, MBzP and MnBP) made the largest contribution to the mixture effect estimates. Several of these compounds (bisphenol A, triclosan, MEP) also tended to be associated with child behaviour in our single-pollutant analysis. Previous studies already highlighted relationships between these biomarkers and child behaviour. However, these associations were not always observed for the same gender or behavioural features. Further research with harmonized study designs, repeated pre and postnatal exposure assessments and relying on statistical methods allowing to account for co-exposure are needed to better understand the associations between phenols, phthalates and child behaviour.

CRediT authorship contribution statement

Ariane Guilbert: Methodology, Software, Formal analysis, Writing - original draft, Visualization. **Matthieu Rolland:** Methodology, Software, Formal analysis, Writing - review & editing. **Isabelle Pin:** Investigation, Writing - review & editing. **Cathrine Thomsen:** Methodology, Investigation, Writing - review & editing. **Amrit K. Sakhi:** Methodology, Investigation, Writing - review & editing. **Azemira Sabaredzovic:** Methodology, Investigation, Writing - review & editing. **Rémy Slama:** Investigation, Methodology, Writing - review & editing, Funding acquisition. **Karine Guichardet:** Resources, Writing - review & editing. **Claire Philippat:** Conceptualization, Methodology, Writing - original draft, Supervision, Funding acquisition. **:** . **E. Eyriey:** . **A. Licinia:** . **A. Vellement:** . **Pin:** . **P. Hoffmann:** . **E. Hullo:** . **C. Llerena:** . **X. Morin:** . **A. Morlot:** . **J. Lepeule:** . **S. Lyon-Caen:** . **C. Philippat:** . **I. Pin:** . **J. Quentin:** . **V. Siroux:** . **R. Slama:** .

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary material

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