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Full length article

Early-life exposure to organophosphate esters and child neurodevelopment in the French national birth cohort

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ABSTRACT

Organophosphate esters (OPEs) are ubiquitous flame retardants and/or plasticizers, raising concerns regarding their possible neurodevelopmental toxicity.

We aimed to explore association between pre- and post-natal exposure to OPEs and cognitive abilities among 3.5-year-old children.

We included 381 mother-child pairs from the French ELFE national birth cohort. Pre- and post-natal exposures were estimated using concentrations of 9 OPEs measured in the hair of mothers collected at birth and children at age 3.5. Children's cognitive development was evaluated using the Picture Similarities Test (PST) from the British Ability Scale. Analyses were weighted in order to transpose results to French births in 2011. For each OPE, the association with PST scores was assessed by linear regression accounting for DAG-selected adjustment covariables.

The only observed association between prenatal exposure to OPEs and PST score was a decrease of 4.5 points (95 %CI: -8.8, -0.3) among the 25 % of mothers having the highest hair-concentrations of tri-n-butyl phosphate (TBP) versus the 25 % having the lowest ones. Regarding childhood exposure, we observed a decrease (-1.9 points, 95 %CI: -3.0, -0.8) in PST score per twofold increase in children's hair-concentrations of ethylhexyl diphenyl phosphate (EHDPP). Decreased scores were also observed for higher childhood exposure levels for triphenyl phosphate (TPHP). An increase in the PST score was observed for the intermediate category of childhood exposure levels for tris(2-chloropropyl) phosphate (TCPP).

While no adverse associations were observed for several OPEs, neurodevelopmental health concerns were raised in the present study for three ubiquitous OPEs, TBP, TPHP and EHDPP.

1. Introduction

Organophosphate esters (OPEs) are chemical compounds added to many consumer products during the manufacturing process – mostly as flame retardants or plasticizers (Kemmlin et al., 2003; van der Veen and de Boer, 2012). They are widely used – for instance in cars, electronics and furniture (Stapleton et al., 2009), nail polishes and textiles (van der Veen and de Boer, 2012). Since OPEs are not chemically bound to products, they are released into the environment via volatilization, leaching and/or abrasion. Thus, they can be found in biota, sediment, soil and water (Pantelaki and Voutsas, 2021), as well as in indoor

environments (Chupeau et al., 2020; Plaisance et al., 2022). OPEs are a ubiquitous presence in the human biological matrices of the general population, including among vulnerable populations such as pregnant women and children (Chupeau et al., 2020; van der Veen and de Boer, 2012; Wei et al., 2015). OPEs are frequently measured in human urine and hair samples, and have also been detected in both human placenta (Ding et al., 2016) and breast milk (Beser et al., 2019; Sundkvist et al., 2010).

Experiments on zebrafish have shown that several OPEs have developmental neurotoxic effects, or modify locomotor activities. Neurodevelopmental toxicity studies on mammals are less consistent, but

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the compilation of recent evidence does suggest various possible modes of action other than the disruption of acetylcholinesterase activities, which is mainly relevant to organophosphate pesticides (Patisaul et al., 2021). It includes disruption of cholinergic and glutamatergic systems, dysregulation of mitochondrial function and neuroinflammation or endocrine disruption. The question of the possible role, during a critical period of development (such as during pregnancy or during the first years of life) of OPE exposure on human neurodevelopmental health therefore needs to be addressed in a comprehensive way.

Nine high-quality epidemiological studies exist; these suggest that prenatal exposure to OPEs has an adverse impact on children's cognition, and in particular, on language ability between the ages of 2 and 3 years (Doherty et al., 2019), fine motor function before the age of 3 years (Doherty et al., 2019; Hernandez-Castro et al., 2024; Zhou et al., 2024), various executive functions (including working memory and inhibition abilities) at the age of 3–4 years (Hall et al., 2023) or 12 years (Vuong et al., 2024), overall development during the first 2 years of life, encompassing cognition, language and social development (Liu et al., 2021; Zhou et al., 2024), and full-scale intelligence at the age of 3–7 years (Castorina et al., 2017; Lu et al., 2024). One other study did not confirm the adverse association between prenatal exposure to OPEs and intelligence score among 8-year-old children (Percy et al., 2021). There is only limited evidence of any adverse association of OPE exposure during early childhood with cognition (Percy et al., 2022; Rosolen et al., 2023). Most of the seven studies that have investigated pre- or post-natal OPE exposure in association with child behavior, observed possible increased behavioral disorders, including hyperactivity or aggressivity (Lipscomb et al., 2017; Doherty et al., 2019; Crawford et al., 2020; Choi et al., 2021; Percy et al., 2023; Hall et al., 2023; Hernandez-Castro et al., 2023). Most of these studies assessed exposure by means of urinary concentrations of OPE metabolites, which were measured in one or more maternal samples collected during pregnancy. Because of the relatively short biological half-lives of organophosphate esters, the urinary concentrations of OPE metabolites showed however short-term variations conducting to only low to moderate reproducibility for exposure assessment over the course of a pregnancy (Bastiaensen et al., 2021; Hoffman et al., 2014). Moreover, only few of these association studies took into account the possible influence of the early-life exposure to the brominated flame retardants, the polybrominated diphenyl ethers (BDE) (Percy et al., 2022; Percy et al., 2023), for which there are strong concern over their developmental neurotoxicity (Herbstman and Mall, 2014) and that some OPEs have replaced (Chupeau et al., 2020).

Human hair is a non-invasive matrix having numerous practical advantages, including simplicity and cost-effectiveness of sampling, transport and storage, sample stability, in addition to the ability of its internal structure to store chemicals present in the bloodstream (Faÿs et al., 2023; Lallmahomed et al., 2024). It has thus been postulated that hair measurements capture the cumulative exposure over a long-term period of several weeks or months (Ren et al., 2024). While there is still no evidence that hair-measurement of OPEs reflects the internal dose, the suitability of hair measurements for exposure assessment of some non-persistent compounds including organophosphate esters used as pesticides, has already been supported by animal models comparing hair concentrations with administered doses (Appenzeller et al., 2017; Faÿs et al., 2023).

Within the French ELFE national birth cohort, we used hair-concentration measurements to explore the association between prenatal exposure to multiple OPEs and cognition at 3.5 years, taking the prenatal exposure to BDE and childhood exposure to OPEs into account.

2. Materials and methods

2.1. Population

ELFE (“*Etude longitudinale française depuis l'enfance*”) is the French national birth cohort, which uses a multidisciplinary approach to study

the determinants of the development, health and socialization of children from birth to adulthood (Charles et al., 2020). The cohort is conducted using a two-stage random stratified sampling design, stratified for maternity units and for selected days. A total of 349 maternity units were randomly selected from across metropolitan France, and the children were recruited at birth from the 320 maternity units that agreed to participate. Recruitment took place over 25 days in 2011, grouped into four periods over the year (April 1–April 4, June 27–July 4, September 27–October 4 and November 28–December 5). Inclusion criteria were single or twin live births at ≥ 33 weeks of gestation, mother ≥ 18 years old with no plan to leave metropolitan France within 3 years, and informed consent signed by either both parents or just the mother, with the father being informed of his right to deny consent for participation. A total of 18,329 mother-child pairs were recruited. Weights calculated from cohort sampling and non-response correction were then estimated to achieve representativeness of the French national population of families with pregnant women in 2011 (Charles et al., 2020).

Biological samples, including hair samples, were collected at birth from women at a subsample of 154 maternity units (of 211 that were eligible). These maternity units were selected for their expected number of deliveries (average > 500 deliveries per year) and their proximity (< 150 km) to the biological treatment and storage units made available by the French blood agency. Biological samples were available for women included during the last three periods of recruitment (from June to December in 2011). 2956 maternal hair samples were collected. Data concerning socio-demographic status, family life, parental health, behavior and life values were collected in the course of a face-to-face interview at birth (Charles et al., 2020).

When the children were 3.5 years old, data concerning day care and school as well as child environmental exposures were collected via telephone. At this stage of the follow-up, home visits were specifically organized to assess the children's cognitive function. Non-invasive biological samples (including hair) were collected from 2044 children for whom maternal biological samples had already been collected at birth. Assuming a hair growth rate of 1 cm per month in humans, we selected all women who had a length of hair strand more than 7 cm, a mass of hair strand ≥ 25 mg to ensure detection, and who did not live in the north-eastern or south-western areas of France (for whom hair samples were not available). OPE concentrations in the first 7 cm (proximal) of maternal hair samples allowed estimation of integrated exposure during the 7 months prior to delivery, which represent an estimate for prenatal exposure. A total of 397 of these women had participated, with their child, in the neurodevelopmental follow-up at 3.5 years old. Of these, 265 had a child's hair strand whose mass was ≥ 25 mg (length limited to 10 cm and with a minimum of 2 cm). Childhood exposure was estimated by the OPE concentrations measured in these hair samples, and we assumed that this reflected integrated exposure over the last 2–10 months prior to hair collection. We excluded seven mothers and three children for whom (due to analytical issues) no concentration was available for at least one chemical. We also excluded two mothers and five children for whom cohort-weighting data were not available at birth and at 3.5 years, respectively. We also excluded families who reported epilepsy or convulsive seizure during the child's early years ($n = 1$), and families with children who had undergone the neuropsychological testing without their prescription glasses, which would have been necessary to see some of the test images clearly ($n = 6$).

Lastly, our main sample comprised 381 families in which the child's neuropsychological development had been assessed at 3.5 years of age and for which prenatal exposure measurements existed – including a subsample of 250 families with additional childhood exposure measurements.

2.2. Hair samples collection and chemical analysis for OPE and brominated flame retardants

Hair strands from mothers and children were cut, using scissors, in

the occipital region (behind the head), at the hairline, then placed in individual envelopes and shipped to the biobank for storage at ambient temperature (Béranger et al., 2018). Hair samples were analyzed by the LERES (Environment and Health Research Laboratory) at the French School of Public Health (EHESP, Rennes, France). A detailed description of the analytical method used (including quality assurance and quality control) is available elsewhere (Chupeau et al., 2022; Yon et al., 2022) and is briefly described below. Hair samples were ground using a mixer mill MM400 (Retsch GmbH, Haan, Germany). Target chemicals were then extracted from the resulting hair powder by pressurized liquid extraction (PLE), using the ASE (Accelerated Solvent Extractor) 350 (Dionex Corporation, Sunnyvale, USA). The organic extracts obtained were concentrated to 0.5 mL using an N-EVAP 111 Organomation Nitrogen Evaporator and then transferred into 1.5 mL amber glass vials prior to analysis by GC/MS/MS using a 7890B GC system coupled to a 7010B GC/MS Triple Quad (Agilent Technologies, Santa Clara, California, United States). Our previous work on these data (Chupeau et al., 2022) has documented pre- and post-natal exposure to 15 OPEs of children born in France in 2011 based on a prioritization ranking (Niang et al., 2019): diethyl ethyl phosphonate (DEEP), ethylhexyl diphenyl phosphate (EHDPP), tris(2-butoxyethyl) phosphate (TBEP), tri-n-butyl phosphate (TBP), tris(2-chloroethyl) phosphate (TCEP), tris(2-chloropropyl) phosphate (TCPP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), tris(2-ethylhexyl) phosphate (TEHP), triethyl phosphate (TEP), tri-m-cresyl phosphate (TMCP), trimethyl phosphate (TMP), tri-o-cresyl phosphate (TOCP), tri-isopropyl phosphate (TiPP), triphenyl phosphate (TPHP) and trixylenyl phosphate (TXP). In this study we focus on 9 OPE parent compounds with a detection frequency higher than 25 %: EHDPP, TBEP, TBP, TCEP, TCPP, TDCPP, TEP, TMCP and TPHP. The brominated flame retardants BDE 209 (BDE congener with the highest volume of use in Europe) and BDE 47, were also measured in maternal hair samples. For some compounds, multiple LODs were provided: the smallest value corresponded to the laboratory validated LOD and the others were slightly higher than the validated LOD and concerned a small proportion of hair samples (<20 %) for which there was smaller available hair mass for analysis.

2.3. Cognition assessment

The children's non-verbal cognitive abilities at 3.5 years of age were assessed using the Picture Similarities subtest from the second edition of the British Ability Scale (The ELFE Survey Protocol). The Picture Similarities Test assessed each child's abilities as follows: non-verbal problem solving (inductive reasoning), visual perception and analysis, assigning meaning to a picture, developing and testing hypotheses, and using verbal mediation. The test was carried out using a set of 33 single-picture and 33 4-picture boards. Each 4-picture board was shown to the child along with the corresponding card, which showed a 5th picture. The child was asked to indicate which image on the board was associated with the image on the card. The first five boards were training boards. The test was stopped as soon as the child had reached six errors on eight consecutive boards. The score was calculated by adding up the number of correct answers (1 point per correct answer). The Picture Similarities Test was studied as a continuous variable. A low score may also partially reflect impulsivity (responding without checking the answer) (The ELFE Survey Protocol).

2.4. Statistical analysis

Initial weights were available for both the maternity surveys (prenatal exposures) and the 3.5-year surveys (childhood exposures). There was then a 3-step weighting process: first, we created Response Homogeneity Groups (RHGs) to reduce non-response bias. To do this we obtained each participant's probability of inclusion in our study. The inverse of this probability was then multiplied by the initial weight from the ELFE cohort sampling. These weights were calibrated to reduce the

variance of estimators with respect to the French population, using the margins of the National Perinatal Survey (ENP) (Blondel and Kermarrec, 2011). All the results were weighted to facilitate transposition of the results to the national French population of families with pregnant women in 2011. The unweighted results are also provided in the [supplementary materials](#).

Associations between OPE hair-concentrations and the Picture Similarities Test score were assessed by linear regression adjusted for covariates. One model per OPE was conducted. For prenatal exposure, the association was studied using the main sample. For childhood exposure, association was reported on the subsample and prenatal exposure to the corresponding OPE was simultaneously included in the model.

The left-censored OPE and BDE concentrations up to 30 % of censored data measured in hair samples were imputed (Helsel, 2011). For each chemical, we used the maximum-likelihood estimation method (MLE) to estimate the parameters of the lognormal probability distribution (Helsel, 2011). These estimates were based on the set of measurements with the lowest LOD for OPEs with multiple LODs (this set constituting at least 80 % of the sample size). Then, for each LOD, censored data were imputed by random values between zero and the LOD from this estimated distribution (Jin et al., 2011). Imputed concentrations were then log₂-transformed to obtain a normal distribution and avoid the influence of outliers and used as continuous in the regression models. The linearity of the associations was then tested using the likelihood ratio test comparing two embedded models with exposure variable in quartiles considered as categorical or ordinal (Clayton and Hills, 1996). When the p-value of this test was greater than 5 %, we considered that the linearity assumption was validated. This was the case for all OPEs, with the exception of TPHP in children and TBP and TPHP in mothers, for which concentrations were therefore categorized in quartiles in the final models. OPEs with 50–70 % of detected values were transformed into exposure variables with three modalities (<LOD; LOD to the median value; >median value). OPEs with less than 50 % of detected values were transformed into binary exposure variables (detected; not detected).

Covariates were determined using a Directed Acyclic Graph, constructed within the research team (following the several meetings it took to achieve consensus; [Supplementary Data Fig. S1](#)). All models were thus adjusted using the same set of covariates, collected at birth or updated at the age of 3.5 years old of the children. These included: pre-pregnancy BMI (<18.5, 18.5–<25, 25–<30, >30 kg/m²), maternal and paternal education level during the pregnancy (high school education or lower, 2 years of university education, more than 2 years of university education), income, maternal age at delivery, BDE209 maternal hair-concentrations (log₂-transformed) and BDE 47 detection in maternal hair sample (yes/no). As the score of the Picture Similarities Test used in our study was not standardized by age, we decided to systematically adjust all our models for the child's age at the time of testing. All covariates had less than 5 % missing data; they were thus simply imputed by the mode or the median.

Models without adjustment on BDE concentrations (due to high correlations between some OPEs and BDE 209 hair measurements) were performed as sensitivity analyses. Associations between prenatal exposure to OPEs and the Picture Similarities Test score were also measured in the subsample of families having both prenatal and childhood exposure measurements in order to report possible heterogeneous findings due to smaller sample and its corresponding weighted approach. Associations between childhood exposure to OPE and Picture Similarities Test scores were also tested without controlling for prenatal exposure to OPE or BDE.

Finally, as complementary analyses, associations between prenatal exposure to BDEs and the Picture Similarities Test score were assessed, with similar covariable adjustment, both with and without taking into account OPE exposure.

SAS software 9.4 was used to impute censored OPE data. The

Table 1
Characteristics of the pregnant women and children included in our study (unweighted results) and in the French population as a whole in 2011 (weighted results).

	Weighted results (%)			Unweighted results (%)		
	Population of French pregnant women in 2011 ^a	Subpopulation with a 3.5-year-old child ^b	Main sample (n = 381)	Population of French pregnant women in 2011 ^a	Subpopulation with a 3.5-year-old child ^b	Main sample (n = 250)
Mother's age at delivery (years)	31.2 (4.8)	31.6 (4.8)	31.8 (4.8)	31.2 (4.8)	31.6 (4.8)	32.1 (4.8)
Pre-pregnancy BMI	8.9	7.3	8.4	8.9	7.3	7.2
	18.5-<25	62.3	69.3	62.3	66.9	71.6
	25-<30	14.3	14.4	14.3	12.4	14.0
	30 or more	14.6	13.4	14.6	13.4	7.2
Mother's educational level at delivery	High school education or lower	44.1	42.2	44.1	42.2	22.4
	2 years of university education	20.5	17.3	20.5	17.3	25.2
	More than 2 years of university education	35.5	40.5	35.5	40.5	52.4
Father's educational level at delivery	High school education or lower	58.9	56.4	58.9	56.4	44.0
	2 years of university education	16.0	16.1	16.0	16.1	20.0
	More than 2 years of university education	25.0	27.4	25.0	27.4	36.0
Monthly household income at delivery (euros)	3419 (1876)	3558 (2057)	3720 (1876)	3419 (1876)	3558 (2057)	3873 (2057)
Sex of child	Boy	53.3	52.1	53.3	52.1	40.4
	Girl	46.8	47.9	46.8	47.9	59.6
Age of child (Months) at the testing	Mean (s.d)	41.6 (1.6)	41.5 (1.6)	41.6 (1.6)	41.5 (1.6)	41.4 (1.6)
Picture Similarities Test score	Mean (s.d)	69.4 (14.5)	69.3 (14.5)	69.4 (14.5)	69.3 (14.5)	69.1 (14.5)

s.d: standard deviation; Missing data imputed by mode or median: in the Main sample, n = 4 for pre-pregnancy BMI, n = 3 for mother's education, n = 19 for father's education, n = 2 for age of the child; in the Subsample, n = 2 for mother's education, n = 10 for father's education.

Weighting process of the cohort calibrated according to the National Perinatal Survey (Blondel and Kermarrec 2011), allowing it to reflect ^(a) the national French population of families including pregnant women in 2011 and ^(b) the subpopulation of these families having a 3.5-year-old child in 2014.

CALMAR macro available in SAS software 9.4 was used for calibration (Deville et al., 1993). Weighted results were calculated using the SURVEY package from R software V4.0. To produce the variance estimators and confidence intervals, the sampling design was treated as a multi-stage one, with selection of maternity hospitals at the first stage according to with-replacement stratified simple random sampling. For variance estimation, a finite population correction was applied in the first-stage strata, but calibration was not taken into account.

2.5. Ethical issues

Ethical approvals for data collection in maternity units and for each data collection wave during follow-up were obtained from the French national advisory committee on information processing in health research (CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé), the national data protection authority (CNIL: Commission Nationale Informatique et Liberté) and, in case of invasive data collection such as biological sampling, the committee for the protection of persons engaged in research (CPP: Comité de Protection des Personnes). The ELFE study was also approved by the national committee for statistical information (CNIS: Conseil National de l'Information Statistique) (Charles et al., 2020).

3. Results

The characteristics of both the main study sample (n = 381; unweighted) and the eligible population of mothers who gave birth in France in 2011 (N = 18,329, weighted results) are shown in Table 1, as well as their corresponding subpopulation for which childhood exposure was available (n = 250 and N = 11,706, respectively). The mean age of mothers who gave birth in France in 2011 was 31.2 years at delivery, and 62.3 % of these mothers had a normal pre-pregnancy BMI (between 18.5 and 25 kg/m²). 35.5 % of mothers had more than 2 years of higher education, while for more than half of the fathers, educational attainment was below high school graduation level. The mean monthly household income was 3419 euros. Picture Similarities Test scores for the 3.5-year-old children was normally distributed, with a mean score of 69.4. There were slightly more boys than girls.

OPE concentrations measured in the hair samples of mothers at birth and 3.5-year-old children, respectively, are presented in Table 2. Five OPEs were detected in >90 % of maternal samples (TPHP, TDCPP, TEP, EHDPP, TBP) while three of them were detected in >90 % of the children's hair samples (TPHP, TDCPP, EHDPP). The highest median concentrations were observed for TCPP in both mothers (265 ng/g) and children (246 ng/g). Median concentrations measured in child hair samples were twice as high as those measured in maternal hair samples for EHDPP, TDCPP and TBEP. For each OPE, no correlation was observed in hair-concentrations between mothers and children, with the exception of a weak positive correlation for TCPP, TBEP and TEP (Supplementary Data Fig. S4). More detailed results on correlations are provided in supplementary data (Fig. S2, Fig. S3) and in our previous paper (Chupeau et al., 2022).

The associations between prenatal exposure to OPEs and Picture Similarities Test score are shown in Table 3. After adjusting for covariates, no association was statistically significant. We observed a possible decrease of 4.2 points (95 %CI: -8.6, 0.1) on the Picture Similarities Test score among the 25 % of mothers having the highest hair-concentrations of TBP (4th quartile) compared to the 25 % having the lowest hair-concentrations (1st quartile), which was statistically significant without adjustment on BDE hair-concentrations: -4.5 points (95 % CI: -8.8, -0.3) (Supplementary Data Table S1). In general, sensitivity analyses without adjustment on BDE hair-concentrations and using unweighted analyses provided similar results (Supplementary Data Table S1 and Table S2).

In the subpopulation for which child hair measurements are also available, we reached different conclusions for TBP and TBEP

Table 2

Hair-concentrations (ng/g) for mothers in 2011 and for children aged 3.5 years in 2014–2015 in France (weighted results).

	CAS number	Maternal hair-concentrations		Child hair-concentrations	
		%>LOD*	Median (IQR)	%>LOD*	Median (IQR)
EHDPP	1241-94-7	92.1	35 (22–58)	94.8	78 (39–217)
TBEP	78-51-3	25.2	<LOD (<LOD-37)	50.0	53 (<LOD-116)
TBP	126-73-8	91.9	35 (26–45)	46.4	<LOD (<LOD-26)
TCEP	15-96-8	60.9	14 (<LOD-23)	68.6	15 (<LOD-28)
TCPP	13674-84-5	73.5	264 (203–398)	65.5	246 (<LOD-399)
TDCPP	13674-87-8	95.3	47 (20–99)	97.2	110 (41–221)
TEP	78-40-0	95.0	51 (22–79)	67.5	13 (<LOD-18)
TMCP	563-04-2	78.0	10 (5–23)	38.5	<LOD (<LOD-4)
TPHP	115-86-6	99.5	63 (38–109)	100	77 (44–14)

* Percentages of values above LOD were unweighted; IQR: Inter-Quartile Range.

(Supplementary Data Table S3). No association was suggested for TBP. A decrease of 7.4 points (95 %CI: –12.3, –2.4) on the Picture Similarities Test score in association with the detection of TBEP in maternal hair samples was observed. Adding the childhood exposure variables in the models did not substantially change the estimates (Supplementary data Table S3). Median OPE concentrations measured in hair samples of mothers were similar in the population and the subpopulation (results not shown).

When investigating associations with childhood exposure to OPEs (Table 4), we observed a statistically significant decrease in the Picture Similarities Test score per twofold increase in child EHDPP hair-concentration (–1.9 points, 95 %CI: –3.0, –0.8). Decreased scores were also observed for higher childhood exposure levels for TPHP, but with a non-linear relationship (–8.3 points, 95 %CI: –14.9, –1.7; –2.0 points, 95 %CI: –7.3, 3.3 and –8.2 points, 95 %CI: –12.3, –3.9, for the 2nd, the 3rd and 4th quartile respectively, in comparison with the 1st quartile). An increase in the Picture Similarities Test score was also observed for the intermediate childhood TCPP exposure levels (+5.4 points, 95 %CI: 1.1, 9.6).

In the sensitivity analyses in which no adjustment on maternal hair-concentrations of OPEs or BDEs was made, all these results were similar (Supplementary Data Table S4). The unweighted analyses provided estimates in the same direction, with lower magnitude and non-statistically significant, (Supplementary Data Table S5): for log2-EHDPP, –1.0 point (95 %CI: –2.1, 0.1); for TPHP, –1.6 points (95 %CI: –7.4, 4.1), –2.1 points (95 %CI: –7.7, 3.5) and –3.7 points (95 %CI: –8.9, 1.4), for the 2nd, 3rd and 4th quartile respectively, in comparison with the 1st quartile; and for intermediate childhood exposure levels for

Table 3

Association between OPE prenatal exposure and Picture Similarities Test score (Weighted analyses; ELFE cohort, France, 2011).

OPE concentration (ng/g)	β	95 %CI
EHDPP log2-scale	0.056	(–0.98, 1.09)
TBEP Not Detected	Ref	
TBEP Detected (>50 ng/g)	–1.02	(–4.37, 2.33)
TBP Quartile 1: <27 ng/g	Ref	
TBP Quartile 2: 27–35 ng/g	2.68	(–1.30, 6.67)
TBP Quartile 3: 35–45 ng/g	2.79	(–0.94, 6.52)
TBP Quartile 4: >45 ng/g	–4.22	(–8.57, 0.13)
TCEP Not Detected	Ref	
TCEP Detected value \leq median: 10–18 ng/g	0.78	(–2.87, 4.43)
TCEP Detected value > median: 18 ng/g	–2.11	(–6.21, 1.99)
TCPP log2-scale	–0.12	(–1.59, 1.35)
TDCPP log2-scale	0.0004	(–0.90, 0.90)
TEP log2-scale	–0.88	(–2.16, 0.39)
TMCP log2-scale	–0.05	(–0.74, 0.63)
TPHP log2-scale	0.56	(–0.31, 1.42)

Weighted linear regression model adjusted on pre-pregnancy BMI, maternal education level and paternal education level during pregnancy, income and mother's age at delivery, and BDE 209 maternal hair-concentrations (log2-transformed), BDE 47 detection in maternal hair sample and age of the child at the testing.

TCPP, +3.0 points (95 %CI: –0.6, 6.7).

BDE 47 was detected in 46.2 % of maternal hair samples. BDE 209 was detected in 100 % of maternal hair samples, with a median concentration of 8 ng/g (Inter-Quartile Range: 4.4–15.8). None of the maternal BDE hair-concentrations was statistically significantly associated with the score of the Picture Similarities Test in the main population (for BDE 47, detection vs non-detection: +2.7 points, 95 %CI: –0.8, 6.1; for BDE 209, the 2nd, the 3rd and the 4th quartile compared to the 1st quartile: –1.7 points (95 %CI: –7.4, 4.1), +2.0 points (95 %CI: –1.7, 5.6) and –2.5 points (95 %CI: –7.7, 2.7) respectively).

4. Discussion

This study explored the relationships between prenatal and childhood exposure to OPEs and non-verbal cognitive abilities at the age of 3.5 years in the French population, using the ELFE cohort.

Our results suggest that higher exposure to TBP during pregnancy and higher exposure to EHDPP and TPHP during childhood prior to the age of 3.5 years were associated with lower Picture Similarities Test scores in 3.5-year-old children, after adjustment for potential confounders. The effect sizes observed would represent a decrease of

Table 4

Association between OPE childhood exposure and Picture Similarities Test score adjusted on prenatal exposure to the corresponding OPE (Weighted analyses; ELFE cohort, France, 2011).

OPE concentration (ng/g)	β	95 %CI
EHDPP log2-concentration	–1.86	(–2.95, –0.76)
TBEP Not Detected	Ref	
TBEP Detected value \leq median: 50–140 ng/g	–3.54	(–8.07, 0.98)
TBEP Detected value > median: 140 ng/g	–2.20	(–6.74, 2.35)
TBP Not Detected	Ref	
TBP Detected (>20 ng/g)	2.08	(–2.20, 6.35)
TCEP Not Detected	Ref	
TCEP Detected value \leq median: 10–20 ng/g	–1.64	(–7.83, 4.56)
TCEP Detected value > median: 20 ng/g	–4.01	(–8.45, 0.42)
TCPP Not Detected	Ref	
TCPP Detected value \leq median: 200–371 ng/g	5.36	(1.10, 9.62)
TCPP Detected value > median: 371 ng/g	–0.79	(–5.38, 3.80)
TDCPP log2-concentration	–0.56	(–1.83, 0.71)
TEP Not Detected	Ref	
TEP Detected value \leq median: 10–17 ng/g	2.36	(–2.98, 7.70)
TEP Detected value > median: 17 ng/g	5.12	(–0.59, 10.82)
TMCP Not Detected	Ref	
TMCP Detected (>5 ng/g)	–2.12	(–6.16, 1.93)
TPHP Quartile 1: <44 ng/g	Ref	
TPHP Quartile 2: 44–77 ng/g	–8.35	(–14.9, –1.72)
TPHP Quartile 3: 77–143 ng/g	–2.01	(–7.28, 3.26)
TPHP Quartile 4: >143 ng/g	–8.16	(–12.3, –3.95)

Weighted linear regression model adjusted on pre-pregnancy BMI, maternal education level and paternal education level during pregnancy, income and mother's age at delivery, and BDE209 maternal hair-concentrations (log2-transformed), BDE47 detection in maternal hair sample, age of the child at the testing and the corresponding OPE maternal hair-concentrations.

approximately 5 % (prenatal TBP) and 10 % (childhood TPHP) in the cognitive abilities for the quarter of children the most exposed, or a decrease (childhood EHDPP) in cognitive abilities of 2.5 % for each doubling of exposure levels. The fact that we observed a possible role of distinct OPEs according to exposure windows might be partly driven by the different exposure levels in mothers and children. For TBP, higher hair-concentrations were observed in mothers, while higher hair-concentrations were observed in children for EHDPP and TPHP. For the latter two OPEs, dust ingestion as well as food contamination, specifically dairy products and baby food for EHDPP, have appeared as major pathways of exposure in Europe (Li et al., 2019, Chupeau et al., 2020). In the present study, we also observed an unexpected increase in the score for the Picture Similarities Test in association with the childhood exposure to TCPP. No clear evidence of association between prenatal exposure to BDEs and Picture Similarities Test score was observed among these 3.5-year children. Prenatal BDE exposure did not appear as a confounder in the associations with OPEs, similarly to the previous study (Percy et al., 2021). Due to the non-continuous nature of exposure data, we did not investigate a possible OPE and BDE mixture effect.

We did not study the associations for different cognitive domains of the children, nor with the full-scale IQ. This study is based on the national ELFE cohort which aims at studying various research questions on child's health in general. At each child examination, a few tests have to be chosen, so as to limit and control both participation time and the child's effort and fatigue. The British Ability Scale which included the Picture Similarities subtest is a validated tool and has previously been used in the Millenium cohort study at 3 and 5 years. The Picture Similarities subtest is individually interpretable and implies complex cognitive processes, such as integrative reasoning processes (Hill, 2005). Neither verbal nor visuo-spatial information processing skills were investigated in the present study.

Chemical incorporation into hair by blood vessels and glands, and the factors explaining their stability are not yet fully understood and are still under studied (Lallmahomed et al., 2024). For drugs in legal medicine or for metals, hair is considered as an effective and well-established biomonitoring tool. Exposure information stored in hair is stable over time and analysis of 1 cm hair length is considered to assess average exposure over a 1-month period (Kintz et al., 2015). Considering the human hair growth rate of 1 cm per month, we reasonably extrapolated for the present study that with a minimal length of 7 cm (and maximum of 10 cm) we could assess prenatal exposure to OPEs for most of the pregnancy. For the 3.5-year-old children, the hair measurements between 2 and 10 cm may reflect various exposure windows from the previous several months to about one year. However, we should note that in the present study the majority (69 %) of the hair samples of the children was between 7 and 10 cm. In the present study, hair-concentrations were assessed using unwashed samples, as washing procedures are still questioned and may extract a part of the internalized compounds. For children of 3.5 years old, we assumed no severe thermal or chemical hair treatments that might have damaged the hair structure, while for women we cannot rule out that these hair treatments might have introduced measurement errors, leading to null associations. Knowing that OPEs are not bounded to particular matters, we might expect hair-concentrations to reflect both external (via deposition from air and dust) and internal (through contact with blood at the hair follicle/root) exposure pathways (Ren et al., 2024). Specifically for OPEs, Kucharska et al. (2015) found very weak or no correlation of concentrations in mothers and children's hair samples collected at the same time, suggesting that hair-concentrations are not driven by the amount of dust deposited onto the hair surface. Also, in a previous analysis on 50 of the same families of the present study, we observed no or weak (for TEP only) correlation between the OPE hair-concentrations of the children and the OPE concentrations measured in dust samples of the households collected the same day as the hair samples (Chupeau et al., 2022). Furthermore, as OPEs are ubiquitous indoor environmental contaminants, we cannot exclude a contamination of the hair samples

from collection to chemical measurement. Identical procedures for hair collection and storage and for quality control during chemical analysis were however likely to lead to similar or at least non-differential measurement errors, which could have then influenced the results towards null association.

The weighting procedure realized in the present study enable us to correct for non-response at various steps of the survey to reduce non-response bias and the variance of estimators. This weighting process allowed us to give results for the population representative of the children born in 2011 in France and has been commonly used in various analyses of the national ELFE cohort (Charles et al., 2020). We should, however, note that the weighting procedure is less certain for the subsample than for the main sample. Although this weighting procedure may alleviate concerns of selection bias, we cannot rule out that the selection of the subsample is not well corrected and that a selection bias may remain without anticipating its direction. Caution should therefore be exercised before extrapolating the findings of the present study on the association between childhood OPE exposure and non-verbal abilities at 3.5 years of age to the national child population. It is also worth noting that these associations using the unweighted approach provided similar directions in estimates for EHDPP, TPHP and TCPP, close to statistically significance for EHDPP in particular, meaning that the weighting process – despite uncertainties – did not artificially generate false associations. In general, unweighted approaches provided similar trends, with lower magnitude in the associations, possibly suggesting that characteristics of non-participants were those driving most the associations observed.

As mentioned above, several epidemiological studies have investigated cognitive outcomes among children in association with OPE exposure during pregnancy and this literature is growing. Most of these existing studies used maternal urine metabolites as indicators of short-term exposure during pregnancy. In general, as in our study, most have found a possible adverse effect of prenatal exposure to OPEs on children's cognition. However, there is little consistency as regards the specific associated OPEs.

Prenatal exposure to TPHP was examined in all these studies four of which observed a negative impact on children's cognitive performance (Castorina et al., 2017; Hall et al., 2023; Lu et al., 2024) or fine motor function (Hernandez-Castro et al., 2024), four others showing no association (Doherty et al., 2019; Liu et al., 2021; Percy et al., 2021; Zhou et al., 2024) as in the present study, and one study reporting a positive association only when exposure was measured during the first trimester of pregnancy (Vuong et al., 2024). Most of these studies used DPHP (diphenyl phosphate) as the urinary metabolite of TPHP. It should be noted that a substantial proportion of DPHP in urine samples could derive from other OPEs, such as EHDPP or compounds other than OPEs (Xu et al., 2019). The present study showed no impact of prenatal exposure to EHDPP on cognitive performance at 3.5 years of age.

The possible adverse impact of prenatal exposure to TBP on child cognitive outcomes observed in the present study was also suggested in two recent studies on the executive functions of children at the same age (3–4 years) as those in our study (Hall et al., 2023) and at 12 years of age (Vuong et al., 2024). Four other studies found no association with either fine motor function before the age of 3 years (Hernandez-Castro et al., 2024; Zhou et al., 2024) or child full-scale IQ in 3–8-year-olds (Percy et al., 2021; Lu et al., 2024). With regard to prenatal exposure to TDCPP, TCEP and TBEP (also called TBOEP), the present study observed no association with cognitive performance at 3.5 years of age. This is in line with the majority of studies that have examined the same compounds (for TDCPP: Doherty et al., 2019, Hall et al., 2023, Liu et al., 2021, Castorina et al., 2017, Percy et al., 2021, Vuong et al., 2024; for TCEP: Liu et al., 2021, Castorina et al., 2017, Percy et al., 2021; and for TBEP: Hernandez-Castro et al., 2024, Liu et al., 2021, Zhou et al., 2024); however, negative, and occasionally positive, associations were also observed in a number of other studies (for TDCPP: Hall et al., 2023, Liu et al., 2021, Zhou et al., 2024; for TCEP: Percy et al., 2021, Vuong et al.,

2024, Lu et al., 2024; and for TBEP: Hall et al., 2023, Lu et al., 2024). Lastly, this present study is among the few studies to investigate the possible role of prenatal exposure to TEP, EHDPP (Zhou et al., 2024), TMCP (Zhou et al., 2024) and TCPP (Hernandez-Castro et al., 2024, Castorina et al., 2017, Lu et al., 2024) in cognitive outcomes among children, and no impact on cognitive performance was observed at 3.5 years of age.

In terms of the childhood exposure period, those findings of the present study suggesting a possible adverse impact on children's cognitive performance were, for TPHP, consistent with one of the two existing studies using child urine measurements of the DPHP metabolite (Percy et al., 2022). For EHDPP, the present findings are newly observed, but may again be seen as consistent with the study by Percy et al. (2022) if we consider that DPHP in urine samples could partly reflect exposure to EHDPP. The absence of an association for TDCPP in the present study is not consistent with the findings of two existing studies, which have shown reduced cognitive performance in association with urinary measurements of BDCIPP (bis 1,3-dichloro-2-propyl phosphate) in children in the Cincinnati region and in parts of Denmark and Slovakia (Percy et al., 2022, Rosolen et al., 2023). This inconsistency may be no more than partly explained by the distinct biological matrices used for exposure assessment. However, since urinary BDCIPP concentrations showed good temporal reproducibility across both short (a few days) and longer periods (Hoffman et al., 2015, Meeker et al., 2013), urinary BDCIPP measurement is considered an appropriate biomarker of TDCPP exposure. One study also found that there is a correlation between TDCPP in hair and BDCIPP in urine, which is more marked in children than in mothers (Kucharska et al., 2015). It should be noted that the reduced cognitive performance associated with urinary BDCIPP measurements in children was observed only among socioeconomically disadvantaged families in the Cincinnati study (Percy et al., 2022). Though there is increasing evidence that the effects of environmental toxicants are modified by socioeconomic stress, the underlying mechanisms are likely to be multiple. Because of the limited sample size, we did not stratify our analysis to avoid multiple testing. Lastly, in the present study we observed an unexpected positive association for TCPP, but only at the intermediate exposure levels, while the previous study conducted in Denmark and Slovakia among children aged 7–11 years observed no association (Rosolen et al., 2023). We cannot exclude chance findings.

5. Conclusion

We found associations between lower non-verbal cognitive abilities and an increase of pre- and post-natal exposure levels to some OPEs (TBP, EHDPP, TPHP). No association was observed for TBEP, TCEP, TDCPP, TEP, TMCP. These results add to the variety of the findings of previous epidemiological studies, most of which were conducted in the US and Europe. This is the first study ever to be conducted on the OPEs prevalent in France. Given the ubiquitous exposure of the general population, further studies are urgently needed before any robust conclusions can be drawn about the neurodevelopmental risks of these compounds. In order to confirm or refute these results, studies are needed to evaluate several subdomains of cognition.

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CRedit authorship contribution statement

Zohra Chupeau: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Fabien Mercier:** Writing – review & editing, Methodology, Data curation. **Barbara Le Bot:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Thierry Siméon:** Writing – review & editing, Formal analysis, Data curation. **Guillaume Chauvet:** Writing – review & editing, Methodology, Formal analysis. **Nathalie Bonvallot:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Cecile Zaros:** Writing – review & editing, Methodology, Data curation. **Marie-Aline Charles:** Writing – review & editing, Methodology, Funding acquisition. **Philippe Glorennec:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Cecile Chevrier:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Glorennec Philippe reports financial support was provided by French National Research Agency. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2025.109558>.

Data availability

Data will be made available on request.

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