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Keywords

chlordecone, organochlorine pesticide, motor function, tremor, visual processing, childhood

Highlights

- Chlordecone, an organochlorine pesticide, is a known endocrine disrupter
- Today it still contaminates food products and the population of French West Indies
- Prenatal chlordecone exposure was associated with child subtle hand tremors
- Childhood exposure was associated with poorer visual processing and fine movement
- Effects on fine motor function confirm reports in early childhood in this cohort

Abstract

Background: Chlordecone is an organochlorine that was largely used as an insecticide to control a species of root borers, the Banana weevil *(Cosmopolites sordidus)*, in the French West Indies, Guadeloupe and Martinique. Its molecules have been shown to be very persistent in the environment as pollution in soils leading to contamination of water sources and foodstuff will last for several decades. Our team previously reported associations between prenatal chlordecone exposure and poorer fine motor development at two points in time during infancy.

Objective: To document whether effects of prenatal exposure to chlordecone previously reported persists until middle-childhood, and whether deleterious effects are observed in domain of visual processing. Associations with postnatal exposure and sex-specific vulnerabilities were also investigated.

Methods: We examined 410 children from the TIMOUN mother-child cohort in Guadeloupe at 7 years of age. Concentrations of chlordecone and other environmental contaminants were measured in cord- and children's blood at age 7 years. Fine motor function was assessed using the Bruininks Oseretsky Test of Motor Proficiency Second Edition (BOT-2). The Computerized Adaptive Testing System (CATSYS) was used to evaluated postural hand tremor, while non-verbal visuospatial processing was measured using the Stanford Binet copying (S-B copying) test. We used adjusted multiple linear regressions to test the relationship between children's scores and both continuous and categorical blood chlordecone concentrations, adding child sex as a moderator in continuous models.

Results: Cord chlordecone concentrations are associated with a regular frequency pattern of subtle hand tremors in both hands, and not related to visual processing and fine motor precision. Chlordecone concentrations in blood sample collected at testing time are associated with poorer visual processing when copying geometric figures, but not significantly related to poorer fine movement precision in tasks requiring pencil, scissors and paper. No sex-specific vulnerability was reported in any of the outcomes.

Conclusions: These results at school aged expand those previously reported in the same cohort during infancy at age 7- and 18 months, and corroborate the negative effects of chlordecone exposure on fine motor function in absence of intoxication. Our results support the need to continue public health efforts aimed at reducing exposure especially among women of child bearing age and young children.

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1. Introduction

Chlordecone is an organochlorine that was used as an insecticide since 1972 to control the banana weevil (Cosmopolites sordidus), a root borer, in the French West Indies, Guadeloupe and Martinique. After two decades of utilization, chlordecone was definitely banned in all French territories. As chlordecone molecules are very persistent in the environment, pollution in soils leading to contamination of water sources and foodstuff, is still present and will last for several decades (Cabidoche et al., 2009; Dromard et al., 2016). The first toxic and harmful effects of chlordecone were observed in 1975 following a poisoning of chlordecone plant workers in the industrial city of Hopewell, VA, USA (Cannon et al., 1978). Symptoms observed among male workers were related to central nervous system, liver and fertility (Cannon et al., 1978; Cohn et al., 1978; Taylor, 1982). Major signs of neurological impairments included appendicular intentional tremors, ataxia, oculomotors dysfunctions and slurred speech. Years later, chlordecone was included on the list of priority pollutants by the Stockholm Convention (Secreteriat of the Stockholm Convention and United Nations Environment Programme, 2010) and since 2003, actions have been taken by the French Government to reduce chlordecone exposure in Guadeloupe and Martinique (Direction générale de la santé, 2015, 2013, 2008; Ministère des solidarités et de la santé, 2021).

During the last decade, our group reported several health effects related to prenatal chlordecone exposure on child development from our prospective Guadeloupean mother-child cohort (TIMOUN study) that has been put in place in 2004. Hypotensive effects during pregnancy (Saunders et al., 2014), decreased length of gestation, increased risk of preterm birth (Kadhel et al., 2014), and decreased weight of newborns from

mothers with excessive prenatal weight gain (Hervé et al., 2016) were reported following prenatal chlordecone exposure. Among infants aged 3 months old, the impact of perinatal exposure to chlordecone on the thyroid hormone system was explored, and sex-specific associations were reported (Cordier et al., 2015). Cord chlordecone was associated with an increase in thyroid stimulating hormone in boys, whereas postnatal exposure, through breastfeeding, was associated with a decrease in free thyroxine in girls and in free tri-iodothyronine overall. At 7-months old, prenatal chlordecone exposure was associated with poorer fine motor development (Dallaire et al., 2012), which was again observed at 18-months of age but only among boys (Boucher et al., 2013). This sex-specific effect might be related to chlordecone's estrogen-like activity, which is now well established (Multigner et al., 2016). Recently, our group published the first results from the follow-up of the TIMOUN cohort at age 7 years. In utero and childhood chlordecone exposure have been associated with impairs visual contrast sensitivity in boys only (Saint-Amour et al., 2020). The objective of the present study is to document whether 1- effects of prenatal exposure to chlordecone previously reported on neuromotor function during infancy are lasting up to middle childhood, 2- deleterious effects are observed in domain of visual processing, 3- deleterious associations with postnatal exposure emerged, and 4- there are sex-specific vulnerabilities.

2. Material and methods

2.1 Population and data collection

The TIMOUN study is an ongoing prospective epidemiological mother-child cohort in the Guadeloupe archipelago (French West Indies). Between November 2004 and December 2007, 1068 women planning to give birth at the public hospitals of Pointe-

à-Pitre, Basse-Terre or at a local antenatal care dispensary were enrolled. At enrolment, a prenatal maternal interview was conducted by trained midwives to assess obstetrical, medical, personal, and sociodemographic characteristics. At birth, maternal diseases, adverse delivery incidents, and newborn anthropometric parameters and health information were collected from child and maternal medical records. At delivery, dietary habits, alcohol consumption and smoking status during pregnancy were collected, and a cord blood sample was obtained to document prenatal exposure to chlordecone and other environmental contaminants.

Follow-ups of a subsample of liveborn singletons in this cohort took place at 3, 7 and 18 months of age to document both potential confounders pertaining to sociodemographic and psychosocial domains, and the quality of stimulation provided by the family through maternal face-to-face interview. In this initial subsample, all children born preterm, or with intrauterine growth retardation, major birth defect or distress at birth, or born to mothers with severe disease during pregnancy were excluded (Dallaire et al., 2012). At 7 years-old, the whole cohort of liveborn singleton children (N = 1033) were invited to participate in one visit involving one maternal interview, direct child assessments of anthropometric and some health parameters, visual, motor and cognitive domains, as well as child's urine and blood sampling. The maternal interview included the administration of the non-verbal Raven Progressive Matrices (1996), which assesses nonverbal reasoning ability from principal caregiver. The test consists of 60 series of visual geometric design with a missing piece, in order of increasing difficulties, where the respondent is given six to eight choices to pick from and fill in the missing piece that fit the best to complement to problems to resolve. In total, 444 families could not be

contacted or refused to participate, thus the remaining 589 children underwent the evaluation. The present analyses focused on visual processing and neuromotor function, and included 410 children with a cord blood sample and at least one score on any of these outcomes. The data collection took place in the Pointe-à-Pitre University hospital site between April 2011 and January 2015.

The study was approved by the relevant ethical committee for studies involving human subjects (Comité de Protection des Personnes Sud-Ouest et Outremer III; n° 2011-AOOSSI--40). Each participant provided written informed.

2.2 Child assessment

Visuospatial processing and neuromotor function were assessed in 7 years old children by trained examiners who followed verbatim of the standardized test administration instructions, with periodic quality control sessions performed by a child psychologist about every 6-months during the data collection period.

2.2.1 Visuospatial Processing. The Stanford Binet copying (S-B copying) test was used to measure the non-verbal visuospatial processing (Becker, 2003). Each child was required to draw 16 two-dimensional geometric designs with pencil and paper. A composite score was derived from the test using the relaxed scoring system designed by Roberta F. White, neuropsychologist from Boston University School of Public health, to assess the overall gestalt (or configural awareness) of the children's drawing following mercury exposure (Chevrier et al., 2009; Cordier et al., 2002). This copying relaxed score ranging from 0 to 16 is described in details in Chevrier et al. (2009) and was proven to be sensitive to detect visuospatial mercury effects in 7-12 years old children from Brazil and

French Guiana (Chevrier et al., 2009; Cordier et al., 2002). A larger value on the S-B copying score indicates a better performance.

2.2.2 Fine Motor Precision. Fine motor function was assessed using the Bruininks Oseretsky Test of Motor Proficiency Second Edition (BOT-2; Bruininks and Bruininks 2005). The BOT-2 is designed to evaluate gross and fine motor skills of individuals aged 4-21 years. In this study, we specifically selected the fine motor precision subtest which includes seven items representing five tasks which can be defined as (a) filling in shapes without protruding (2 items) (b) drawing lines through paths that are crooked and curved (2 items); (c) connecting dots; (d) folding paper; (e) cutting out a circle. In conformity with the test manual, item raw scores were converted into point scores with varying category width (i.e., 0-3 to 0-7). These seven items were then summed to obtain a total score of fine motor precision with a maximum of 41, indicating a better performance. Internal consistency in our sample was acceptable ($\alpha_{cronbach} = 0.56$).

2.2.3 Hand Tremor. The Computerized Adaptive Testing System (CATSYS) was used to evaluated postural hand tremor (Danish Product Development Ltd, 2000). Postural hand tremor was recorded bilaterally during 30 seconds by asking children to hold a light stylus in front of their abdomen, free of body contact or any obstacles. During the recording, the participants were asked to breathe normally and relax. The included measures were : 1) Tremor Intensity – the root mean square of accelerations, recorded in the 0.9-15.0 Hz band during the test period, where a larger values indicate larger tremor amplitude; and 2) Harmonic Index – comparison of the tremor frequency pattern with a single harmonic oscillation, which decreases when they are many oscillations (Després et al., 2000). A more regular tremor, represented by higher values, is considered as

detrimental to health. The calculation of the Harmonic Index developed by Edwards and Beuter 1999 was used. Technical problems involving the CATSYS equipment, principally caused by humidity in the data collection center, made it impossible to record the hand tremor for 44 children on either the dominant or the non-dominant hand. When more than one trial was needed either because of a technical problems or children not respecting the protocol, two scores were recorded, and the best performance score obtained between the two trials was kept for statistical analysis (n = 14).

2.3 Exposure assessment

Samples of cord blood and child blood at the 7-year visit were collected in EDTA tubes to document respectively prenatal and childhood exposure to chlordecone and to other environmental contaminants. Plasma samples were stored at – 30°C in the Nunc® polypropylene tubes following centrifugation. Chlordecone, *p,p′*-dichlorodiphenyl dichloroethylene (DDE), PCB congener 153 (PCB-153), and lipids were measured in plasma. Determination of chlordecone, *p,p′*-DDE, and PCB-153 concentrations were done by the Center for Analytical and Research Technology at Liege University (Belgium). Contaminant concentrations were analyzed by high-resolution gas chromatography (Thermo Quest Trace 2000 gas chromatograph, Milan, Italy) quipped with a Ni36 electron capture detection. Preparation of samples and quantification method were previously described (Debier et al., 2003; Multigner et al., 2010). The limit of detection (LOD) was 0.06 µg/L for cord chlordecone and 0.05 µg/L for cord PCB-153 and cord *p,p′*-DDE. The LOD for chlordecone, PCB-153 and *p,p′*-DDE in child plasma sample was 0.02 µg/L. Total cholesterol and triglyceride concentrations in plasma were determined by standard enzymatic procedures (DiaSys Diagnostic Systems GmbH;

Holzheim, Germany), and total lipid concentrations were calculated as described by Bernert et al. (2007). Total mercury (Hg), lead (Pb), and selenium (Se) concentrations were quantified in whole blood sampled from the cord and child, and were measured by inductively coupled plasma mass spectrometry (ICP-MS) at the laboratory of the Centre de toxicologie du Québec. For Hg determination, blood samples were diluted 20-fold in a solution containing ammonium hydroxide before analysis. The LOD values for child Hg, Pb, and Se were 0.4 µg/L, 2 µg/L and 20 µg/L respectively. No values under LOD (Hg = 0.1 µg/L; Pb = 0.21 µg/L; Se = 7,87 µg/L) were observed in cord concentrations.

2.4 Confounding variables

The following variables were considered as potential confounders in the study of the association between prenatal and childhood chlordecone exposure and child outcomes documented at age 7 years: (1) maternal and family characteristics : birthplace of the mother, maternal age at 7-years old visit, parity before child birth, marital status at 7-years old visit (% living with a partner), maternal education at recruitment (none or some elementary school; high school diploma; superior education), and monthly family income at 7-years old visit (≤ 1500 euros; 1501-3000 euros; ≥ 3001 euros); (2) child characteristics : birth weight (grams), breastfeeding duration (no breastfeeding; 0 < 7 months; 7 < 18 months; ≥ 18 months); (3) other prenatal and postnatal exposures : maternal smoking (no; yes) and alcohol consumption during pregnancy (no; yes), cord and child concentrations of PCB-153, *p,p′*-DDE, Hg, Pb, and Se. These components were selected based on their known influence on child neurodevelopment (Budnik and Casteleyn, 2019; Pessah et al., 2019; Santa Maria et al., 2018; Skröder et al., 2017; Vrijheid et al., 2016) and their presence in blood samples in this population.

2.5 Statistical analyses

Normality of distribution was inspected visually for each variable and checked for skewness and kurtosis (normality range: - 3.0 to 3.0). All exposure variables were $\log_2$-transformed and variables with extreme values (> 3.0 standard deviations from the mean) were recoded to the highest observed non-outlying values (Winter, 1971). This was the case for tremor intensity scores on one hand (n = 3) and both hands (n =3) and S-B copying scores (n = 2). Because high percentage of chlordecone concentrations were below the LOD (21% and 29% for cord blood and child blood samples, respectively), both cord and child concentrations were categorized into three groups: ≤ LOD, low exposure, and high exposure, where low and high chlordecone exposure groups were determined by the median value of the blood chlordecone's distribution (Table 1). A $\log_2$-transformed continuous variables was also computed with both, cord and child chlordecone. Missing value patterns were performed to assess potential bias. The proportion of missing data ranged from 0% to 29% (highest proportion on CATSYS hand tremor scores). Little's MCAR test indicated no systematic bias arising from missingness (χ^2 =434.65, df = 404, p = 0.14; Little 1988).

Sex, child age and maternal non-verbal IQ score obtained from the Raven' Progressive Matrices (Raven scores; Raven, Court, & Raven, 1992) were treated as obligatory covariates in all models. When some maternal Raven scores were missing at the 7-years follow-up (n = 24), we used the Raven score obtained at the 3-months postnatal visit. Linear regressions between potential confounding variables and child outcomes were performed to identify the final selection of confounding variables for each model. We first retained covariates associated (p < 0.20) with both the outcome and

either cord or child chlordecone exposure. Associated variables were included together in multiple regression models to assess their confounding influence by removing them one by one and retained if their removal altered the association by ± 10% (Rothman et al., 2008).

We tested linear regressions with a Full information maximum likelihood (FIML) estimator to minimise the exclusion of participants because of missing values (Enders and Bandalos, 2001). Our data were considered missing completely at random based on Little's MCAR test (Asparouhov and Muthén, 2010). The bias-corrected and accelerated 95% confidence intervals (95% CI) were estimated by bootstrap (5000 resamples; Hayes and Scharkow 2013). We explored associations with cord and child exposure separately and with mutual adjustment. An interaction term (child sex × chlordecone concentrations) was also added to the corresponding model while controlling for the same covariates with continuous chlordecone concentrations.

Descriptive statistics and correlations were performed using IBM SPSS 26 for Windows. Missing data pattern analysis and the missing completely at random (MCAR) assumption were performed with the *BaylorEdPsych* package using R 4.0.1 software (Beaujean, 2012; R Core Team, 2018). Regression models and sex interactions were tested with Mplus 8.1 (Muthén and Muthén, 2017).

3. Results

3.1 Descriptive statistics

Descriptive data for the study participants, children's scores from the visual, motor and cognitive tests, and concentrations of contaminants are presented in Table 1.

Most of the mothers were born in the French West Indies and more than a half achieved superior education. The child mean age at testing was 7.7 years, half were female and 42% were still breast fed at 7 months. While the vast majority of children had a score on the S-B copying (n =405) and BOT-2 fine motor precision (n =407), CATSYS hand tremor scores were obtained only for 71% children (n =292). Smoking and alcohol consumption during pregnancy was relatively uncommon (less than 4%). Chlordecone was detected in 79% and 71% of cord and child blood samples, respectively. The median chlordecone concentration in cord blood (0.21 µg/L) was four times higher than the one observed in child blood samples (0.05 µg/L). The percentage of detected values for prenatal and postnatal exposure to other chemicals were all greater than 80% except for cord PCB-153 where 54% of the values were detected. Cord and child chlordecone blood concentrations were poorly associated (r_{sp} = 0.09, p = 0.14) and were only slightly correlated with other chemicals: the highest correlation with cord chlordecone was with cord *p,p'*-DDE (r_{sp} = 0.16, p < 0.01; data not shown), while the contaminants most highly related to child chlordecone was child Pb (r_{sp} = -0.22, p < 0.01; data not shown).

Spearman correlation coefficients among child assessment scores are presented in supplemental materials. The correlation between scores of S-B copying and BOT-2 fine motor precision is moderate (r_{sp} = 0.39, p < 0.01). No significant correlation was observed between S-B copying score and hand tremor scores (Table S1). A significant association was observed between BOT-2 fine motor precision score and Harmonic Index scores with dominant hand (r_{sp} = 0.16 p < 0.01). Harmonic index (non-dominant hand) was negatively correlated with tremor intensity (both hands; r_{sp} = -0.16 to -0.17, p < 0.01) and positively with dominant hand harmonic index (r_{sp} =0.22, p < 0.01). Tremor intensity

(non-dominant hand) was positively correlated with dominant hand tremor intensity (r_{sp} =0.68, $p < 0.01$) and negatively with harmonic index (r_{sp} = -0.12, $p = 0.04$).

304 Table 1 – Descriptive characteristics of the study sample

Variables	*N*	Mean ± SD or *n* (%)	Median	Range
Maternal and family characteristics				
Birthplace of mother	410			
Guadeloupe or Martinique		321 (78.3)		
Others Caribbean		40 (9.8)		
French Mainland or others		49 (12.0)		
Maternal age at 7-years old visit	410	38.99 ± 6.79	40.00	22.00 – 52.00
Parity before child birth	410	1.19 ± 1.32	1.00	0.00 – 8.00
Marital status at 7-years old visit (% living with a partner)	410	262 (63.9)		
Education at recruitment (achieved level)	410			
Primary or none		18 (4.4)		
High school		185 (45.1)		
Superior education		207 (50.5)		
Family income at 7-years old visit (per month)	402			
≤ 1500 euros		163 (40.5)		
1501-3000 euros		138 (34.3)		
≥ 3001 euros		101 (25.1)		
Maternal RAVEN score[a]	406	35.69 ± 12.38	38.00	9.00 – 59.00
Child characteristics				
Age at visit (years)	410	7.67 ± 0.21	7.7	7.00 – 8.00
Sex (% female)	410	217 (52.9)		
Birth weight (g)	410	3136.44 ± 517.72	3160.00	1315.00 – 4585.00
Gestational age (weeks)	410	38.72 ± 1.68	39.00	32.30 – 41.30
Breastfeeding duration (months)	408			
No breastfeeding		65 (15.9)		
0 ≤ 6		173 (42.4)		
7 < 18		91 (22.3)		
≥ 18		79 (19.4)		
Child outcomes				
Stanford-Binet copying score	405	13.25 ± 1.70	14.00	7.00 – 16.00
BOT-2 fine motor precision score	407	34.64 ± 4.20	36.00	12.00 – 41.00
CATSYS hand tremor scores				
Tremor Intensity, dom.	292	0.27 ± 0.13	0.23	0.02 – 0.72
Harmonic Index, dom.	292	0.85 ± 0.05	0.85	0.69 – 0.99
Tremor Intensity, non-dom.	287	0.31 ± 0.18	0.26	0.06 – 1.00
Harmonic Index, non-dom.	287	0.86 ± 0.05	0.86	0.74 – 0.98
Prenatal exposures				
Cord chlordecone (µg/L)[b]	380	0.12 ± 8.20	0.21	< LOD – 29.78
≤ LOD (0.06)		81 (21.3)		
Low exposure (0.061-0.29)		149 (39.2)		
High exposure (> 0.29)		150 (39.5)		
Tobacco during pregnancy (% yes)	410	13 (3.2)		
Alcohol during pregnancy (% yes)	398	10 (2.4)		
Cord PCB-153 (µg/L)[b]	379	0.02 ± 13.50	0.06	< LOD – 1.75
Cord *p,p'*-DDE (µg/L)[b]	379	0.20 ± 7.41	0.28	< LOD – 12.50
Cord Hg (µg/L)[b]	401	6.18 ± 1.82	6.60	0.69 – 46.12
Cord Pb (µg/L)[b]	401	13.85 ± 1.59	13.3	3.52 – 99.46
Cord Se (µg/L)[b]	401	116.49 ± 1.22	118.44	64.00 – 221.09

Child exposures at 7-year (µg/L) [b]				
Chlordecone (µg/L)	318	0.02 ± 12.47	0.05	< LOD – 7.01
≤ LOD (0.02)		91 (28.62)		
Low exposure (0.021-0.07)		110 (34.6)		
High exposure (> 0.07)		117 (36.8)		
PCB-153 (µg/L)	318	0.05 ± 3.94	0.06	< LOD – 1.29
p,p′-DDE (µg/L)	318	0.20 ± 3.48	0.19	< LOD – 26.43
Hg (µg/L)	316	1.62 ± 2.27	1.80	< LOD – 19.00
Pb (µg/L)	316	20.88 ± 1.55	21.9	4.50 – 213.00
Se (µg/L)	316	105.66 ± 1.15	110.00	70.00 – 170.00

Abbreviations: Maternal RAVEN score, Raven's Progressive Matrices continuous score (Raven et al. 1992); BOT-2, Bruininks Oseretsky Test of Motor Proficiency Second Edition; CATSYS, Computerized Adaptive Testing System; dom., dominant hand; non-dom., non-dominant hand; LOD, limit of detection; PCB 153, polychlorinated biphenyl congener 153; *p,p′*-DDE, *p,p′*-dichlorodiphenyl dichloroethylene; Hg, mercury; Pb, lead; Se, selenium.

[a]Maternal Raven score at the 7-years old visit (n = 382) but when missing (n = 24), the RAVEN score obtained the 3-month postnatal visit was used.

[b]Blood concentrations, geometric mean ± geometric standard deviation calculated on all values.

3.2 Multiple linear relationships between chlordecone concentrations and child outcomes

Results from confounder-adjusted multiple regression models presented in Table 2 showed that S-B copying score was not significantly related to cord chlordecone concentrations, nor with child chlordecone concentrations on a continuous scale. However, analysis conducted according to 3 categorical child chlordecone levels indicated that this association with the S-B copying score reached the significance in the low exposed group, and was marginally significant (p = 0.06) in the high exposed group. Stronger negative association was found after accounting for other environmental exposures in Model 3.

With regard to the associations with BOT-2 fine motor precision score, no significant association with prenatal or child chlordecone exposure was observed (Table 2).

Table 2 – Regression coefficients examining the relation between prenatal and postnatal chlordecone exposure, Stanford-Binet copying relaxed scores and BOT-2 fine motor precision scores (n = 410)

	Model 1	Model 2	Model 3
Exposures	β (95% CI)	β (95% CI)	β (95% CI)
Stanford-Binet copying scores			
Cord levels (µg/L)			
≤ LOD	Reference	Reference	Reference
Low chlordecone (≤ 0.29)	0.22 (-0.27, 0.72)	0.19 (-0.31, 0.70)	0.23 (-0.27, 0.76)
High chlordecone (> 0.29)	-0.08 (-0.58, 0.45)	-0.06 (-0.56, 0.47)	0.03 (-0.47, 0.58)
Continuous (log_2)	-0.02 (-0.07, 0.04)	-0.02 (-0.07, 0.05)	-0.01 (-0.06, 0.06)
Sex interaction [a]	0.02 (-0.10, 0.15)	0.03 (-0.09, 0.15)	0.02 (-0.11, 0.14)
Child levels (µg/L)			
≤ LOD	Reference	Reference	Reference
Low chlordecone (≤ 0.07)	-0.44 (-0.88, 0.02)	**-0.46 (-0.90, -0.01)**	**-0.47 (-0.89, -0.03)**
High chlordecone (> 0.07)	-0.44 (-0.90, 0.02)	-0.46 (-0.91, 0.01)	-0.45 (-0.90, 0.01)
Continuous (log_2)	-0.04 (-0.09, 0.01)	-0.04 (-0.09, 0.01)	-0.05 (-0.09, 0.01)
Sex interaction [a]	0.04 (-0.05, 0.14)	0.05 (-0.05, 0.15)	0.06 (-0.03, 0.16)
BOT-2 fine motor precision scores			
Cord levels (µg/L)			
≤ LOD	Reference	Reference	Reference
Low chlordecone (≤ 0.29)	-0.05 (-1.12, 1.21)	-0.12 (-1.20, 1.11)	0.04 (-1.03, 1.24)
High chlordecone (> 0.29)	-0.45 (-1.62, 0.83)	-0.41 (-1.60, 0.86)	-0.14 (-1.28, 1.10)
Continuous (log_2)	-0.04 (-0.17, 0.10)	-0.04 (-0.16, 0.11)	-0.01 (-0.13, 0.13)
Sex interaction [a]	0.21 (-0.05, 0.48)	0.22 (-0.03, 0.50)	0.18 (-0.07, 0.46)
Child levels (µg/L)			
≤ LOD	Reference	Reference	Reference
Low chlordecone (≤ 0.07)	-0.41 (-1.43, 0.67)	-0.44 (-1.44, 0.64)	-0.36 (-1.38, 0.70)
High chlordecone (> 0.07)	-0.86 (-1.95, 0.18)	-0.86 (-1.95, 0.19)	-0.58 (-1.65, 0.43)
Continuous (log_2)	-0.10 (-0.21, 0.01)	-0.10 (-0.21, 0.01)	-0.09 (-0.19, 0.02)
Sex interaction [a]	-0.09 (-0.30, 0.12)	-0.09 (-0.30, 0.12)	-0.06 (-0.26, 0.14)

Abbreviations: CI, Confidence interval; LOD, limit of detection; BOT-2, Bruininks Oseretsky Test of Motor Proficiency Second Edition.

[a] Sex variable where 1 = boy and 0 = girl.

Stanford-Binet: Model 1: both prenatal and child chlordecone exposure models adjusted for child sex and age and maternal Raven score. Child chlordecone exposure models were also adjusted for breastfeeding duration. Model 2: additional adjustments for complementary chlordecone exposure (i.e., child levels when

cord levels was the variable of interest and vice versa). Model 3: additional adjustments for prenatal and child contaminants exposure. Cord models included child PCB-153 and child selenium. Child models included cord mercury exposure and child selenium exposure.
BOT-2: Model 1: both prenatal and child chlordecone exposure models are adjusted for child sex and age and maternal Raven score. Model 2: additional adjustments for complementary chlordecone exposure (i.e., child levels when cord levels was the variable of interest and vice versa). Model 3: additional adjustments for prenatal and postnatal environmental exposure: cord and child models included child PCB-153 and child selenium.

Results with scores from the computerized CATSYS system are presented in Table 3. Cord and child chlordecone concentrations were not associated with Tremor Intensity scores. Significant associations were found between prenatal exposure and Harmonic Index scores with both dominant [Model 3: 0.02 (0.002, 0.03)] and non-dominant hands [Model 3: 0.02 (0.01, 0.04)], while child exposure was not. That meant that higher cord chlordecone concentrations were associated with a pattern of regular subtle tremor in both hands (as indicated by the Harmonic Index), which may suggest a detrimental-type of tremor (Table 3).

Finally, we did not find significant moderation by sex between continuous cord or child chlordecone exposure and any outcome scores (Tables 2 and 3), nor between categorical cord or child chlordecone exposure and any child outcomes (results not shown).

Table 3 – Regression coefficients examining the relation between prenatal and postnatal chlordecone exposure and CATSYS tremor scores with dominant and non-dominant hand (n = 410)

	Tremor Intensity			**Harmonic Index** [b]		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Exposures	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Dominant hand						
Cord levels (µg/L)						
≤ LOD	Reference	Reference	Reference	Reference	Reference	Reference
Low chlordecone (≤ 0.29)	0.003 (-0.04, 0.04)	0.002 (-0.04, 0.04)	0.01 (-0.03, 0.05)	0.12 (-0.01, 0.26)	0.11 (-0.02, 0.25)	**0.14 (0.01, 0.27)**
High chlordecone (> 0.29)	-0.002 (-0.04, 0.04)	-0.002 (-0.04, 0.04)	0.004 (-0.04, 0.04)	0.12 (-0.01, 0.25)	0.12 (-0.003, 0.26)	**0.15 (0.02, 0.29)**
Continuous (log_2)	0.000 (-0.01, 0.004)	0.000 (-0.01, 0.004)	0.000 (-0.004, 0.01)	0.02 (-0.002, 0.03)	0.02 (-0.001, 0.03)	**0.02 (0.002, 0.03)**
Sex interaction [a]	0.002 (-0.01, 0.01)	0.002 (-0.01, 0.01)	0.001 (-0.01, 0.01)	0.03 (-0.01, 0.06)	0.03 (-0.01, 0.06)	0.02 (-0.02, 0.05)
Child levels (µg/L)						
≤ LOD	Reference	Reference	Reference	Reference	Reference	Reference
Low chlordecone (≤ 0.07)	-0.001 (-0.04, 0.04)	-0.001 (-0.04, 0.04)	0.003 (-0.04, 0.05)	-0.09 (-0.24, 0.08)	-0.09 (-0.24, 0.08)	-0.09 (-0.25, 0.07)
High chlordecone (> 0.07)	-0.02 (-0.06, 0.02)	-0.02 (-0.06, 0.02)	-0.01 (-0.05, 0.03)	-0.14 (-0.28, 0.01)	-0.13 (-0.27, 0.01)	-0.14 (-0.28, 0.01)
Continuous (log_2)	0.000 (-0.01, 0.004)	0.000 (-0.01, 0.004)	0.000 (-0.01, 0.01)	-0.01 (-0.03, 0.003)	-0.01 (-0.03, 0.003)	-0.01 (-0.03, 0.003)
Sex interaction [a]	-0.01 (-0.01, 0.01)	-0.01 (-0.01, 0.01)	-0.01 (-0.02, 0.004)	0.01 (-0.02, 0.04)	0.01 (-0.03, 0.04)	0.01 (-0.03, 0.04)
Non-dominant hand						
Cord levels (µg/L)						
≤ LOD	Reference	Reference	Reference	Reference	Reference	Reference
Low chlordecone (≤ 0.29)	-0.02 (-0.08, 0.04)	-0.02 (-0.08, 0.04)	-0.02 (-0.09, 0.05)	**0.14 (0.03, 0.25)**	**0.13 (0.03, 0.25)**	**0.16 (0.05, 0.27)**
High chlordecone (> 0.29)	-0.04 (-0.11, 0.02)	-0.04 (-0.11, 0.02)	-0.04 (-0.11, 0.03)	**0.15 (0.03, 0.26)**	**0.14 (0.04, 0.26)**	**0.17 (0.05, 0.29)**
Continuous (log_2)	-0.004 (-0.01, 0.002)	-0.003 (-0.01, 0.002)	-0.003 (-0.01, 0.003)	**0.02 (0.01, 0.04)**	**0.02 (0.01, 0.04)**	**0.02 (0.01, 0.04)**
Sex interaction [a]	-0.01 (-0.02, 0.01)	-0.004 (-0.02, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.02)
Child levels (µg/L)						
≤ LOD	Reference	Reference	Reference	Reference	Reference	Reference
Low chlordecone (≤ 0.07)	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)	-0.001 (-0.14, 0.13)	0.002 (-0.13, 0.13)	0.001 (-0.13, 0.13)

High chlordecone (> 0.07)	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)	-0.10 (-0.22, 0.03)	-0.10 (-0.22, 0.04)	-0.10 (-0.22, 0.03)
Continuous (log_2)	-0.001 (-0.01, 0.01)	-0.001 (-0.01, 0.01)	-0.001 (-0.01, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.01)
Sex interaction [a]	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.02, 0.01)	0.02 (-0.01, 0.05)	0.02 (-0.01, 0.05)	0.02 (-0.01, 0.05)

Abbreviations: CI, Confidence interval; LOD, limit of detection.

[a] Sex variable where 1 = boy and 0 = girl. [b] Based on the calculation developed by Edwards and Beuter 1999.

Model 1: both prenatal and child chlordecone exposure models are adjusted for child sex and age, and maternal Raven score.

Model 2: additional adjustments for complementary chlordecone exposure (i.e., child levels when cord levels was the variable of interest and vice versa).

Model 3: additional adjustments for prenatal and postnatal environmental exposure: cord models included child PCB-153 and child models included cord mercury

4. Discussion

The main objective of this study was to document whether associations between prenatal exposure to chlordecone and neuromotor functions reported at two points in time during infancy in the TIMOUN cohort are still observed at school age, and whether exposure occurring during childhood is associated with negative outcomes. We are reporting that cord chlordecone concentrations are associated with a regular frequency pattern of subtle hand tremors in both hands, and not related to visual processing and fine motor precision. Additionally, chlordecone concentrations in child blood sample collected at testing time are associated with poorer visual processing when copying geometric figures (S-B copying test). No sex-specific vulnerability was reported in any of the outcomes.

In this same cohort, parental reports of deficits on fine motor skills assessed at 7-months (Dallaire et al., 2012) and at 18-months old (Boucher et al., 2013) were associated with higher cord blood chlordecone concentrations. We found no such association at 7 years old when using the fine motor precision subtest from the BOT-2, which includes seven tasks involving paper, pencil and scissors. While this subtest was selected to document fine motor skills independent from parental assessment, as we previously reported deleterious effects of prenatal chlordecone exposure on this developmental domain, its internal consistency was only acceptable in our population. This suggests we may have faced a lack of sensitivity using this measure, which could have resulted in this negative result. We used the CATSYS to evaluate postural hand tremor, which is a test proven to be sensitive in evaluating neurologic and neurodegenerative disorders, showing its ability to discriminate pathologic from

physiologic (normal) tremor in Parkinson's disease (Papapetropoulos et al., 2010) and also in the assessment of subtle neurological impact of exposure to toxic agents such as in manganese exposed population, but also within populations exposed to methylmercury, and tobacco (Beuter et al., 2004; Bowler et al., 2016; Chiu et al., 2017; Ellingsen et al., 2006, 2015; Kim et al., 2011; Kornblith et al., 2018; Netterstrøm et al., 1996). In our study population exposed to chlordecone, we are reporting associations of cord chlordecone concentrations with a regular frequency pattern of subtle tremors in both hands, considered as detrimental to health (Després et al., 2000). This specific sign is in accordance with the severe and consistent tremors observed among Hopewell employees accidently intoxicated during chlordecone production (Cannon et al., 1978), and with the results of experimental animal's studies exposed either during neonatal period (Mactutus et al., 1984) or in adulthood (Dietz and McMillan, 1979). In animal studies, tremors were apparent at earlier times when higher doses were used compared to lower doses (Agency for Toxic Substances and Disease Registry, 2019).

The S-B copying test measures both visuospatial processing and fine motor skills, as the child is required to do a visual integration of two-dimensional geometric figures and to transpose them using pencil and paper. This task elicits two distinctive neuromotor functions at the same time. Thus, in our study, although no association was observed with prenatal exposure, the negative associations we observed of child chlordecone concentrations with the visual processing score from the S-B copying test can emerge partly from poorer manual dexterity and coordination required to copy geometric figures in addition to alterations in visuospatial processing per se. In parallel to the present study, we previously reported that higher child chlordecone concentrations were related to

deficits in contrast sensitivity at low spatial frequencies in boys using the Freiburg Visual Acuity and Contrast Test (FrAcT; Saint-Amour et al., 2020). The vast majority of children (91%) had visual acuity within the normal range, and chlordecone was unrelated to visual acuity. In concordance with what was already proposed by Waksman and Brody (2007), Saint-Amour and his colleagues concluded that the "deficits in contrast sensitivity observed at low spatial frequencies reflect predominantly defects in post-retinal neural processing" (Saint-Amour et al., 2020; Waksman and Brody, 2007).

In this same cohort, sex-specific effects from cord chlordecone exposure were observed in boys at 18-months on fine motor functions (Boucher et al., 2013) and at 7 years from current chlordecone exposure on visual contrast sensitivity (Saint-Amour et al., 2020). In the present study, no sex-specific effect was found on fine motor functions evaluated at 7-years. Still, chlordecone hormone-like properties have been clearly established both in vivo and in vitro (Eroschenko, 1981; Hammond et al., 1979). The integration of sex-specific analyses while investigating exposure to chlordecone, as well as other endocrine disruptor chemicals, in relation with children neurodevelopment needs to be pursued.

Furthermore, the reduced chlordecone concentration overtime observed in our study sample might be explained by some actions taken by the French Government since 2003 (Direction générale de la santé, 2015, 2013, 2008). The main activities were to withdraw food from the market and water from the distribution system when chlordecone was above the limit values (Agence Française de Sécurité Sanitaire des Aliments, 2007). In 2009, the "Family Gardens" program was put in place in Guadeloupe to inform and support families who cultivate a vegetable garden potentially contaminated by

chlordecone, products that were not included in the market control system (IREPS Guadeloupe and ARS Guadeloupe - Saint-Martin, 2014; Nedellec et al., 2016). Finally, the fourth action plan proposed by the French Government was put in place in February 2021, aiming to strengthen the measures already undertaken to reduce the exposure of populations to chlordecone in Guadeloupe and Martinique, as well as to deploy appropriate support measures to meet the population needs (Ministère des solidarités et de la santé, 2021).This study has several strengths and limits. The main strengths are its prospective design with assessment of both prenatal and childhood exposure using sensitive biomarkers, repeated neurodevelopmental assessments during infancy and at school-aged, and collection of extensive data on potential confounders and co-exposures from the prenatal to the school-aged period. A large number of socioeconomic and medical covariates, and other recognized neurotoxicants (Hg, Pb, *p,p'-DDE* and PCB-153) were examined in the analyses. Nevertheless, we cannot completely exclude residual confounding. We considered potential bias from socioeconomic status by running sensitivity analyses since children from higher-income families might have better access to pencils and materials for creative work. In the same way, additional adjustment for family income did not modify the strength of any association between chlordecone exposure and any outcome measured at school age. Finally, as children vulnerability to neurotoxicants continue to be high during the first years of life when systems are immature, it is crucial to keep documenting hand tremors and other possible impact on neuromotor functions using comprehensive screening tools.

5. Conclusions

These results we are reporting here at school aged expand those previously reported in the same cohort during infancy at age 7- and 18 months, and corroborate the long lasting negative effects of prenatal chlordecone exposure on fine motor function in absence of intoxication. Negative associations of child chlordecone exposure with the visual processing score from the S-B copying test can be related to alterations in visuo-spatial processing per se in coherence with deficits in contrast sensitivity at low spatial frequencies in boys reported in a parallel evaluation. The investigation of these neuromotor functions needs to be further explored since abilities like fine motor writing and object manipulation are significant predictors of later academic achievement (Dinehart and Manfra, 2013).

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Supplemental Material

Table S1 – Spearman correlation coefficients (*p*-value) between children neuromotor functions scores

	S-B copying	BOT-2 Fine motor precision	Tremor Intensity, dom	Harmonic Index, dom [a]	Tremor Intensity, non-dom	Harmonic Index, non-dom [a]
S-B copying	-	**0.39 (< 0.01)**	-0.09 (0.13)	0.08 (0.16)	-0.07 (0.22)	0.01 (0.90)
BOT-2 Fine motor precision		-	-0.10 (0.09)	**0.16 (< 0.01)**	-0.02 (0.71)	0.08 (0.16)
Tremor Intensity, dom			-	-0.11 (0.06)	**0.68 (< 0.01)**	**-0.17 (< 0.01)**
Harmonic Index, dom[a]				-	**-0.12 (0.04)**	**0.22 (< 0.01)**
Tremor Intensity, non-dom					-	**-0.16 (< 0.01)**
Harmonic Index, non-dom[a]						-

[a] Based on the calculation developed by Edwards and Beuter 1999.
Abbreviations: S-B copying, Stanford-Binet relaxed copying; BOT-2, Bruininks Oseretsky Test of Motor Proficiency Second Edition; dom., dominant hand; non-dom., non-dominant hand.