

Mixture of Plasticizer Chemicals and Child Intelligence: A Weight-of-Evidence and Meta-Analysis-Informed Bayesian Approach in a Cohort with Improved Exposure Assessment

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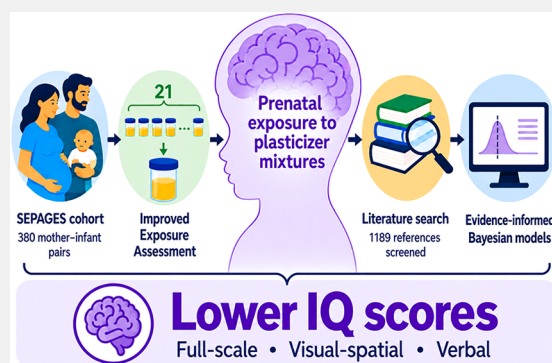
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ABSTRACT: Early-life exposure to plasticizer chemicals can affect child neurodevelopment. However, accurately characterizing exposure to these short-lived chemicals remains challenging. To address knowledge gaps, we examined the association between prenatal and infant exposure to a plasticizer mixture and child intelligence quotient (IQ) in a cohort with improved exposure assessment, informing the statistical analysis using the existing toxicological and epidemiological evidence. This work included 380 mother-infant pairs from the SEPAGES study, a French new-generation population-based birth cohort recruited between 2014 and 2018. Sixteen phenols and phthalate metabolites were quantified in pools of multiple urine samples collected at four time points during pregnancy and infancy (up to 21/week). Children's IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence at age 3. A structured review of the toxicological and epidemiological evidence was conducted to prioritize the chemicals with the highest weight of evidence (WoE) to be analyzed as a mixture. Meta-analyses of the retrieved epidemiological studies were performed and used as priors in single-chemical Bayesian regression models. Of 1189 references screened, we retrieved data from 30 toxicological and 57 epidemiological studies supporting the prioritization of bisphenol A and S, diethylhexyl phthalate metabolites, monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MnBP), and mono-isobutyl phthalate (MiBP). Each quartile increase in maternal third-trimester concentrations of the high-WoE plasticizer mixture was associated with decreased full-scale (β : -2.86; 95% Credibility Interval, CrI: -5.05, -0.91), visual-spatial (-2.79; 95% CrI: -5.39, -0.82) and verbal (-1.95; 95% CrI: -3.84, 0.00) child IQ scores. Bayesian single-chemical models informed by meta-analysis-based priors also found that third-trimester concentrations of four of the six prioritized chemicals (bisphenol A, MEP, MnBP, and MiBP) were associated with reduced IQ scores. This novel evidence-based framework increased the biological plausibility and external validity of results, supporting that pregnancy exposure to a mixture of common plasticizers affects child IQ and represents a public health concern. The findings underscore the need to protect fetuses and children from plastic-associated chemicals and regulate them by class.



1. INTRODUCTION

Plastic pollution is a major environmental and health challenge. Hundreds of chemicals are known to leach from plastic, resulting in widespread human exposure.^{1,2} Among plastic-associated chemicals, phthalates and phenols constitute two major chemical groups used as plasticizers and additives to improve plastic materials' flexibility and durability.³ Widely present in food packaging and cosmetics, phthalates and phenols are detected in virtually all the population,^{4,5} and some of them are known endocrine-disrupting chemicals (EDCs) capable of altering the neuroendocrine system during critical windows of development.^{3,6}

Neurobehavioral impairments, including intelligence quotient (IQ) point loss and intellectual disability, affect millions of children worldwide, resulting in enormous societal burdens.⁷ Apart from genetic, medical, and lifestyle factors, early-life

exposure to EDCs can play a role, with economic costs estimated in millions annually.⁸ While evidence from mother-child cohorts is mounting,^{9,10} it remains limited for newer substitutes such as bisphenol S and di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and for some critical periods such as early infancy.¹¹ Importantly, some methodological shortcomings in exposure assessment have precluded regulatory agencies from evaluating epidemiological findings.¹² Among

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the limitations of previous studies, most collected few urine samples (often one) to assess phenols and phthalates, leading to exposure misclassification issues due to the short half-life and high within-day variability of these chemicals.^{13,14} The current work mitigates this shortcoming by collecting and pooling multiple urine samples over sensitive exposure windows.¹⁵

Another issue has been the handling of multiple comparisons.^{16,17} In single-chemical models, classical corrections for multiple comparisons assume an equal weight of evidence (WoE) for all investigated chemicals, which is often not the case,^{18,19} and for high-WoE chemicals, results in a disproportionately increased risk of type II errors (i.e., discarding true associations).¹⁶ Additionally, incorporating numerous chemicals with a low WoE in mixture models may reduce the precision of estimates.^{20,21}

To overcome these limitations, we combined a structured literature review with meta-analyses to determine the WoE for each investigated chemical. This WoE was then used to feed priors in Bayesian single-chemical models and to prioritize the most relevant chemicals in the mixture model. Therefore, the aim of this study was to examine whether early-life life exposure to a mixture of phenols and phthalates is associated with children's IQ, using an improved exposure assessment protocol and accounting for the previous evidence.

2. METHODS

2.1. Study Population

We used data from the French new-generation SEPAGES mother-child cohort, which recruited 484 pregnant women from Grenoble and nearby areas between July 2014 and July 2017.²² Eligibility criteria included singleton pregnancies up to gestational week 19, being older than 18 years, being affiliated to the French national security system, and planning to deliver in one of the four Grenoble maternity clinics. The current analysis included children with child IQ assessed at 3 years of age and exposure biomarkers measured in at least one of the following time windows (Figure S1): early pregnancy (N = 381), late pregnancy (N = 374), neonates (N = 359) and infants (N = 343). The study was approved by the corresponding ethic committees (CPP: Comité de Protection des Personnes Sud-Est V and CNIL: Comité Nationale Informatique et Liberté). Both the mother and the father of the expected child provided written informed consent.

2.2. Repeated Urine Collection and Exposure Assessment

Pregnant women collected 3 urine samples each day (morning, midday and evening), for 7 consecutive days, twice during pregnancy: in the second trimester (median: 17 gestational weeks), and during the third trimester (median: 33 gestational weeks). After birth, parents collected one child's urine per day for a week by inserting a piece of cotton gauze into the child's diaper, during both the neonatal (median: 8 weeks of age) and infant (median: 13.5 months of age) periods. Compliance with the protocol was excellent: the median number of samples collected was 21 per pregnancy trimester, and 7 and 6 for neonates and infants, respectively. Families stored samples in their home freezer until field workers transported them to a biobank at the end of each collection week. For each of the four windows evaluated, within-subject weekly pools were performed by combining equal volumes of all the urine samples obtained over a collection week as previously validated (Figure S2).²³

Aliquots of weekly urine pools were stored at -80°C and then shipped on dry ice, with a temperature sensor, to the Norwegian Institute of Public Health (Oslo, Norway), a certified laboratory that has participated in inter-laboratory comparisons.²⁴ The concentrations of 12 phenols, 12 phthalates, and 2 non-phthalate plasticizer metabolites were measured (Table S1) using high-performance liquid

chromatography coupled to mass spectrometry.^{25,26} The limits of detection (LOD) and quantification (LOQ) ranged from 0.04 to 0.7 ng/mL and 0.10–2 ng/mL, respectively (Table S1). Due to budget limitations, phthalate metabolites were only assessed in a subset of 152 neonates at 2 months of age,²⁷ thus, this chemical family at this time point was not considered in the current analysis.

A previous SEPAGES analysis compared total and free phenol concentrations, suggesting some degree of external contamination for bisphenol A in neonates and infants, and methylparaben in infant samples, but not for any of the remaining chemicals.²⁸ For these specific chemicals/periods, conjugated concentrations (estimated as the total minus the free concentration) were used for the main associations reported.

2.3. Outcome Assessment

Child IQ was assessed by trained neuropsychologists at a median (IQR) age of 36.9 (36.5, 37.5) months using the French version of the validated Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV).²⁹ This scale was translated, culturally adapted to French norms, and calibrated in a representative sample of French children aged between 2.5 and 7.25 years by the Editions of the Center in Applied Psychology.³⁰ Full-scale, verbal, visual-spatial, and working memory IQ scores were calculated and used in the analysis. Higher WPPSI-IV scores indicate better cognitive abilities.

2.4. Statistical Analysis and WoE Definition

2.4.1. Exposure Biomarkers. Triclocarban and bisphenols AF, B, and F were excluded since they were quantified in less than 5% of samples. Bisphenol S was dichotomized as detected/quantified versus not detected. The remaining exposure biomarkers were detected in more than 90% of the urine samples (except ethylparaben, detected in 70% of the samples), and concentrations below the LOD and between the LOD and LOQ were singly imputed with values randomly selected from 0 to LOD and from LOD to LOQ, respectively, considering a log-normal distribution as previously recommended.³¹

Factors related to urine collection and processing may affect the concentration of the measured exposure biomarkers, including (i) transport time of urine samples from the participant's home to the biobank, (ii) time samples remained at 4°C during the pooling procedure, and (iii) the analytical batch. We first fitted a multiple linear regression model for each biomarker, including these factors and potential confounders (maternal age, education, pre-pregnancy body mass index, etc.). If processing factors predicted the measured biomarkers (Wald test, $p < 0.20$), concentrations were standardized to reduce between-sample variability as previously reported.³² The standardized concentrations estimate the concentrations that would have been obtained if all samples were transported and processed under the same batch and conditions. High correlations (Spearman $\rho > 0.90$ in most cases) have been observed between these standardized and non-standardized biomarker concentrations.¹⁸

For metabolites belonging to the same parent compound, molar sums ($\mu\text{mol/L}$) were computed (i.e., $\sum\text{DEHP}$ (sum of MEHP, MEHHP, MEOHP, and MECPP), $\sum\text{DiNP}$ (sum of OH-MiNP, oxo-MiNP, and cx-MiNP), and $\sum\text{DINCH}$ (sum of OH-MiNCH and oxo-MiNCH)). The molar sum of parabens (methyl-, ethyl-, and propylparaben) was also calculated to limit the number of statistical tests. Butylparaben was not included in this sum due to a low detection frequency ($<30\%$).

For association analyses, biomarker concentrations were natural-log transformed to reduce skewness and the influence of extreme values.

2.4.2. Covariates and Confounding Factors. A directed acyclic graph (DAG) allowed us to identify the most relevant adjustment variables and confounders (Figure S3). Covariates controlled for included maternal factors including age (continuous), education (below vs. Master's degree or higher), pre-pregnancy BMI (continuous), parity (nulliparous vs. uniparous/multiparous), anxiety and depression at third trimester (continuous, assessed using the "Hospital Anxiety and Depression scale"),³³ maternal IQ score (continuous) estimated with the similitude subscale of the Wechsler Adult Intelligence Scale (WAIS-IV), and child factors including sex, age at IQ assessment (months), breastfeeding duration (weeks),

daycare attendance up to 1 year of age (daycare *vs.* at home/others), family environment (continuous Home Observation Measurement of the Environment (HOME) score) and the psychologist in charge of the WPPSI assessment (3 categories). A variable combining maternal active smoking and maternal and infant passive smoking was also included in the models (exposed *vs.* non-exposed). Data on covariates were collected by self-administered questionnaires and questionnaires administered by a fieldworker during study visits. Missing covariate values (range 0–16%) were single-imputed using a random forest algorithm.

2.4.3. Assessment of Linearity. The exposures introduced in the adjusted models were coded into quantiles, and Wald's test for heterogeneity was conducted, with P-trend estimated using the median of each quantile in the regression models. Because most associations (98%) did not depart from linearity, the main analyses were performed using continuous exposure variables.

2.4.4. Literature Search and Criteria for Bayesian Prior Definition. Before performing the statistical analysis, a structured literature search was performed in the PubMed/MEDLINE database, adapting the main points of the Navigation Guide systematic review methodology for environmental health studies.³⁴ Extended details on search terms and selection of studies are provided in the [Supporting Information](#) (section Extended Literature Search Methods).

The search aimed to identify epidemiological and rodent experimental studies that investigated associations between exposure to the phenols and phthalates examined in this work and cognitive abilities. Results of these studies were then used to define two types of priors: 1) Quantitative priors corresponding to the estimates obtained from meta-analyses of retrieved comparable epidemiological studies used to inform single-chemical Bayesian models (Table S2); and 2) Qualitative priors defined based on the WoE of each chemical for a potential effect on child IQ, derived from both toxicological and epidemiological studies, and used to prioritize the chemicals to be considered in mixture models (Table S3).

2.4.5. Bayesian Single-Chemical Models. The priors for the single-chemical models were derived from observational studies retrieved through the literature search meeting the following meta-analysis inclusion criteria: biomarkers for phthalate or phenol measured in urine during pregnancy or infancy (up to 2 years of age), exposure analyzed on a continuous scale, and child IQ outcomes measured by either WPPSI or WISC (Wechsler Intelligence Scale for Children). A hierarchical approach based on the availability and robustness of existing evidence was followed:

- 1. Meta-Analysis-Based Priors:** When at least two eligible studies were retrieved for an exposure-outcome pair, a meta-analysis was conducted. Effect estimates and 95% confidence intervals were extracted from eligible studies, excluding those that reported results in interquartile-range units. Effect estimates and confidence intervals reported on different logarithmic scales were transformed to the natural logarithmic scale using the formula: $\text{est}_{\ln} = \text{est}/\ln(\log_base)$, where $\log_base$ corresponds to the transformation base (e.g., 2 for $\log_2$). A random-effects meta-analysis was then performed.³⁵ The resulting meta-analytic effect size and standard error (SE) were subsequently used in our Bayesian models to define a normal prior distribution, with the effect size as the mean and the SE as the standard deviation (SD).
- 2. Single-Study-Based Priors:** If only one study was available for an exposure-outcome pair, its effect size and SE served as the prior. This study had to adhere to the same aforementioned meta-analysis criteria, with an additional requirement that the sample size exceed 200.
- 3. Weakly Informative Priors:** In the absence of studies meeting our criteria, we defaulted to weakly informative priors and used a normal distribution with a mean of 0 and a scaled SD calculated as 2.5 times the SD of the outcome over the SD of the exposure ($\text{SD}(y) / \text{SD}(x)$).³⁶

Posterior distributions were examined for effect sizes and 95% credible intervals (CrI). We used the probability of direction (pd) to

assess the certainty that an effect was positive or negative. This Bayesian measure is conceptually similar to a one-sided p-value. The Gelman-Rubin statistic and effective sample sizes were used to evaluate Markov Chain Monte Carlo convergence, ensuring that multiple chains had mixed well. Convergence was deemed satisfactory when the Gelman-Rubin statistic was <1.1 for all parameters of interest.³⁷ Additionally, residuals from our models were examined for any patterns that suggested misfit, such as heteroscedasticity or nonlinearity. Effect estimates (β) represented the adjusted mean difference in IQ scores for each natural-log-unit increase in standardized biomarker concentrations (or detected versus non-detected in the case of bisphenol S).

2.4.6. Bayesian Mixture Models. Mixture models were informed by a qualitative prior (prioritized/non prioritized chemicals), based on the WoE defined for each chemical's considering: 1) the quantity and quality of *in vivo* rodent and human evidence for an effect on child IQ; and 2) additional judgement and consensus between V.M., A.P.-C. and C.P., considering the consistency of the evidence, mechanistic support, structural analogy, and association with other neurodevelopmental end points (Table S3).

Bayesian Weighted Quantile Sum Regression (BWQS) was then used to investigate the mixture effect of the prioritized chemicals. BWQS is a quantile-based approach that combines multiple independent variables additively into a weighted index, with weights that estimate each component's contribution to the mixture.³⁸ BWQS effect estimates (β) were interpreted as the mean change in child IQ scores for a simultaneous quartile increase in the concentration of each chemical included in the mixture.

2.4.7. Secondary Sex Interaction Analysis. Bayesian single-chemical models were re-run to include exposure-sex interaction terms. As interaction tests are often underpowered, models were stratified by sex if the 90% credible interval of the sex interaction term did not include zero.³⁹

2.4.8. Sensitivity analyses. To evaluate the impact of priors on results, a classical frequentist single-chemical model was performed. BWQS models were also re-run, including all the measured chemicals (prioritized and non-prioritized).

The potential influence of extreme values was assessed by winsorizing the top and bottom 1% of IQ scores and biomarker concentrations.

2.4.9. Interpretation Criteria and Software. Results were interpreted considering the WoE and patterns of associations (e.g., across IQ scales and exposure windows), rather than solely considering statistical significance (CrI not including the null value).⁴⁰

All analyses were conducted using R version 4.4.1. Bayesian single-chemical modeling was performed with the *rstanarm* package, covariate missing data were imputed using the *missForest* package, and meta-analyses were conducted with the *meta* package. A statistical plan was pre-registered before running the analysis (<https://osf.io/b3vnn/>). The analysis code is publicly available (<https://gricad-gitlab.univ-grenoble-alpes.fr/iab-env-epi/mustieles-bayesian-2025>).

3. RESULTS

3.1. Literature Search and Weight of Evidence (WoE)

Of the 1189 publications identified, 30 *in vivo* toxicological, 57 epidemiological, and 7 review studies were selected (Figure S4, Table S3), enabling the prioritization of 6 chemicals (bisphenol A and S, Σ DEHP, MEP, MnBP, and MiBP) based on their WoE for an effect on child IQ (see Table 1 and Table S3 for details).

3.2. Meta-Analytic Priors Used in Single-Chemical Bayesian Models

The quality evaluation of the studies included in the meta-analysis, together with the retrieved estimates, are reported in the Supplemental Excel file. Meta-analysis-based priors for the pregnancy time point and full IQ-scale were derived for 8 out of the 13 measured chemicals (BPA, BPS, DEHP, MnBP,

Table 1. Summary of the Weight of Evidence (WoE) for Each Chemical and Prioritization Strategy (Extended Version Presented in Table S3)^a

Chemical/Metabolite	Prioritized	Toxicology	Epidemiology	WoE Justification
BPA	Yes	Two systematic and one narrative review reported declines in spatial learning and memory caused by early-life exposure in both sexes. ^{41–43} MoA: Estrogenic and anti-androgenic (ER α , ER β , ERR γ , GPER, aromatase, AR). ^{44,45} GPER is an especially plausible MoA at low (0.5 μ g/kg) doses. ⁴⁶ Anti-thyroid and glutamatergic pathways. ⁴⁷ Preliminary support from limited rodent studies suggests that perinatal exposure is linked to spatial and memory deficits. ^{55–57} MoA: Estrogenic and anti-androgenic. ⁵⁸ Impaired neurogenesis. ⁵³	The meta-analysis (Table S2) included up to 7 studies focused on WISC/WPPSI tests. ⁴⁸ – ⁵⁴ Prenatal BPA exposure was borderline-associated with lower full-scale IQ scores (β : -0.52; 95%CI: -1.21, 0.17). This association was driven by boys (-0.81; -1.73, 0.11) and not by girls (0.08; -0.69, 0.85).	Consistent evidence of reduced cognitive abilities in rodents and humans, together with plausible modes of action.
BPS	Yes	Seven rodent studies showed that maternal exposure altered spatial learning, memory, and working memory in male offspring. ^{59–65} MoA: Estrogenic and anti-androgenic. ⁵⁸ Impaired neurogenesis. ⁵³	The meta-analysis (Table S2) included 2 studies. ^{49,50} Prenatal BPS exposure was not associated with full-scale IQ score (β : 0.04; 95%CI: -0.74, 0.65) but a marginal inverse association with Working Memory was observed (-0.76; -1.67, 0.14).	Although still limited, there is growing toxicological and epidemiological support, along with structural and biological analogies to BPA.
DEHP	Yes	Perinatal exposure was associated with neurocognitive alterations in pups. ^{77–79} while other studies reported inconsistent findings. ^{80,81} Seven postnatal exposure studies in rodents showed alterations in memory and learning. ^{82–88} MoA: Anti-androgenic. ⁶⁶ Thyroid disruption. ⁶⁷ Impaired hippocampal synaptic plasticity, ⁶⁸ and neuronal differentiation. ⁸⁹	The meta-analysis (Table S2) included up to 8 studies. ^{53,70–76} Prenatal DEHP exposure was not associated with full-scale IQ in the whole population (β : -0.52; 95%CI: -1.32, 0.28). However, it was associated with lower full-scale IQ in boys (-1.31; -2.56, -0.06), whereas a non-significant opposite trend was observed in girls (1.14; -0.80, 3.08).	Consistent evidence of deleterious neurocognitive effects in both rodent and human studies, along with plausible modes of action.
MnBP	Yes	No specific rodent or animal data. MoA: Anti-androgenic potential. ⁶⁶	The meta-analysis (Table S2) included up to 5 studies. ^{53,72,74–76} Although prenatal MiBP exposure was not associated with IQ scores in the overall population, a large study reported associations with lower full-scale IQ in the total population, individual studies reported associations with lower visual-spatial IQ in the overall population (β : -0.32; 95% CI: -0.62, -0.02) and full-scale IQ in girls (β : -3.15; 95% CI: -5.44, -0.86). Studies investigating cognitive tests other than the WISC/WPPSI reported adverse associations between prenatal MnBP exposure and children's neurocognitive development, expressive language, and mental development index scores (Table S3).	Consistent evidence in rodents and overall supportive in humans, together with plausible modes of action.
MiBP	Yes	Reduced neural cell migration and proliferation. ⁸⁹	The meta-analysis (Table S2) included up to 5 studies. ^{53,72,74–76} Although prenatal MiBP exposure was not associated with IQ scores in the overall population, a large study reported associations with lower full-scale IQ in girls (β : -2.38; 95% CI: -4.50, -0.26), and this association was mediated by lower white matter brain volume, increasing its biological plausibility. ⁷⁵ Additional studies using cognitive tests beyond the WISC/WPPSI reported that maternal exposure to DiBP was associated with adverse neuro-outcomes, including expressive language, general cognitive development index, and mental development index (Table S3).	Lack of rodent studies, but prioritized based on its anti-androgenic activity and overall supportive human literature.
MEP	Yes	A study in rats reported impaired memory and motor function of rats exposed early in life to a mixture of diethyl phthalate (MEP parent compound) and BPS. ⁵⁶ MoA: Androgen-independent developmental toxicity in rodents. ^{90,91} Indirect estrogen receptor modulation. ⁹² Reduced neural cell migration and proliferation. ⁸⁹	The meta-analysis (Table S2) included up to 5 studies. ^{53,72,74–76} Prenatal MEP exposure was not associated with full-scale IQ in the total population (β : -0.01; 95% CI: -0.34, 0.33). However, there were opposing trends for working memory (-0.11; -0.25, 0.03) and visual-spatial IQ scores (0.24; -0.00, 0.48). A large study (n = 775) included in the meta-analysis found that prenatal MEP was associated with lower IQ scores, and that reduced gray matter volume mediated this association, providing additional evidence of plausibility. ⁵ Another large study (n = 585) that could not be included in the meta-analysis (estimates reported per IQR increase), found that children born to mothers in the highest tertile of MEP exposure showed significantly lower IQ scores. ⁷⁰	Inconsistent meta-analysis results, but two large epidemiological studies (one not meeting the meta-analysis criteria) supported the association between early-life MEP exposure and altered cognition, including a mediating effect of reduced brain gray matter. Together with plausible modes of action and deleterious associations observed with other cognitive tests distinct from WISC/WPPSI, we decided to prioritize MEP.
Benzophenone-3	No	A study investigated prenatal and juvenile exposure to BP-3 in rats, reporting alterations in spatial memory. ⁹³ MoA: Estrogenic and anti-androgenic pathways. ⁹⁴	The meta-analysis did not show any significant association but only included 2 studies for boys, while only one study was available for either girls or the whole population. ^{53,54}	Limited rodent and limited and inconsistent epidemiological studies.
Parabens	No	No rodent/animal data. Estrogenic pathways at high doses. ⁹⁵	The unique study usable for our meta-analysis only included boys and reported no significant associations between maternal urinary parabens and child IQ. ⁵³	Lack of <i>in vivo</i> rodent data, together with inconsistent findings in humans.
Triclosan	No	Two rodent studies reported deleterious effects of early-life TCS exposure on neurocognitive functions. ^{96,97} MoA: Anti-thyroid activity. ⁹⁸ Retinoic acid pathway. ⁹⁹ Gut microbiota alterations. ¹⁰⁰ Estrogenic mechanisms. ¹⁰¹	The meta-analysis included up to 4 studies. ^{53,54,102,103} Prenatal triclosan exposure was not associated with full-scale IQ or subscales in the overall population or boys and girls separately.	Although there is mechanistic and some <i>in vivo</i> rodent support, human studies show mixed and inconsistent evidence.

Table 1. continued

Chemical/Metabolite	Prioritized	Toxicology	Epidemiology	WoE Justification
MBzP	No	No rodent/animal data. MoA: Anti-androgenic. ⁶⁶ Reduced neural cell migration but not proliferation. ⁸⁹	The meta-analysis included up to 5 studies. ^{53,74–76,104} Prenatal MBzP was not associated with full-scale IQ or subscales in the overall population or boys and girls separately.	Lack of <i>in vivo</i> rodent data, together with inconsistent findings in humans.
OH-MPHP	No	No rodent/animal data. Lack of data on potential MoAs.	No epidemiological data.	No rodent or human data available.
DiNP	No	One study reported memory alterations in male mice, ¹⁰⁵ while another reported an improvement. ¹⁰⁶ A review concluded that exposure to DiNP at high doses showed no adverse effects on learning in female rodents. ¹⁰⁷	No IQ studies using WISC/WPPSI tests were found to perform a meta-analysis or serve as an individual prior. Inconsistent human evidence.	Limited and inconsistent rodent and human literature.
DINCH	No	No rodent/animal data. Interaction with ER, AR, and PPAR receptors at high doses. ¹⁰⁸	No epidemiological data.	No rodent or human data available.

^aAbbreviations: MoA: Mechanism of action; BPA: Bisphenol A; ER α : Estrogen Receptor alpha; ER β : Estrogen Receptor beta; ERR γ : Estrogen-Related Receptor gamma; GPER: G Protein-coupled Estrogen Receptor; AR: Androgen Receptor; WISC: Wechsler Intelligence Scale for Children; WPPSI: Wechsler Preschool and Primary Scale of Intelligence; BPS: Bisphenol S; DEHP: Diethylhexyl phthalate; IQ: Intelligence Quotient; DEP: Diethyl phthalate; MEP: Mono-ethyl phthalate; DBP: Dibutyl phthalate; MnBP: Mono-*n*-butyl phthalate; DiBP: Di-isobutyl phthalate; MiBP: Mono-isobutyl phthalate; MBzP: Mono-benzyl phthalate; DiNP: Di-isononyl phthalate; TCS: Triclosan; BP-3: Benzophenone-3; IQR: Interquartile range; DINCH: Di(isononyl)cyclohexane-1,2-dicarboxylate; PPAR: Peroxisome proliferator-activated receptors OH-MPHP: Mono-(2-propyl-6-hydroxyheptyl) phthalate.

MiBP, MEP, MBzP, and triclosan) using 2 to 7 studies, depending on the chemical (Table S2). While most of the meta-analytic estimates showed a negative direction, none were statistically significant, with the exception of pregnancy Σ DEHP exposure, which was associated with lower full-scale IQ among boys (Table S2). For other chemicals, we relied either on a single comparable study (e.g., benzophenone-3 and full-scale IQ) or weakly informative priors when no comparable study was retrieved (e.g., Σ parabens, OH-MPHP, Σ DiNP, and Σ DINCH). For the infancy exposure period, data were limited (only one meta-analysis was possible for MBzP and full-scale IQ), so weakly informative priors were applied in most cases.

3.3. Study Population Characteristics

Most mothers were Caucasian (97%), held a master’s degree or more (59%) (Table 2), and presented a normal BMI (median: 21.3 kg/m²). Median maternal age at delivery was 32.4 years (IQR: 30.1, 35.4), and half (45%) of the mothers were nulliparous at recruitment. Children were tested for IQ at a median age of 37 months (IQR: 36.5, 37.6). The mean children’s Full Scale IQ score was 110 (IQR: 103, 118). Although differences between included and excluded mothers were modest, mothers not included in the analysis were younger, breastfed their infants longer, and presented slightly higher BMI and anxiety/depression scores (Table 2).

Except for bisphenol S, exposure biomarkers were detected and quantified in most samples (Table S4). Data on exposure levels and their predictors have been previously published.^{27,28}

3.4. Bayesian Single-Chemical Associations with Child IQ

Results of Bayesian single-chemical associations using meta-analytically informed priors are presented following the prioritized vs. non-prioritized chemical classification (Table 1 and Table S3). Results are reported for both the overall population (Figure 1 and Table S5) and sex-stratified analyses (Figure 2 and Table S6).

3.4.1. Prioritized Chemicals: BPA, BPS, MEP, MnBP, MiBP and DEHP. Bisphenol A exposure in the third pregnancy trimester was associated with decreased full-scale IQ scores (β : -0.61; 95% Credible Interval (CrI): -1.21, -0.02). In 1-year-old infants (M12), bisphenol A was also negatively associated with full IQ (-1.08; -2.20, 0.08) and visuospatial scores (-1.43; -2.61, -0.28). No interactions with child sex were observed. Bisphenol S was not associated with any IQ subscale.

MEP exposure in the third trimester was associated with lower full IQ (β : -0.57; 95% CrI: -1.00, -0.13) and visual-spatial scores (-1.82; -2.92, -0.73) in the whole population. The inverse association with visual-spatial scores was stronger in girls (-2.53; -4.35, -0.74) than in boys (-1.03; -2.53, 0.50).

MnBP exposure at the third pregnancy trimester was associated with reduced visual-spatial scores (β : -1.93; 95% CrI: -3.73, -0.17) and a marginal trend towards lower working memory (-0.93; -1.96, 0.11). No evident sex-specific associations were observed.

MiBP exposure in the third pregnancy trimester tended to be inversely associated with verbal IQ scores (β : -0.87; 95% CrI: -1.81, 0.03). Sex-stratified analyses showed that this association was stronger in boys (-2.28; -4.42, -0.19) than in girls (-0.80; -2.34, 0.71).

Σ DEHP exposure was not associated with child IQ scores in the whole population. However, sex modified this association (99% probability of posterior distribution mean being different from zero), with second-trimester Σ DEHP

Table 2. Characteristics of Included and Excluded Participants in the SEPAGES Cohort (France, 2014–2017)^a

Characteristic	N	Included N = 380 ^b	Not included N = 104	P-value ^c
Maternal age at conception, years	380	32.4 (30.1, 35.4)	31.2 (28.8, 34.1)	0.003
Maternal BMI before pregnancy (kg/m ²)	379	21.3 (19.7, 23.7)	22.0 (20.0, 24.4)	0.044
Maternal IQ ^d	319	12.0 (10.0, 14.0)	13.0 (9.0, 19.0)	0.698
Breastfeeding (weeks) until week 48	372	26 (17, 43)	18 (6, 26)	<0.001
Mother's anxiety/depression symptoms (HAD)	367	10.0 (7.0, 13.0)	11.0 (8.0, 16.0)	0.006
HOME total score (Family environment)	370	25.0 (23.0, 26.0)	22.0 (21.0, 24.0)	0.059
Parity	380			0.340
Nulliparous		170 (45%)	52 (50%)	
Multiparous		210 (55%)	52 (50%)	
Maternal education	378			0.052
≥Master		222 (59%)	50 (48%)	
<Master		156 (41%)	54 (52%)	
Early-life tobacco exposure ^e	376	120 (32%)	28 (32%)	0.986
Mode of child day care by 1 year of age	331			0.269
Collective day care		117 (35%)	11 (28%)	
Nursery assistant		162 (49%)	18 (46%)	
Other		52 (16%)	10 (26%)	
Child sex	380			0.955
Boys		204 (54%)	54 (54%)	
Girls		176 (46%)	46 (46%)	
Child age at IQ assessment (months)	380	36.9 (36.5, 37.6)	-	-
Neuropsychologist who evaluated the WPPSI	380			-
Neuropsychologist 1		163 (43%)	-	-
Neuropsychologist 2		81 (21%)	-	-
Other Neuropsychologists		136 (36%)	-	-
Full-scale IQ - WPPSI	380	110 (103, 118)	-	-
Verbal IQ - WPPSI	380	113 (104, 120)	-	-
Visual-spatial IQ - WPPSI	380	106 (100, 115)	-	-
Working memory IQ - WPPSI	380	106 (100, 112)	-	-

^aAbbreviations: BMI: Body Mass Index; HAD: Hospital Anxiety and Depression Scale, assessed in mothers during the third trimester visit; HOME: Home Observation for Measurement of the Environment Scale; SEPAGES: Assessment of Air Pollution Exposure during Pregnancy and Effects on Health Cohort; WPPSI: Wechsler Preschool and Primary Scale of Intelligence. ^bn (%); Median (p25, p75). ^cPearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test. ^dIntelligence Quotient measured by the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV). ^eCombined active and passive smoking during pregnancy, and child passive smoking at 1 year of age.

exposure being associated with worse full-scale IQ scores among boys (-1.15; -2.28, -0.02), while associated with improved full-scale IQ (β : 1.93; 95% CrI: 0.30, 3.65) and enhanced visual-spatial scores (β : 3.48; 0.23, 6.73) in girls.

3.4.2. Non-Prioritized Chemicals: Benzophenone-3, Parabens, Triclosan, MBzP, OH-MPHP, DiNP, and DINCH. Benzophenone-3 exposure in the third trimester was inversely associated with working memory (β : -0.77; 95% CrI: -1.59, -0.00) in the whole population.

Σ Parabens exposure in the second trimester was positively associated with full-scale IQ (β : 0.85; 95% CrI: 0.12, 1.60) and verbal IQ scores (0.84; 0.10, 1.60). When analyses were sex-stratified, exposure to Σ Parabens in the third trimester was associated with lower visual-spatial IQ scores in boys (-1.01; -1.84, -0.14), and higher scores among girls (0.97; 0.11, 1.82).

Triclosan exposure during the second and third trimesters of pregnancy was associated with higher verbal IQ scores (β : 0.41; 95% CI: 0.04, 0.78; and β : 0.39; 95% CI: -0.01, 0.78, respectively).

MBzP exposure was not associated with any IQ scale at any time point.

OH-MPHP exposure in the third trimester was associated with higher working memory scores (β : 1.98; 95% CI: 0.09, 3.86) across the entire population.

Σ DiNP exposure was not associated with child IQ scores in either the whole population or sex-stratified analyses.

Σ DINCH exposure was not associated with any IQ scale.

3.5. Mixture Associations

BWQS mixture models showed that, in the third pregnancy trimester, a simultaneous quartile increase in the concentration of each prioritized chemical included in the mixture (BPA, BPS, MEP, MnBP, MiBP and Σ DEHP) was associated with decreased full scale (β : -2.86; 95% CrI: -5.05, -0.91), visual-spatial (-2.79; -5.39, -0.82) and verbal (-1.95; -3.84, 0.00) IQ scores among all children (Figure 3 and Table S7). BPA and MEP showed the highest relative contribution to the mixture association, together accounting for approximately 50% of the mixture weight (Figures S5 and S6). Although these mixture associations were observed in both boys and girls, the inverse associations with full and verbal IQ scores were more evident in boys. No association was observed for the other time points when boys and girls were studied together. However, the sex-stratified analysis suggested that second-trimester exposure to the prioritized mixture was associated with higher child verbal IQ scores, but only among girls (2.53; 0.04, 5.75) and not boys. Σ Parabens, triclosan, and bisphenol S showed higher weights for this latter association (Figures S7 and S8).

When the full mixture was tested in a sensitivity analysis, the negative mixture associations observed in the third trimester

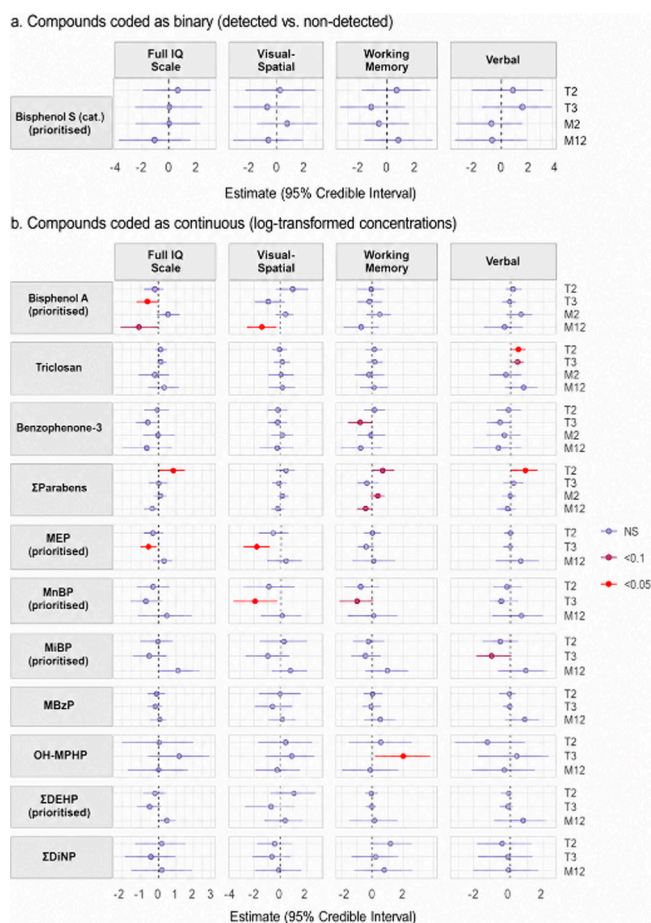


Figure 1. Bayesian single-chemical models accounting for meta-analytic-informed priors. T2: second pregnancy trimester; T3: third pregnancy trimester; M2: month 2 or neonatal exposure window; M12: month 12 or infant exposure window at 1 year of age. a and b shows associations for chemicals coded as binary.

were shrunken towards the null value, while the second-trimester positive association with verbal IQ scores observed in girls was strengthened (Figure 3, Table S7).

3.6. Sensitivity Analyses of Single-Chemical Models

3.6.1. Bayesian Single-Chemical Winsorized Models.

When the top and bottom 1st-percentile exposure concentrations and IQ scores were winsorized, most previous Bayesian single-chemical associations observed in the whole population (Figure S9 and Table S8) and sex-specific analyses (Figure S10 and Table S9) were qualitatively unchanged. While the previously observed isolated protective association for OH-MPHP was attenuated to marginal significance, the deleterious association for benzophenone-3 was strengthened (Table S8).

3.6.2. Bayesian vs. Frequentist Single-Chemical Analyses. Frequentist and Bayesian models provided similar conclusions. However, the meta-analysis-informed priors moderately influenced associations in diverse directions for the whole population (Figure S11 and Table 10) and sex-specific models (Figure S12 and Table 11), especially for those associations that were closer to the null value in frequentist models.

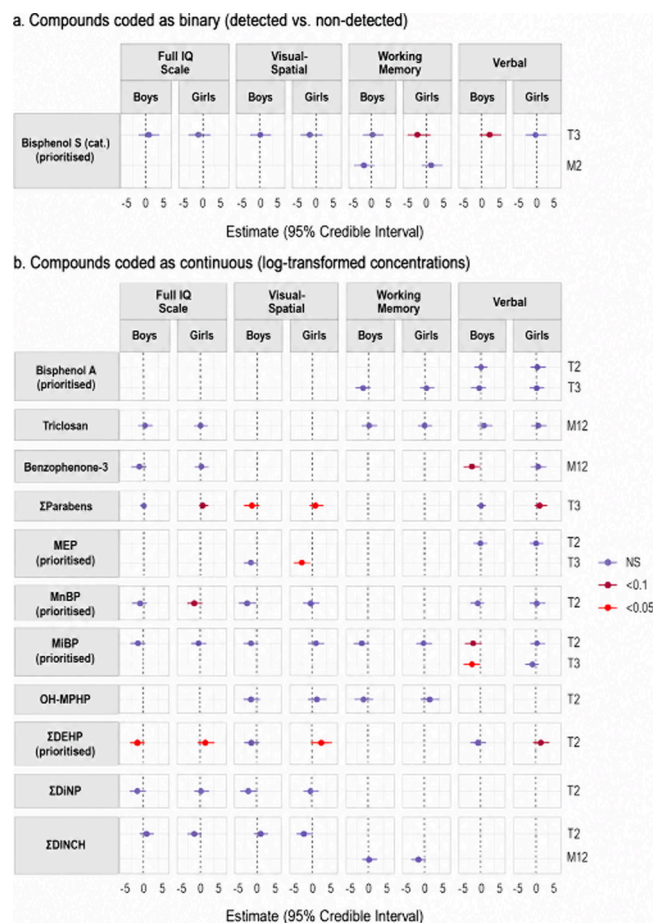


Figure 2. Bayesian single-chemical models incorporating meta-analytic-informed priors, sex-stratified only if the 90% credible interval for the sex interaction term did not include zero. T2: second pregnancy trimester; T3: third pregnancy trimester; M2: month 2 or neonatal exposure window; M12: month 12 or infant exposure window at 1 year of age.

4. DISCUSSION

Our literature search identified two bisphenols (A and S) and four phthalate metabolites (Σ DEHP, MEP, MnBP, and MiBP) as the plasticizer compounds with the highest WoE for effects on child IQ, based on both human and animal toxicological studies. When studied as a mixture, maternal third-trimester exposure to these six chemicals was associated with lower full-scale, visual-spatial, and verbal IQ scores in 3-year-old children. When the non-prioritized chemicals were also included in the mixture, these associations were weakened and became marginally significant. Bayesian single-chemical models also identified prenatal third-trimester exposure to four out of the six prioritized chemicals (BPA, MEP, MnBP, and MiBP) as potential risk factors for reduced IQ scores in children.

Our results showed that each quartile increase in the mixture of prioritized chemicals in the third trimester of pregnancy was associated with an average loss of almost 3 IQ points in offspring. This effect magnitude appears substantial, since the contribution of the plasticizer mixture could be comparable to that of early-life lead exposure.^{109,110} At a public health level, and as learned from known neurotoxins such as lead and methylmercury, even moderate shifts in the population distribution of IQ scores can lead to a significant increase in

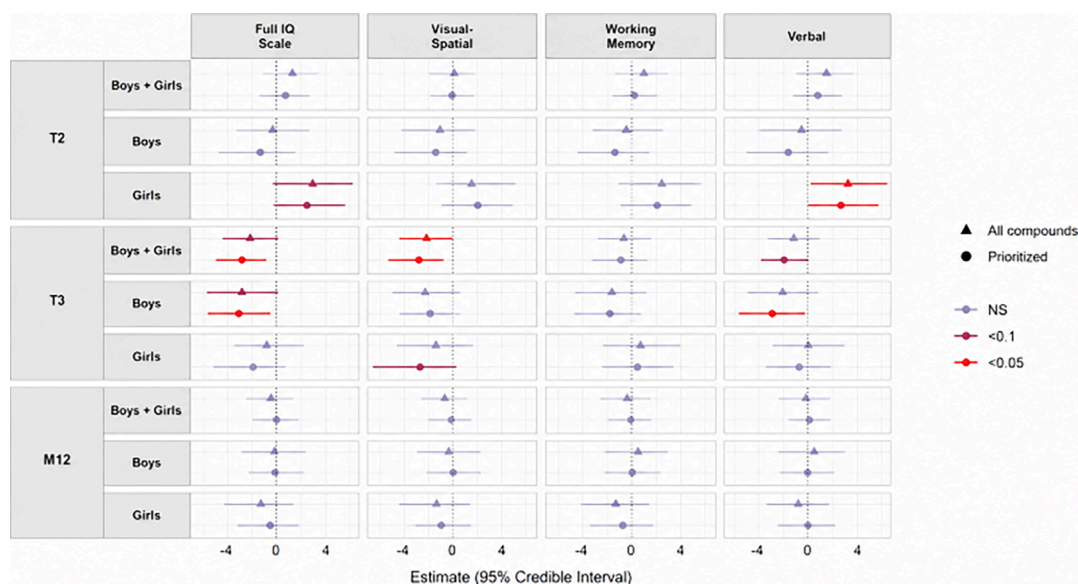


Figure 3. Bayesian weighted quantile sum (BWQS) mixture models considering prioritized chemicals vs. all compounds. T2: second pregnancy trimester; T3: third pregnancy trimester; M12: month 12 or infant exposure window at 1 year of age. Note: Exposure to the mixture at M2 was not performed because, at this period, only phenols, but not phthalates, were available across the entire sample size.

the incidence of intellectual disability cases.^{111,112} The fact that exposure to phenols and phthalates is widespread but modifiable, highlights a great opportunity for primary prevention. Interestingly, our recent work showed that exposure to a very similar evidence-based mixture of plasticizer chemicals (BPA, MEP, MnBP, MiBP, and DEHP metabolites) was prospectively associated with a higher risk of all-cause mortality among U.S. adults.¹¹³ The combined results support that these plasticizer chemicals should be regulated as a mixture rather than as individual chemicals.

4.1. Biological Plausibility

Among synthetic phenols, the evidence was highly supportive for bisphenol A, possibly acting through estrogenic, thyroid, and/or glutamatergic pathways (Table 1).⁴⁷ Our results showed that third-trimester bisphenol A exposure was associated with lower full-scale IQ (in both single-chemical and mixture models). Additionally, we showed for the first time that bisphenol A exposure at one year of age was also associated with lower full-scale and visual-spatial IQ, highlighting the need for studies exploring this sensitive but understudied period. These findings further support the European Commission's ban on bisphenol A in food contact materials.^{12,114,115}

Bisphenol S had scarce data available, but was prioritized based on its structural analogy to bisphenol A, similar *in vitro* biological effects to bisphenol A, and emerging neurotoxicological evidence in rodents (Table 1). Although our study population was exposed to relatively low prenatal urinary BPS concentrations, and we did not observe meaningful associations, expected increases in its use warrant further investigation on the potential neurobehavioral health effects of this replacement.

Among phthalates, the WoE was high for MnBP and DEHP, which may act through anti-androgenic, thyroid, and other pathways (Table 1).^{116,117} Third-trimester MnBP exposure was associated with poorer visual-spatial IQ scores in the whole population, without observing sex-specific associations. Regarding DEHP, we found results that may be consistent with

an anti-androgenic mode of action. Maternal exposure in the second trimester, near the male fetal-derived testosterone peak,¹¹⁸ was associated with reduced full-scale IQ scores only among boys, whereas girls showed improved scores. The toxicological literature (Table S3) also showed adverse DEHP neurological effects in males but not in females.^{43,119}

While the WoE was more limited/heterogeneous, we also prioritized MiBP, as it has shown anti-androgenic activity similar to that of MnBP.⁶⁶ Indeed, our data showed that prenatal MiBP exposure was associated with reduced verbal IQ, especially among boys. MEP can act as an indirect estrogen receptor modulator and alter developmental programming.^{90,92} In Bayesian models, prenatal MEP exposure was associated with reduced full-scale and visual-spatial IQ scores in the overall population. Interestingly, a previous study found that prenatal MEP exposure was associated with lower offspring IQ scores, and that this effect was mediated by a reduction in brain gray matter volume, adding another level of biological plausibility.⁷⁵

Regarding the remaining non-prioritized chemicals, inconsistent and isolated associations were found, including protective trends (triclosan and OH-MPHP), deleterious trends (benzophenone-3), and for parabens, both protective and deleterious associations depending on the exposure window. Together with the limited or mixed WoE available for these chemicals (Table 1), no meaningful conclusions could be drawn, suggesting that additional studies are needed to clarify potential associations.

Concerning the associations observed with higher IQ scores, they tended to cluster within the second-trimester exposure window, including $\sum$ Parabens, triclosan, and $\sum$ DEHP. Indeed, sex-stratified models suggested that second-trimester exposure to the mixture was associated with higher child verbal IQ scores only among girls, and this association was driven by non-prioritized chemicals such as $\sum$ Parabens and triclosan. Although these findings should be interpreted with caution, alterations in the estrogen-androgen balance can differentially affect sexually dimorphic brain development in males and females.¹²⁰ Since human female fetuses tend to exhibit earlier

structural maturation of language-related brain areas than males starting in the second trimester,^{121,122} estrogens increase verbal fluency,¹²³ and parabens and triclosan are estrogenic chemicals (Table 1), this association could be interpreted as an exacerbation of sexually dimorphic verbal abilities among girls. Although this potential explanation warrants further validation, rodent toxicological studies have shown that EDCs and EDC mixtures can increase or decrease sexually dimorphic brain areas and behaviors in a chemical-, sex-, and timing-dependent manner.^{120,124}

4.2. Implications of the Prioritization and Meta-Analytic-Informed Approaches

Relying on prior knowledge to inform statistical analyses offers several advantages. First, selecting the chemicals to include in a mixture model based on their WoE may reduce noise and strengthen the signal compared to an agnostic approach that includes all measured chemicals. This was supported by our findings, which showed stronger associations for the prioritized mixture when associations were in the expected direction.

Results from single-chemical models were also consistent with the defined WoE prioritization. We observed adverse associations for five out of the six prioritized chemicals, while associations for non-prioritized chemicals were generally null, mixed or not in the expected direction. Compared to classical agnostic correction for multiple comparisons, which disproportionately increases type 2 over type 1 errors for high-WoE chemicals, our WoE-based approach may decrease type 1 error (i.e., false positives) without affecting sensitivity.¹²⁵ Although we could have applied a multiple-comparison correction to non-prioritized chemicals,¹⁸ from our point of view, the gathered WoE made such a correction unnecessary, as it showed that the evidence was limited and inconsistent.

The impact of the Bayesian modeling using meta-analytic priors was variable. In some cases, it strengthened negative associations (e.g., bisphenol A and full-scale IQ), while in others it tended to pull estimates towards the null (e.g., MEP and full-scale IQ). Overall, this approach increased the external validity of our results. Although our evidence-based approaches offered numerous advantages, we also encountered some shortcomings related to natural disparities in data availability across chemicals. Meta-analytic priors were available for the 8 chemicals more frequently investigated in previous epidemiological studies. For the remaining 5 chemicals, we relied on single-study or weakly informative priors. Another limitation of the WoE definition is that novel chemicals are more likely to be non-prioritized simply due to limited data availability. This issue was considered when evaluating the evidence, as exemplified by bisphenol S (limited evidence but prioritized based on emerging toxicological data and structural analogy to bisphenol A). In any case, this limitation will tend to self-correct over time in parallel with the generation of new evidence.

4.3. Strengths and Limitations

To our knowledge, this is the first study to implement a meta-analytically informed Bayesian approach in environmental epidemiology. This approach increased the confidence and external validity of the results. The WoE prioritization also increased the biological plausibility of our analysis and helped to interpret the findings. The SEPAGES cohort is one of the first to pool multiple repeated urine samples, resulting in substantially improved exposure estimates. The intensive biospecimen collection comes at the cost of a modest sample

size. However, our improved exposure characterization is expected to provide substantially greater statistical power than in previous similarly sized cohorts that relied on a single or a few spot urine samples. Apart from pregnancy, we investigated exposure during the neonatal and infancy periods, two sensitive windows of exposure that have rarely been investigated before. It should be noted that phthalate metabolites could not be measured in the entire neonatal sample due to budget limitations; consequently, we may have missed potential associations during this period. Although we accounted for the most important known covariates based on causal knowledge, unmeasured confounding cannot be fully ruled out. However, the fact that our Bayesian models accounted for meta-analyses of previous studies with different confounding structures argues against this concern. Although children's intelligence was assessed at 3 years of age using a valid and internally consistent instrument, younger children show greater individual variability in IQ scores over time.¹²⁶ While relevant at the individual level, this concern is expected to be less pronounced in population-based studies that assess average changes in IQ scores. Additionally, cognitive abilities exhibit the highest reproducibility over time compared with other neurobehavioral domains.⁵² Notwithstanding, future cognitive re-evaluations in SEPAGES's children will help examine the long-term effects of chemical plasticizers.

CONCLUSIONS

Relying on an improved exposure assessment protocol and a novel statistical approach integrating *a priori* knowledge, maternal third-trimester exposure to a mixture of prioritized chemicals frequently used as plasticizers (BPA, BPS, MEP, MnBP, MiBP, and Σ DEHP) was associated with reduced IQ scores at 3 years of age. Our literature review provided a higher WoE for the effect of these prioritized chemicals on IQ, reinforcing the biological plausibility of these findings. Associations were also observed with exposure to individual chemicals in the third pregnancy trimester (BPA, MEP, MnBP, and MiBP). These findings provide compelling evidence that early-life exposure to specific synthetic phenols and phthalate metabolites, as well as their mixture, represents a public health concern for children's cognitive development. There is a need to keep exposure levels as low as practicable and develop policies and interventions to protect children's neurodevelopment from the effects of plasticizer mixtures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/EHP.6c00297>.

Excel file reporting the quality evaluation and estimates of the studies included in the meta-analysis (XLSX)

Figures, tables, and discussion as detailed in the main text (PDF)

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Notes

Except for the graphical abstract, the authors did not use artificial intelligence tools in the methods or manuscript preparation.

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