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Exposure to DDT and DDE and functional neuroimaging in adolescents from the CHAMACOS cohort

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Abstract

Background: Epidemiological studies suggest that exposure to *p,p'*-dichloro-diphenyl-trichloroethane (*p,p'*-DDT) is associated with poorer cognitive function in children and adolescents, but the neural mechanisms underlying this association remain unclear.

Objective: We investigated associations of prenatal and childhood exposure to *p,p'*-DDT and its metabolite *p,p'*-dichloro-diphenyl-dichloroethylene (*p,p'*-DDE) with cortical activation in adolescents using functional near-infrared spectroscopy (fNIRS).

Methods: We administered fNIRS to 95 adolescents from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) aged 15–17 years. We assessed cortical activity in the frontal, temporal, and parietal brain regions while participants completed tasks of executive function, language comprehension, and social cognition. We measured serum *p,p'*-DDT and -DDE concentrations at age 9 years and then estimated exposure-outcome associations using linear regression models adjusted for sociodemographic characteristics. In secondary analyses, we back-extrapolated prenatal concentrations using prediction models and examined their association with cortical activation.

Results: Median (P25-P75) *p,p'*-DDT and -DDE concentrations in childhood were 1.4 (1–2.3) and 141.5 (75.0–281.3) ng/g lipid, respectively. We found that childhood exposure to *p,p'*-DDT and -DDE was associated with altered patterns of brain activation during tasks of cognition and executive functions. For example, we observed increased activity in the left frontal lobe

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during a language comprehension task (β per 10 ng/g lipid increase of serum *p,p'*-DDE at age 9 years=3.4; 95% CI: 0.0, 6.9 in the left inferior frontal lobe; and β=4.2; 95% CI: 0.9, 7.5 in the left superior frontal lobe). We found no sex differences in the associations of childhood *p,p'*-DDT and -DDE concentrations with neural activity. Associations between prenatal *p,p'*-DDT and *p,p'*-DDE concentrations and brain activity were similar to those observed for child *p,p'*-DDT and -DDE concentrations.

Conclusions: Childhood *p,p'*-DDT and -DDE exposure may impact cortical brain activation, which could be an underlying mechanism for its previously reported associations with poorer cognitive function.

Keywords

Cohort studies; neuroimaging; pesticide exposure

Introduction

Dichloro-diphenyl-trichloroethane (DDT), an organochlorine pesticide, is one of the 12 pesticides recommended by the World Health Organization (WHO) to combat malaria (World Health Organization (WHO) 2011). Although DDT use was banned in the U.S. in 1972, it was used in Mexico until 2000 and continues to be used under the Stockholm Convention for public health vector control in several countries worldwide (United Nations Environment Programme 2017). DDT persists in the environment for 2–15 years (ATSDR (Agency for Toxic Substances and Disease Registry) 2019) and has a half-life of more than 4 years in the human body. It is metabolized into 1,1′-dichloro-2,2'-bis(p-chlorophenyl)ethylene (*p,p'*-DDE) and other minor breakdown products (ATSDR (Agency for Toxic Substances and Disease Registry) 2019). Human exposure to *p,p'*-DDT and -DDE can occur by consumption of contaminated fish, vegetables grown in contaminated soil, or food imported from countries that use DDT, or by drift from nearby applications (Byard et al. 2015; Schafer and Kegley 2002).

Early life exposure to low levels of *p,p'*-DDT and -DDE is of concern due to the sensitivity of the developing brain and other organ systems to environmental stressors (Eskenazi et al. 2006, 2017; Grandjean and Landrigan 2006; Rice and Barone 2000). *p,p'*-DDT can cross the placenta and expose the fetus during pregnancy (Saxena et al. 1981) and, as a highly lipophilic compound, has been frequently detected in breastmilk (Sala et al. 2001).

Epidemiological studies indicate that *prenatal p,p'*-DDT and -DDE exposure may have adverse effects on child neurodevelopment (Jurewicz et al. 2013). Studies have shown that higher *p,p'*-DDE concentrations in maternal serum during pregnancy or cord serum were associated with poorer cognitive function, including poorer quantitative, and verbal skills, poorer spatial orientation and memory (Ogaz-González et al. 2018; Osorio-Valencia et al. 2015; Torres-Sánchez et al. 2013, poorer executive function and working memory (Ribas-Fitó et al. 2006) and higher odds of attention deficit and hyperactivity disorder (ADHD)-related behaviors (Sagiv et al. 2010, 2012). In the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort, in which the current cohort is set, maternal serum *p,p'*-DDE concentrations measured during pregnancy were associated

with delayed processing speed in 7-year-old children, particularly among girls (Gaspar et al. 2015). In contrast, several cohort studies from Mexico, South Africa, Greece, the U.S., and the Netherlands observed null associations between prenatal *p,p'*-DDT exposure and neurodevelopmental outcomes assessed at various ages from infancy to adolescence (Bahena-Medina et al. 2011; Berghuis et al. 2015; Eskenazi et al. 2017; Jusko et al. 2012; Kyriklaki et al. 2016).

Studies of *childhood p,p'*-DDT and *p,p'*-DDE exposure and neurodevelopment are sparse. The few studies that have examined associations found that postnatal *p,p'*-DDE exposure was associated with higher risk of conduct disorder and hyperactivity (Rosenquist et al. 2017), slower response speed (Forns et al. 2012), and poorer cognitive and motor function (Gladen and Rogan 1991). A Norwegian study of 13-year-old children reported that exposure to *p,p'*-DDT during the first two years of life was associated with lower odds of ADHD (Lenters et al. 2019).

These previous epidemiological studies have examined neurodevelopment using neuropsychological assessment tools or scales completed by parents; identification of the neural mechanisms underlying associations with *p,p'*-DDT and -DDE remains limited, however. In this study, we aimed to examine the association of prenatal and childhood *p,p'*-DDT and -DDE exposure with cortical brain activation, assessed using fNIRS while completing tasks of executive function, language comprehension, and social cognition, in a subset of 95 adolescent CHAMACOS participants.

Methods

Study Population

In the present study, we included youth enrolled in the CHAMACOS cohort when they were 9 years old (n=305; 2009–2011; henceforth referred to as CHAM2). Participants are Mexican-origin families living in the agricultural Salinas Valley community in Monterey County, California. We recruited families for CHAM2 using the following criteria: children born between 2000–2002; Spanish- or English-speaking mothers; mothers who were at least 18 years of age at CHAM2 child delivery; mothers who were eligible to receive state-supported medical coverage during pregnancy and received prenatal care; and mother-child pairs residing in the Salinas Valley from pregnancy until the time of recruitment. CHAM2 children were demographically similar to the children included prenatally in the original CHAMACOS cohort (Gaspar et al. 2015). From the CHAM2 children, 288 (94%) attended the 14-year-old follow-up visit (2014–2016). In 2017, we invited (by phone or in-person) a subset of these 288 youth to participate in this preliminary fNIRS study. Our target recruitment sample size was between 80 and 100 youth. Reasons for non-participation were loss to follow-up, including moving of town; refusal to participate (n=7) and youth was in house arrest (n=2). This resulted in 95 youth who participated in this preliminary fNIRS study.

Parents provided written permission and youth (aged 15–17 years) provided written assent to participate. The Office for the Protection of Human Subjects at the University of California Berkeley approved the study.

DDT and DDE exposure assessment

Child p,p'-DDT, and -DDE concentrations were directly measured in blood samples collected in CHAM2 participants at age 9 years (one child was missing a sample). Chemical analyses were conducted at the Centers for Disease Control and Prevention (CDC) using gas chromatography-high resolution mass spectrometry (Sjödin et al. 2004). *p,p'*-DDT and -DDE levels were based on a serum-lipid concentration (nanograms per gram lipid). Total lipid concentrations were estimated using the method described by (Phillips et al. 1989) and based on serum levels of triglycerides and total cholesterol measured using standard enzymatic methods (Roche Chemicals, Indianapolis, IN).

Maternal *p,p'*-DDT and -DDE concentrations during pregnancy (henceforth referred to as prenatal *p,p'*-DDT and -DDE concentrations) were predicted from the *p,p'*-DDT and -DDE concentrations measured in venous blood samples collected from CHAM2 mothers and/or children when they were recruited (9 years after birth). We used additional health and lifestyle data (i.e., maternal weight before pregnancy, maternal pregnancy weight gain, parity, and breastfeeding), collected by questionnaire (Gaspar et al. 2015; Verner et al. 2015). Prediction models were built with a weighted Super Learner algorithm, using data from a subsample of study participants recruited during pregnancy (1999–2000; henceforth referred to as CHAM1) who had measured *p,p'*-DDT and -DDE concentrations during pregnancy (in mothers) and at 9 years of age (in mothers and/or children) (Bradman et al. 2007; Gaspar et al. 2015; Verner et al. 2015).

Child and *prenatal p,p'*-DDT and -DDE concentrations were transformed on a log10. *p,p'*-DDT and -DDE concentrations of all samples measured during childhood were above the limit of detection.

Functional neuroimaging data collection

We measured cortical neural activation using fNIRS, synchronized with a computerized neurobehavioral test battery, to monitor hemodynamic changes during specific stimuli and engaging tasks (Cui et al. 2010; Sagiv et al. 2019). We selected cognitive tasks and cortical regions of interest based on previous epidemiological studies of prenatal organophosphate pesticide exposures (Sagiv et al. 2019) and previous neuroimaging studies in children (Rauh et al. 2012). Details about cognitive tasks, fNIRS acquisition and processing were published previously (Sagiv et al. 2019) and are provided as Supplementary Material.

In brief, participants engaged in a total of six tasks, including four tasks that assess attention and executive function (i.e., attention and response inhibition with the Go/No-Go task, working memory with the Sternberg working memory and the visuospatial N-back tasks, and cognitive flexibility with the Wisconsin Card Sorting task (WCST)); the Dynamic Social Gestures task that assesses social cognition, and the Pyramid and Palm Trees task that assesses language comprehension with. In the Go/No-Go, the participant was asked to press a button when seeing any letter but 'X' (i.e., go trials), and withhold otherwise (i.e., no-go trials). For the Sternberg working memory task, the participant viewed a string of 7–8 letters and then was asked if a presented "target" letter occurred in the previous letters. In the visuospatial N-back, the letter "O" was presented on the screen in a 3×3 matrix, and the

participant was asked whether the letter was presented at the same location in the previous trial (1-back) or two trials previous (2-back). In the WCST, the participant was asked to match cards based on an unstated rule (shape, number, or color). For the Dynamic Social Gestures task, the participant viewed video clips portraying social gestures (e.g., friendly wave) and non-social gestures (e.g., looking at a book) and was asked to press when the dot on the screen turned red (a device to ensure that the participant was attending to the video clip). In the Pyramids and Palm Trees task, the participant was asked to decide which of two words was semantically related to a stimulus word. To avoid bias associated with test fatigue, task presentations were randomized across two testing sessions, except the Go/No-Go, which was always presented at the end of one of the two sessions.

While study participants completed the six cognitive tasks, we collected hemodynamic activity data (i.e., oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR)), from 36 detector channels positioned on the scalp. We then estimated brain activation for each task with a generalized linear model (GLM) approach using trial onsets, duration of each condition, and HbO hemodynamic activity (Plichta et al. 2007).

Potential confounders

We collected sociodemographic and lifestyle data during in-person maternal interviews conducted at several follow-up visits between enrollment and the child's age 14 year visit. We identified potential confounders for our regression models *a priori* using a causal model framework (see Supplementary Material, Figure S1). We adjusted for maternal education at delivery (<6th grade, 7–12th grade, completed high school or more), parity (nulliparous, one child, at least 2 children), breastfeeding duration (<1 month, 1–6 months, 6–12 months, more than 12 months), child age at assessment (years), and child sex (boy, girl).

Statistical analysis

We grouped channels into 15 functional localization clusters across both brain hemispheres based on proximity to allow for anatomical variation of task-responsive brain regions across participants (Figure 1). Clusters were located as follows: 1=left inferior frontal pole (channels 1, 3, 5); 2=left superior frontal pole (channels 2, 6); 3=left Broca's/Brodmann areas 44 and 45 (channels 4, 7); 4=left dorsolateral prefrontal cortex (channels 10,11); 5=left Broca's/Brodmann areas 44 and 6 (channels 8, 12); 6=left superior/inferior temporal gyrus/postcentral gyrus (channels 9, 13); 7=left inferior parietal lobule (channels 14, 15, 17); 8=left superior parietal lobule (channels 16, 18); 9=right inferior frontal pole (channels 19, 21, 24); 10=right Broca's/Brodmann areas 44 and 45 (channels 23, 25); 11=right superior frontal pole/dorsolateral prefrontal cortex (channels 20, 22, 26; 12=right premotor/somatosensory cortex (channels 27, 28); 13=right posterior superior/middle temporal sulcus (channels 29, 33, 34); 14=right inferior parietal lobule (channels 30, 31, 35); and 15=right superior parietal lobule (channels 32, 36). As in previous work (Sagiv et al. 2019), we employed a functional localization procedure in which we chose the channel with the greatest contrast value within each cluster to represent activation for that cluster (Baker et al. 2021; Hosseini et al. 2017).

In our main analyses, we examined associations (β and 95% confidence interval (CI)) of log10 child *p,p'*-DDT and --DDE concentrations with cortical brain activity using linear regression models adjusting for potential confounders. β coefficients were contrasted between the task of interest and its corresponding control condition to capture the brain activation specific to task demands. Contrast conditions were: "No-Go vs. Go" for the Go/No-Go task, "maintenance/encoding vs. recall" for the Sternberg working memory task, "2-back vs. 1-back vs. control" for the N-back, "card sort vs. exact match" for the WCST, "social vs. non-social gestures" for the Dynamic Social Gesture task, and "semantic meaning vs. size" for the Pyramids and Palm Trees task), Each β coefficient indicates the direction (positive/negative) and the intensity, for the sign and the magnitude, respectively, of blood oxygen level-dependent change (i.e., brain activity) that occurs during each condition. Assumptions of linear regression models were met. Technical problems with data collection (i.e., task presentation and/or recording) and preprocessing (i.e., correlations between HbO and HbR concentrations, poor signal-to-noise ratio, and/or low signal quality) led to some exclusions. Missing values varied across tasks and localization clusters (Supplementary Material, Table S1). To correct for multiple testing, we controlled for type I error using the Benjamini-Hochberg FDR at <0.05. We examined sex-specific effects by including an interaction term between childhood *p,p'*-DDT or -DDE concentrations and sex in our linear regression models and computing sex-specific effect estimates. In sensitivity analyses, we adjusted linear regression models for enrichment in the home with the Home Observation for the Measurement of the Environment-Short Form (HOME) score, administered at age 10.5 (Bradley and Caldwell 1984).

In secondary analyses, we examined associations of log10 prenatal *p,p'*-DDT and -DDE concentrations with cortical brain activity. In addition, we examined associations of childhood and prenatal *p,p'*-DDT and -DDE concentrations with task performance (i.e., errors, accuracy, and reaction time). Performance indicators varied across tasks. We also built a composite performance score for each task by subtracting response latency from accuracy, following standardization (Collignon et al. 2010). We did not investigate task performance for Dynamic Social Gestures because the performance aspect of this task (i.e., pressing a button when seeing a red dot) was to ensure participation in the task and was not a test of social cognition.

Results

Study population

As shown in Table 1, youth included in the present study had a median (P25-P75) age of 15.8 (15.5–16.1) years and 7.4% were left-handed. Most of their mothers were born in Mexico (89.5%) and did not graduate from high school (70.6%). We did not observe differences in sociodemographic characteristics between fNIRS participants and non-participants, except that mothers of participants were older at delivery (46.3% were age 30+ y at delivery) than mothers of non-participants (24.7%) (see Supplementary Material, Table S2).

Median (P25-P75) serum *p,p'*-DDT and -DDE concentrations in childhood were 1.4 (1–2.3) and 141.5 (75.0–281.3) ng/g lipid, respectively (Table 2). Median back-extrapolated

prenatal serum *p,p'*-DDT and -DDE concentrations were 14.4 (9.8–82.0) and 522.1 (324.3–1770.7) ng/g lipid, respectively. Both childhood and prenatal serum *p,p'*-DDT and -DDE concentrations were highly variable (Table 2). For example, childhood *p,p'*-DDE concentrations ranged from 32 to 14,000 ng/g lipid. Correlations between childhood and prenatal *p,p'*-DDT and -DDE concentrations were moderate to high (r=0.64 between childhood *p,p'*-DDT and -DDE; r=0.81 between prenatal *p,p'*-DDT and -DDE; Table 2).

Childhood DDT/DDE and cortical activation

We found associations of childhood *p,p'*-DDT and -DDE concentrations with increased cortical activition during a language comprehension task (Pyramid and Palm Trees) in the left inferior frontal lobe (cluster 1: β_{DDT}=3.2; 95% CI: −0.7, 7.0; and β_{DDE}=3.4; 95% CI: 0.0, 6.9) and in the left superior frontal lobe (cluster 2: β_{DDT}=3.1; 95% CI: −0.6, 6.8; and β_{DDE}=4.2; 95% CI: 0.9, 7.5) (Figure 2-A). We also found associations of childhood *p,p'*-DDT and -DDE concentrations with altered patterns of activation during the tasks of working memory (Sternberg and N-back) (Figures 2-B and 2-C). Like in the language comprehension task, childhood *p,p'*-DDE concentrations were associated with increased activation in the left inferior frontal lobe during the Sternberg working memory task (cluster 1: β_{DDE}= 4.8; 95% CI: 0.5, 9.0) and the visuospatial N-back task (cluster 1: β_{DDE}=3.7; 95% CI: −0.3; 7.7). We also observed associations of childhood *p,p'*-DDT and -DDE concentrations with increased activation in the right frontal cortex and the right inferior parietal lobe, but only for the Sternberg test (cluster 11: β_{DDT}=3.0; 95% CI: −1.9, 7.9; and β_{DDE}=5.1; 95% CI: 0.7, 9.5, cluster 12: β_{DDT}=5.1; 95% CI: 0.6, 9.6; and β_{DDE}=4.3; 95% CI: 0.3, 8.3, and cluster 14: β_{DDT}=3.5; 95% CI: −1.4, 8.4; and β_{DDE}=4.6; 95% CI: 0.3, 8.9). During the WCST task, childhood *p,p'*-DDE concentrations were associated with a slight increase in activation in the left inferior parietal lobe (cluster 7: β_{DDE}=4.1; 95% CI: −0.1, 8.4) (Figure 2-D). We found null associations of childhood *p,p'*-DDT and -DDE concentrations with cortical brain activation during the Go/No-Go task and the Dynamic Social Gestures task (Figure 2-E and 2-F). Notably, no estimates remained statistically significant after adjusting for multiple comparisons (FDR-corrected p-value <0.05).

Associations remained the same when further adjusting for HOME score (see Supplementary Material, Table S3). When we stratified childhood *p,p'*-DDT and -DDE concentrations and brain activation associations by child sex, we found no notable sex differences for any of the six tasks (see Supplementary Material, Figure S2). In addition, we found null associations of childhood *p,p'*-DDT and -DDE concentrations with task performance (see Supplementary Material, Table S4).

Prenatal DDT/DDE and cortical activity

Overall, associations of estimated *p,p'*-prenatal DDT and -DDE concentrations with brain activity were similar to those observed for childhood *p,p'*-DDT and -DDE concentrations (Supplementary Material, Figure S3). Some associations were attenuated and were not statistically significant (e.g., associations in the right frontal cortex and the right inferior parietal lobe during the Sternberg task: cluster 11: β_{DDE}=2.7; 95% CI: −1.4, 6.7, cluster 12: β_{DDE}=2.1; 95% CI: −1.5, 5.8, and cluster 14: β_{DDE}=2.6; 95% CI: −1.2, 6.5). We observed additional associations between prenatal *p,p'*-DDE concentrations and increased cortical

activity in the right temporal cortex during the Dynamic social gestures task (cluster 13: β_{DDE}=1.9; 95% CI: 0.3, 3.5), and in the right superior parietal lobe during the visuospatial N-back task (cluster 15: β_{DDE} = 3.2; 95% CI: 0.2, 6.0), but decreased cortical activity in the left superior parietal lobe during the Go/No-Go task (cluster 8: β_{DDE}=−3.7; 95% CI: −6.4, −1.1). No associations were statistically significant after correcting for multiple testing (FDR-corrected p-value <0.05).

We found null associations for prenatal *p,p'*-DDT and -DDE concentrations and task performance except for the WCST for which both prenatal *p,p'*-DDT and -DDE concentrations were associated with longer response latencies (β_{DDT}=0.32, 95% CI: 0.06, 0.58; and β_{DDE}=0.36, 95% CI: 0.02, 0.70) (see Supplementary Material, Table S4).

Discussion

We used fNIRS to investigate the relationship of *p,p'*-DDT and -DDE exposure measured at 9 years of age with brain function in adolescence. We found altered patterns of cortical activation during tasks of language comprehension and executive function in association with both childhood serum *p,p'*-DDT and -DDE concentrations. We observed similar associations with estimated prenatal serum *p,p'*-DDT and -DDE concentrations.

Childhood *p,p'*-DDT and -DDE concentrations were associated with increased brain activity in the frontal lobe during the Pyramid and Palm Trees Test, a language comprehension task. Prenatal *p,p'*-DDT and -DDE concentrations showed similar associations. The frontal lobes of the brain are involved in decision-making and planning processes (Ogawa et al. 2019); our findings suggest that higher exposure may be associated with the need to recruit more neural resources to respond to the task. Although no previous studies has investigated *p,p'*-DDT or -DDE in relation to brain activity, a study of 400 British girls found that prenatal *p,p'*-DDT concentrations were associated with poorer verbal comprehension scores at 38 months, though the opposite associations were found at 15 months (Jeddy et al. 2018). Serum *p,p'*-DDT concentrations in the mothers of these girls (median DDT of 11.4 ng/g lipids) were similar to those measured in our study at 9 years of age, and *p,p'*-DDE concentrations were considerably lower (median *p,p'*-DDE of 309.5 ng/g lipids). This study did not investigate postnatal exposure to *p,p'*-DDT.

In the present study, we found increased brain activition in the left prefrontal area during both working memory tasks (i.e., visuospatial N-Back and Sternberg tasks) in children with higher prenatal and childhood *p,p'*-DDE exposure. Our results are consistent with those of a Spanish population-based birth cohort (Menorca, Spain, n=326), which found that cord serum *p,p'*-DDT concentrations were associated with poorer executive function, working memory scores, and memory skills at age 4 years (Ribas-Fitó et al. 2006). Similarly, higher *p,p'*-DDE concentrations measured in maternal serum collected during the third trimester of pregnancy were associated with reduced memory scores at ages 42, 48, 54, and 60 months in a Morelos cohort (Mexico, n=203) (Ogaz-González et al. 2018; Osorio-Valencia et al. 2015; Torres-Sánchez et al. 2013). These findings suggest that exposure to *p,p'*-DDT and -DDE during early life may be associated with poorer working memory in childhood and that the prefrontal cortex may be a target of *p,p'*-DDT and *p,p'*-DDE exposure.

We observed that childhood *p,p'*-DDE concentrations were linked with an increase in brain activition in the left parietal lobe during a cognitive flexibility task (WCST). The parietal cortex is known to be involved in selective attention (Behrmann et al. 2004; Salo et al. 2017). In addition, higher prenatal *p,p'*-DDE exposure was associated with increased response latency during this task. This is consistent with a Spanish study that reported associations of cord serum *p,p'*- DDE concentrations with slower reaction time on a continuous performance test (Forns et al. 2012).

We did not find sex-specific differences for childhood *p,p'*-DDT and '-DDE exposure on brain function, but previous studies indicate that girls may be more prone to adverse effects. In Spain, cord serum DDT concentrations were associated with worse verbal, memory, quantitative, and perceptual-performance skills at age 4 years, particularly among girls (Ribas-Fitó et al. 2006). In the CHAMACOS study, (Gaspar et al. 2015) found stronger associations between prenatal *p,p'*-DDT concentrations and delayed processing speed among girls at age 7 years. Our statistical power to detect sex-specific effects may have been limited by our small sample size (n=95).

Although previous epidemiological studies have reported associations of *p,p'*-DDT and -DDE exposure with impaired executive function, memory, and cognition (Ogaz-González et al. 2018; Osorio-Valencia et al. 2015; Ribas-Fitó et al. 2006; Torres-Sánchez et al. 2013), in our study, we did not observe associations of *p,p'*-DDT and -DDE exposure with task performance. The absence of these associations may suggest that children exposed to *p,p'*-DDT and -DDE during pregnancy or childhood may present compensatory brain mechanisms to prevent cognitive troubles. On the other hand, we cannot ignore the possibility that our tasks, adapted for an fNIRS assessment, may have been insufficiently challenging and sensitive to detect associations of *p,p'*-DDT and -DDE exposure with task performance. Furthermore, we reported low correlations between task performances and cortical activity in all our tasks, suggesting that cortical activity alone cannot be considered as a predictor of cognitive performances. While outside of the scope of the current study, future studies with larger sample sizes should address the relationship between brain activity and cognition (Marek et al. 2022). The human brain matures into adulthood and windows of vulnerability are not limited to *in utero* development (Rice and Barone 2000). By assessing both prenatal and childhood exposure to *p,p'*-DDT and -DDE in our study, we considered a broader developmental window. DDT has more than a 4-year half-life in humans (ATSDR (Agency for Toxic Substances and Disease Registry) 2019), so we expect that the *p,p'*-DDT and -DDE concentrations that we measured in children at 9 years of age reflect their exposure up until that age. In addition, the use of biomarkers enabled us to account for all sources of DDT and DDE exposure (i.e., residential and dietary). In contrast to previous epidemiological studies that have used neuropsychological tests to investigate the effects of exposures to environmental contaminants, we used fNIRS to examine subtle effects of prenatal and childhood *p,p'*-DDT and -DDE exposure on cortical neural activity.

We also faced several limitations. First, fNIRS evaluates neural activity indirectly by measuring hemodynamic changes at the cortical surface. We were not able to investigate the possible associations between *p,p'*-DDT and -DDE concentrations and hemodynamic changes in subcortical regions. Second, our sample size (N=95) is small for an

epidemiological study on environmental toxicants and may have resulted in a lack of statistical power to detect subtle associations. Further studies should conduct population-based neuroimaging studies in larger sample sizes to confirm the effects of *p,p'*-DDT and -DDE on the brain. Third, associations in our primary analyses were no longer statistically significant after FDR correction for multiple comparisons. This is likely due to our small sample size and the conservative approach of the FDR correction; however, we cannot rule out the possibility that the associations that we found in our main analyses were due to chance and should be interpreted with caution. Lastly, prenatal *p,p'*-DDT and -DDE concentrations were estimated using a prediction model based on *p,p'*-DDT and -DDE concentrations measured in venous blood samples collected from CHAM2 mothers and/or children when they were recruited (9 years after birth) and additional questionnaire data. However, as observed in CHAM1 participants (who had both measured maternal *p,p'*-DDT and -DDE concentrations during pregnancy and repeated *p,p'*-DDT and -DDE measures in either the mother or child when the child was 9 years old), our models were strongly predictive of prenatal *p,p'*-DDT and -DDE concentrations (R2s ranged from 0.86 to 0.97) (Verner et al. 2015).

Conclusions

In a Mexican American population-based cohort, we found associations of childhood exposure to *p,p'*-DDT and -DDE with alteration in cortical brain activation in adolescents while they completed language and executive tasks. Previous epidemiological studies have shown that exposure to DDT during vulnerable windows of brain development may alter cognitive function using neuropsychological tests. This study suggests that DDT and DDE exposure may have persistent adverse effects on the brain and confirms the added value of neuroimaging techniques for increasing knowledge about the possible mechanisms through which environmental toxicants exert their effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Dichloro-diphenyl-trichloroethane (DDT) is a persistent organochlorine pesticide.
- *p,p'*-DD/E were measured in child serum at 9 years and back-extrapolated during pregnancy.
- Functional near-infrared spectroscopy was performed in 95 children aged 15–17 years.
- *p,p'*-DDT/E concentrations were associated with altered patterns of cortical activation.
- Most associations were found for language comprehension and executive function tasks.

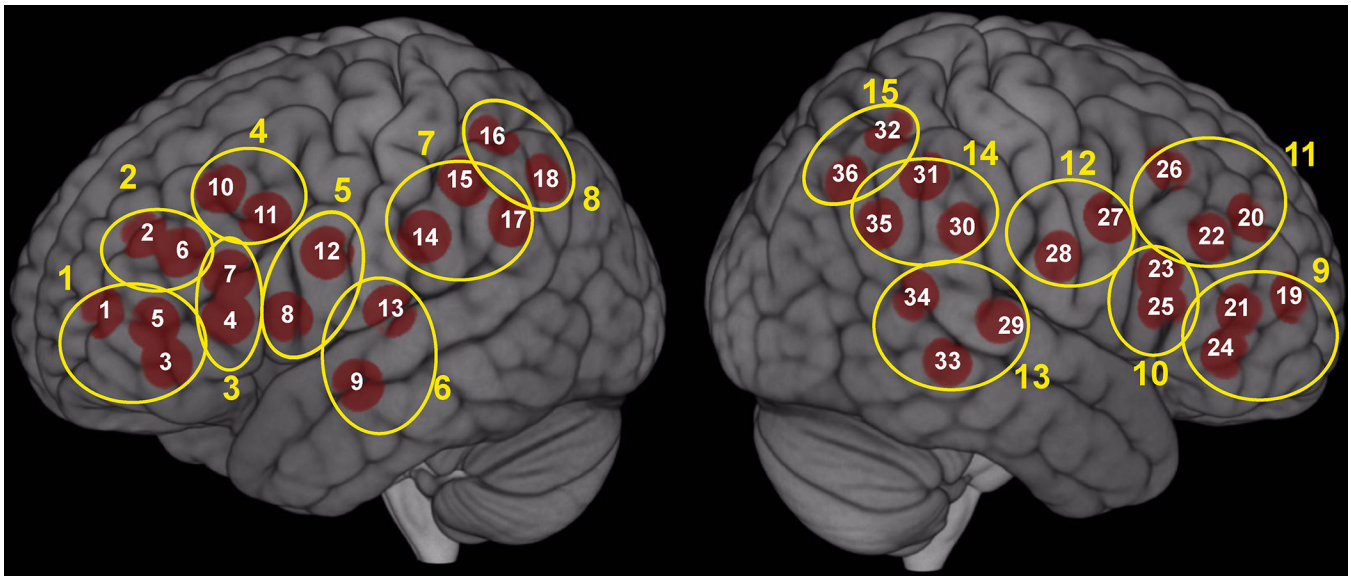
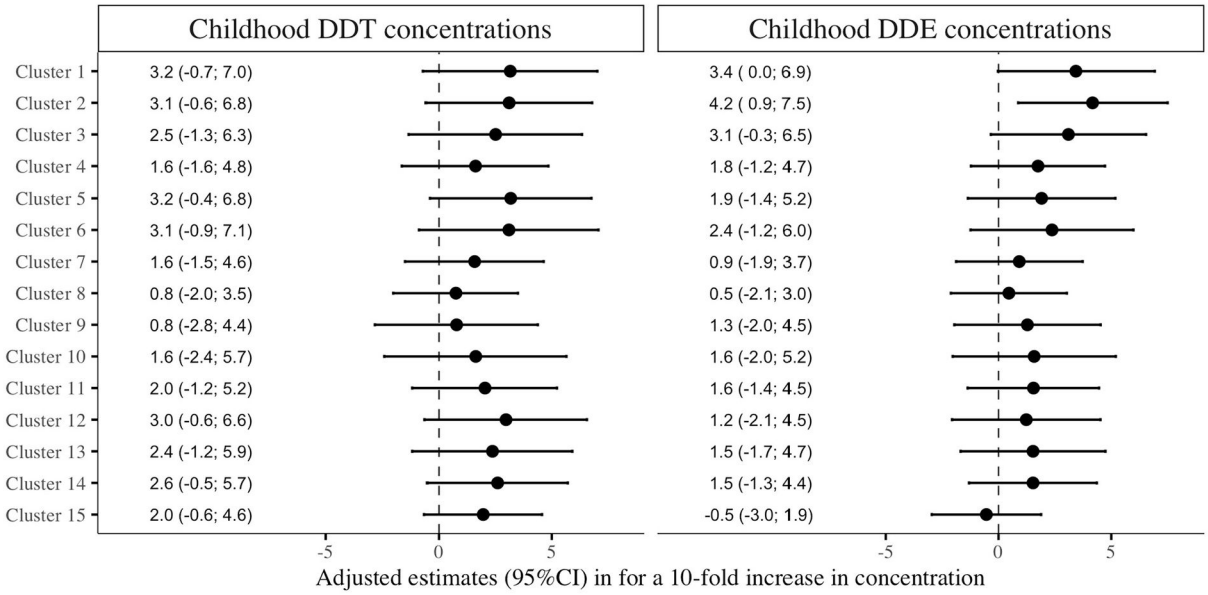


Figure 1.

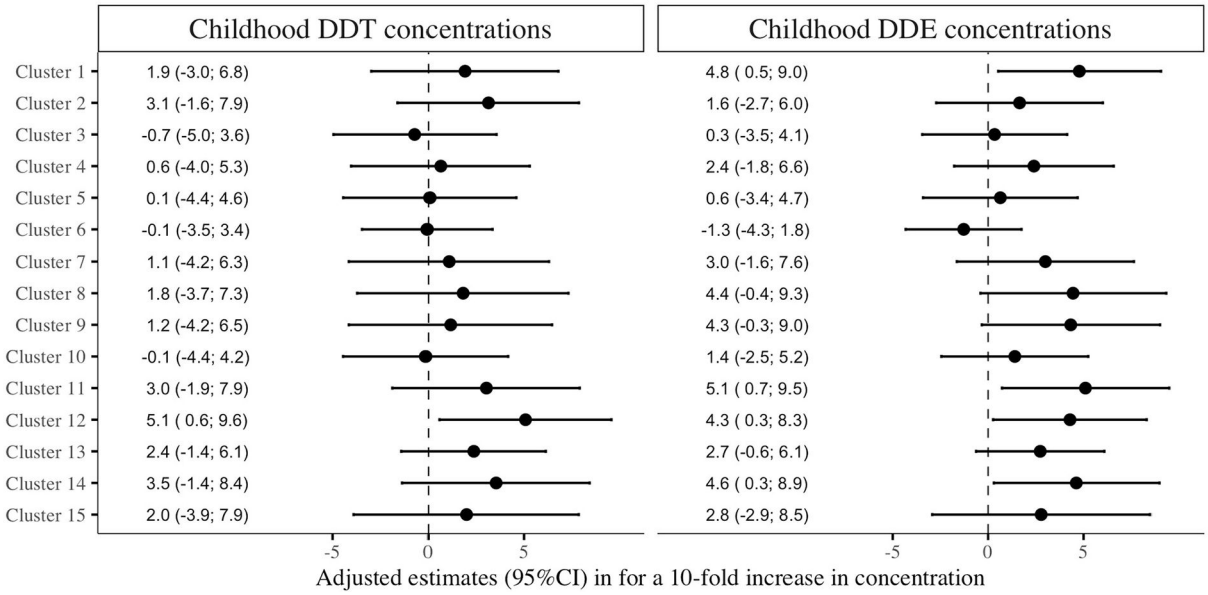
fNIRS channel (n=36) placement and localization clusters (n=15) in the CHAMACOS study, enrolled in 2009 in Salinas Valley, California.

Red circles represent a channel (source and detector pair). Yellow circles are localization clusters based on proximity of channels and anatomy: 1=left inferior frontal pole; 2=left superior frontal pole; 3=left Broca's/Brodmann areas 44 and 45; 4=left dorsolateral prefrontal cortex; 5=left Broca's/Brodmann areas 44 and 6; 6=left superior/inferior temporal gyrus/postcentral gyrus; 7=left inferior parietal lobule; 8=left superior parietal lobule; 9=right inferior frontal pole; 10=right Broca's/Brodmann areas 44 and 45; 11=right superior frontal pole/dorsolateral prefrontal cortex; 12=right premotor/somatosensory cortex; 13=right posterior superior/middle temporal sulcus; 14=right inferior parietal lobule; 15=right superior parietal lobule.

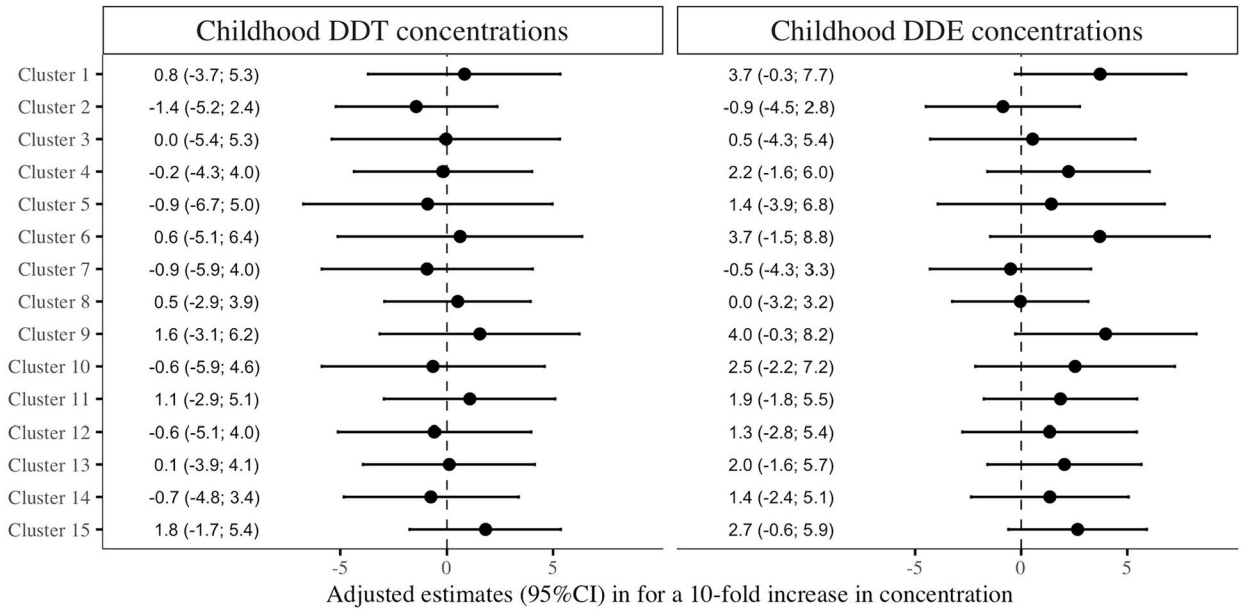
A—Pyramid and palm trees



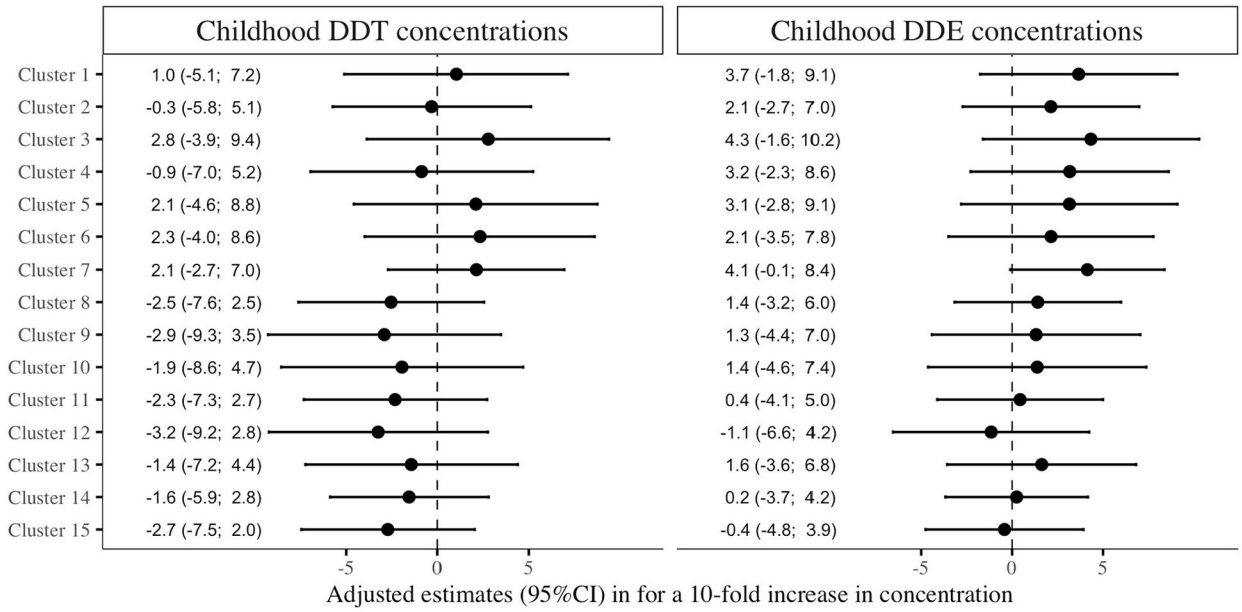
B—Sternberg working memory



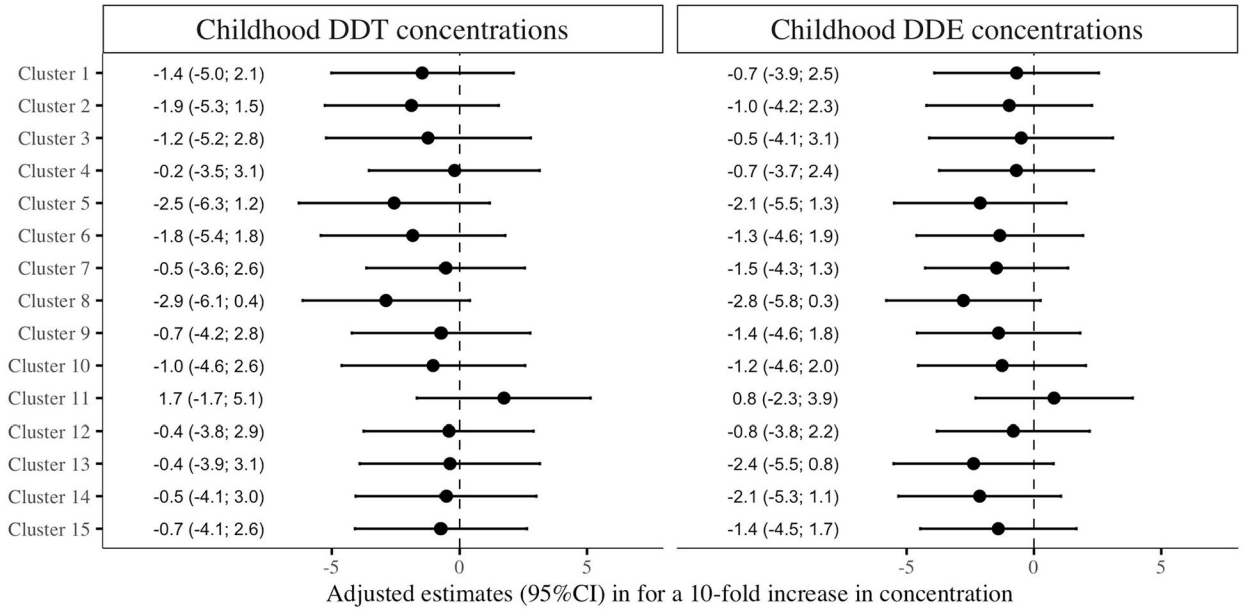
C—Visuospatial N-back



D—Wisconsin sorting card



E—Go/No-go



F—Dynamic social gestures

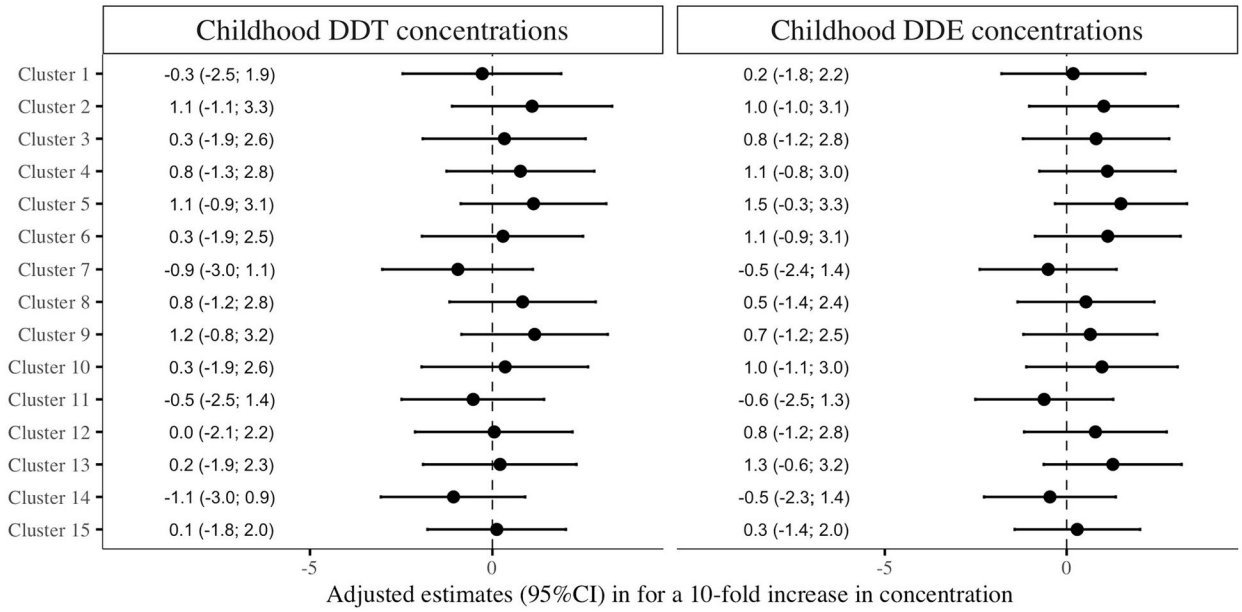


Figure 2.

Adjusted associations (β (95% CI)) for a 10-fold increase in childhood *p,p'*-DDT and -DDE concentrations and fNIRS brain activation by task in the CHAMACOS cohort (Salinas Valley, California) (n=95).

Adjusted for maternal education at delivery (<6th grade, 7–12th grade, completed high school or more), parity (nulliparous, one child, at least 2 children), duration of breastfeeding (<1 month, 1–6 months, 6–12 months, more than 12 months), age of child at assessment (continuous variable), and child's sex.

Clusters: 1=left inferior frontal pole; 2=left superior frontal pole; 3=left Broca's/Brodmann areas 44 and 45; 4=left dorsolateral prefrontal cortex; 5=left Broca's/Brodmann areas 44 and 6; 6=left superior/inferior temporal gyrus/postcentral gyrus; 7=left inferior parietal lobule; 8=left superior parietal lobule; 9=right inferior frontal pole; 10=right Broca's/Brodmann areas 44 and 45; 11=right superior frontal pole/dorsolateral prefrontal cortex; 12=right premotor/somatosensory cortex; 13=right posterior superior/middle temporal sulcus; 14=right inferior parietal lobule; 15=right superior parietal lobule.

Table 1.

Characteristics of participants with fNIRS data from the CHAMACOS cohort (Salinas Valley, California) (n=95).

Characteristics		n (%) or median (P25-P75)
Maternal birth country	Mexico	85 (89.5)
	U.S. or other	10 (10.5)
	Median (P25-P75) years in the U.S.	9.8 (3–13.5)
Maternal age at delivery (years)	17–24	32 (33.7)
	25–29	19 (20)
	30–34	27 (28.4)
	35–45	17 (17.9)
	Median (P25-P75)	28.2 (22–33)
Maternal education level	≤6th grade	41 (43.2)
	7–12th grade	26 (27.4)
	≥High school graduate	28 (29.4)
Parity	Nulliparous	32 (33.7)
	1 child	25 (26.3)
	≥2 children	38 (40)
	Median (P25-P75)	1 (0–2)
Duration of breastfeeding (months)	≤1	18 (18.9)
	>1–6	29 (30.5)
	>6–12	26 (27.4)
	>12	22 (23.2)
	Median (P25-P75)	7 (2–12)
Child's sex	Female	49 (51.6)
	Male	46 (48.4)
Child's age at assessment (years)	15	54 (56.8)
	16	40 (42.1)
	17	1 (1.1)
	Median (P25-P75)	15.8 (15.5–16.1)
Child's handedness	Right	88 (92.6)
	Left	7 (7.4)

Table 2.

Serum DDT and DDE concentrations (ng/g lipid) in the CHAMACOS cohort (Salinas Valley, California, from 2009) (n=95).

	N	Range (min-max)	P25	P50	P75	Correlation (spearman rho)			
						Childhood		Prenatal	
						***p,p'*-DDT**	***p,p'*-DDE**	***p,p'*-DDT**	***p,p'*-DDE**
Childhood									
***p,p'*-DDT**	94	0–665	1	1.4	2.3	1	0.64	0.54	0.63
***p,p'*-DDE**	94	31.8–14000	75.0	141.5	281.3		1	0.60	0.57
Prenatal[a]									
***p,p'*-DDT**	95	2.6–6371.1	9.8	14.4	82.0			1	0.81
***p,p'*-DDE**	95	127.4–29090.8	324.3	522.1	1770.7				1

P25: 25th percentile, P50: 50th percentile, P75: 75th percentile.

[a]Prenatal DDT and DDE concentrations were predicted using *p,p'*-DDT and -DDE concentrations measured in venous blood samples collected from CHAM2 mothers and/or children when they were recruited (9 years after birth) and using additional questionnaire data (i.e., maternal pre-pregnancy weight, maternal pregnancy weight gain, maternal parity, and breastfeeding history).