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Cognitive, visual, and motor development of 7-month-old Guadeloupean infants exposed to chlordecone

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ABSTRACT

Background: The insecticide chlordecone was extensively used in the French West Indies to control banana root borer. Its persistence in soils has led to the widespread pollution of the environment, and human beings are still exposed to this chemical. Chlordecone has been shown to impair neurological and behavioural functions in rodents when exposed gestationally or neonatally.

Objectives: The aim of the study was to evaluate the impact of prenatal and postnatal exposure to chlordecone on the cognitive, visual, and motor development of 7-month-old infants from Guadeloupe.

Methods: Infants were tested at 7 months ($n=153$). Visual recognition memory and processing speed were assessed with the Fagan Tests of Infant Intelligence (FTII), visual acuity with the Teller Acuity Card, and fine motor development with the Brunet-Lezine. Samples of cord blood and breast milk at 3 months ($n=88$) were analyzed for chlordecone concentrations. Postnatal exposure was determined through breast feeding and frequency of contaminated food consumption by the infants.

Results: Cord chlordecone concentrations in tertiles were associated with reduced novelty preference on the FTII in the highly exposed group ($\beta=-0.19$, $p=0.02$). Postnatal exposure through contaminated food consumption was marginally related to reduced novelty preference ($\beta=-0.14$, $p=0.07$), and longer processing speed ($\beta=0.16$, $p=0.07$). Detectable levels of chlordecone in cord blood were associated with higher risk of obtaining low scores on the fine motor development scale (OR=1.25, $p<0.01$).

Conclusion: These results suggest that pre- and postnatal low chronic exposure to chlordecone is associated with negative effects on cognitive and motor development during infancy.

1. Introduction

Chlordecone (Kepone) is an organochlorine developed in 1958 to control pest insects. This molecule was intensively used in the French West Indies from 1973 to 1992 to control banana root borers (Cellule interrégionale d'épidemiologie Antilles Guyane, 2005). Because of its low biotic and abiotic degradation in the environment, a large scale contamination of soils, water sources and crops by chlordecone was observed in Guadeloupe and Martinique (Cabidoche et al., 2009). Exposure to this chemical is still ongoing in those French West Indies populations through consumption of contaminated foodstuffs and will probably persist for several hundred years (Dubuisson et al., 2007; Guldner et al., 2010).

Chlordecone is neurotoxic, spermatotoxic, potentially carcinogenic in humans and possess well defined estrogenic activity (Cannon et al., 1978; Cohn et al., 1978; Hammond et al., 1979;

Abbreviations: BMI, Body mass index; DDE, p,p′-dichlorodiphenyl dichloroethylene; DHA, Docosahexaenoic acid; FTII, Fagan test of infant intelligence; LD, Limit of detection; Hg, Mercury; OR, Odd ratio; Pb, Lead; PCB 153, Polychlorinated biphenyl congener 153; Se, Selenium; TAC, Teller visual acuity card test II

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Hudson et al., 1984; Multigner et al., 2010). This chemical accumulates preferentially in the liver, followed by fat tissues, the nervous system, and kidneys (Faroon et al., 1995). A substantial portion of the chlordecone in blood is associated with proteins and high-density lipoproteins (Soine et al., 1982). Neurological symptoms associated with chlordecone were reported following intoxication of workers in a production facility in Hopewell, Virginia, USA. Signs of central nervous system toxicity, such as tremors, ataxia, oculomotor dysfunctions, slurred speech, and headaches were observed, as well as psychological and cognitive symptoms including irritability, mood disorders and memory loss (Cannon et al., 1978; Taylor, 1982). Reversibility of neurotoxic signs with decreasing chlordecone concentrations in blood (half-life = 120–160 day) were reported for most workers, but some individuals still complained of tremors and memory loss several years after cessation of exposure (Cohn et al., 1978; Taylor, 1982). In experimental studies, adult and prenatally/neonatally-exposed rats have shown similar neurological manifestations and signs of permanent organisational effects of chlordecone on neural and behavioural functions were reported after *in utero* exposure (Mactutus and Tilson, 1985; Mactutus and Tilson, 1984; Mactutus et al., 1982). In humans, chlordecone is known to cross the placental barrier and was previously detected in cord blood and breast milk of nursing mothers (Multigner, 2006). Despite these findings, the potential effect of prenatal exposure to environmental level of chlordecone on the developing brain and child development remains completely unknown due to lack of prospective cohort studies with follow-up of prenatally exposed newborns.

This paper aims to evaluate the effects of prenatal and postnatal exposure to chlordecone on cognitive, visual, and motor development of 7-month-old infants from Guadeloupe.

2. Materials and methods

2.1. Population and data collection

Guadeloupe is an archipelago situated in the Caribbean Sea, with a population of more than 450,000 inhabitants. A prospective epidemiological mother–child cohort (TIMOUN study) is currently being followed in Guadeloupe in order to study the impact of prenatal chlordecone exposure on pregnancy outcome and infant development. Women in the second trimester of pregnancy who planned to give birth in the public hospitals of Grande-Terre and Basse-Terre (accounting for 70% of all deliveries in Guadeloupe) from December 2004 to December 2007 were invited to participate in the study. A detailed informed consent was obtained from 1068 pregnant women. The research procedures were approved by the Guadeloupean Ethics Committee for biomedical studies involving human subjects. A prenatal maternal face-to-face interview was conducted at enrolment by trained midwives to assess obstetrical, medical, personal, and socioeconomic characteristics. Maternal diseases, adverse delivery incidents as well as newborn anthropometric parameters and health information were collected from child and maternal medical records. Cord blood samples were obtained to document prenatal exposure to chlordecone and to other environmental contaminants and nutrients. Breast-milk samples were collected 3 months after delivery for chlordecone quantification. Infants were tested at 7 months of age to evaluate their visual acuity, cognition, and motor development. Maternal interviews were conducted at that time to assess potential confounders pertaining to sociodemographic and psychosocial domains as well as the quality of stimulation provided by the family.

Exclusion criteria associated with maternal diseases were history of diabetes, gestational diabetes mellitus, hypertension, epilepsy, human immunodeficiency virus infection, and long-term corticotherapy ($n=254$). Exclusion criteria for newborns ($n=223$) were not singleton, gestational age <37 wk, APGAR <7 at 5 min, intrauterine growth restriction <10th percentile of birth weight for gestational age, severe respiratory distress, severe icterus with 3 sessions (2–3 h/session) of intensive phototherapy, hypoglycemia and confirmed materno-foetale infection treated with antibiotics >48–72 h. For the remaining 591 participants, 373 were not contacted because of incorrect address or refusal to participate, and 65 had incomplete data regarding chlordecone quantification in umbilical cord or important sociodemographic information.

2.2. Biomarkers and laboratory procedures

Chlordecone, polychlorinated biphenyl congener 153 (PCB 153), dichlorodiphenyl dichloroethylene (*p,p′*-DDE), and lipids were measured in cord plasma, whereas total mercury (Hg), lead (Pb), selenium (Se) and docosahexaenoic acid (DHA) were measured in cord whole blood. Chlordecone concentrations were also measured in breast milk obtained at the 3-month postnatal visit. All the laboratory procedures are presented in Supplemental material Section 1.

2.3. Postnatal exposure to chlordecone

2.3.1. Exposure from breast milk

Potential effects of infants' exposure to chlordecone through breast milk on neurodevelopment were evaluated by several approaches. First, we considered if breastfeeding status (yes or no), duration of breastfeeding, and duration of exclusive breastfeeding were associated with any of the outcomes. Second, we evaluated if the concentration of chlordecone in breast milk alone or multiplied by the number of weeks of breastfeeding was related to the outcomes variables. Measurement of chlordecone concentrations in breast milk was made for 88 out of 96 breastfed infants. For the remaining breastfed infants, a value equal to the median concentration of chlordecone was imputed. Then, we examined if the daily intake of breast milk multiplied by the concentration of chlordecone in breast milk could be associated with the infants' developmental outcomes.

2.3.2. Exposure from contaminated food

At the 7-month visit, a semiquantitative food frequency questionnaire was administrated by a trained interviewers to the mother in order to obtain information on the infant dietary intake including breast milk, baby formula milk, solid food, cow milk, juice, and tap and bottle water. Information regarding the age of introduction of the food item, portion size, number of days per week the items were consumed, and type of supplies (market, short circuit, small or large distributions) were documented.

Contamination of food items was obtained from a survey conducted in Guadeloupe from July 2006 to January 2007 by the public health authorities (AFSSA, 2007) and designed to be representative of consumption habits and sources of supply of the Guadeloupean population, according to the WHO guidelines (FAO/WHO, 1997; FAO/WHO, 2000). Data on water pollution were obtained from the Guadeloupe Health and Social Development Directory control campaigns undertaken in 2005. Daily dietary intake of chlordecone in μg/kg body weight/day was assessed by multiplying the quantity of each food (or beverage) item eaten daily by its mean estimated chlordecone level and divided by infant body weight. Residue levels were modulated according to the type of supplies described in the questionnaire. Use of contaminated tap water for preparation of baby formula milk was also considered in the dietary intake calculation.

2.4. Outcomes

2.4.1. Fagan test of infant intelligence (FTII)

The FTII, which has been found to be sensitive to prenatal exposure to environmental contaminants, such as PCBs, and maternal substance use (Jacobson et al., 1985; Jacobson et al., 1993), was administered to assess visual recognition memory and speed of processing visual information (Fagan and Singer, 1983; Jacobson et al., 1992). The infant is shown two identical target photos for a fixed period and is then shown the familiar target paired with a novel one. Two measures are computed: novelty preference, defined as the proportion of looking time devoted to the novel stimulus, and average duration of the infant's visual fixations to the stimuli. Novelty preference is thought to reflect recognition memory and is based on the infant's tendency to look longer at novel stimuli compared to familiar ones. Visual fixations are used to represent the speed of processing the visual stimuli for memory encoding (Jacobson et al., 1992). Novelty preference and fixation duration during the first year of life are moderately predictive of childhood IQ scores (McCall and Carriger, 1993; McGrath et al., 2004).

2.4.2. Teller visual acuity card test II (TAC)

This test was developed to assess binocular visual acuity based on preferential looking testing method for pre-verbal infant. This test consists of a presentation of a series of cards containing increasingly narrow patches of black and white square-wave grating. The distance between the infant and examiner at this age is 55 cm. The trained tester starts with a coarse grating (0.23 cycles/cm) and then proceeds with a finer grating at a 0.5 octave steps until the infant shows no more visual preference or when the tester reaches 38.0 cycles/cm. The final grating indicates the infant's visual acuity.

2.4.3. Brunet-Lezine scale of psychomotor development of early childhood (revised Brunet-Lezine)

The revised version of the Brunet-Lezine was developed to evaluate four developmental domains (fine and gross motor development, language, and socialization) for infants aged 2 to 30 months (Josse, 1997). In this study, our assessment focused on motor functions. In order to reduce the length of testing, only a limited number of items were administrated. Three out of 11 (7 to 9 months) and 6 out of 13 items (7 to 10 months) on the fine and gross motor development subscales were

assessed, respectively. Assessment of the infants' motor development was based on maternal report (see Supplemental material Section 2).

2.5. Statistical analyses

Cord chlordecone concentrations were categorized into three groups (limit of detection (LD), > LD– ≤ median, > median), because more than 30% of chlordecone levels in blood samples were below the LD of the analytical method. The group with chlordecone concentration < LD was considered the group of reference. Chlordecone concentrations in breast milk were measured in a subsample of 88 nursing mothers. A value equal to half the LD of the analytical method was attributed to samples with nondetected concentrations of chlordecone in breast milk as well as PCBs and *p,p′*-DDE in plasma. Also, a value equal to the median concentration of chlordecone (median=0.70 μg/L) quantified in the subsample was imputed to the remaining breastfed infant ($n=8$) for which chlordecone concentrations in breast milk were missing. To satisfy criteria of normality, processing speed scores derived from the FTII and postnatal intake of contaminated food were log-transformed and squared, respectively.

The following variables were considered as potential confounders: all socioeconomic and medical characteristics of mothers and infants presented in Table 1, maternal vitamin supplementation during pregnancy (yes/no), cord Se concentration, and infant medications use at time of assessment (yes/no for antipyretics and drugs inducing drowsiness or agitation) as well as maternal non verbal intellectual functioning assessed with the Raven's Progressive Matrices continuous score (Raven et al., 1992), single parenting (yes/no) and maternal depression from continuous score on the Edinburgh Postnatal Depression Scale (Cox et al., 1987). Cries, hits, and threats between parents were considered domestic violence. Birth complications were defined as any of the following delivery incidents: placental abruption, foetal heart rate abnormalities, maternal fever, emergency caesarean section, amniotic fluid with meconium, funicular vascular anomalies, and APGAR < 4 at 1 min.

Simple and multiple linear regression models were used to evaluate in separate models the relation of cord chlordecone groups, postnatal intake of contaminated food, and postnatal exposure through breast milk with outcomes assessed through the FTII and the TAC. In order to evaluate the overall potential effect of prenatal and postnatal exposure to chlordecone on cognitive and visual development, categories of cord chlordecone concentrations as well as postnatal exposure to contaminated food and breast milk were also evaluated jointly in models. Linear trends were tested in categorical models of prenatal exposure to chlordecone.

Logistic regression models were conducted to assess the associations between chlordecone exposures and motor function. Due to low percentage of detection, chlordecone concentrations were categorised as below and over the LD, and fine and gross motor parameters as low and high scores. Postnatal exposure through breastfeeding and consumption of contaminated food on infants' motor development were also evaluated individually and jointly with prenatal exposure by logistic regression models.

Simple regressions between potential confounding variables and developmental outcomes were performed to determine which covariates should be included in multiple linear and logistic regression models. Covariates associated at a p value ≤ 0.20 were included together in multiple regression models to assess their confounding influence by removing them one by one, starting with the least significant with the outcomes. Covariates modifying the regression coefficients of any of the two chlordecone exposure groups by more than 10% were included in adjusted models. Models were systematically adjusted for laboratory batch of analysis of chlordecone. Interaction terms between exposure groups and gender in relation to developmental outcomes were tested in full models. Because all of the interaction terms were not significant, potential developmental effects of chlordecone on male and female infants were examined jointly.

Lipophilic molecule concentrations are routinely expressed on a per-unit serum-lipid basis, but this approach is more prone to estimate bias (Schisterman et al., 2005). Nevertheless, to take into account the chlordecone fraction transported by lipids we considered total lipids in adjustment models. Whole cord blood Hg concentration was found to be a confounder in the multiple logistic model of cord chlordecone with gross motor scores. A bilateral p-value < 0.05 was considered statistically significant. Outliers were defined as more than 2.5 standard deviations from the mean of the residuals. All statistical analyses were performed with SAS (version 9.2; SAS Institute Inc., Cary, NC, USA).

3. Results

Sociodemographic and medical characteristics of participating mothers and infants are presented in Table 1. Most of the mothers were 18 years of age or older, were born in Guadeloupe, and had completed high school. At recruitment, 21% of mothers were obese (BMI ≥ 30). Only 6% reported smoking, and 2% drinking alcohol during pregnancy. Four percent of infants were macrosomes at birth (> 4000 g). No infant had clinically diagnosed visual problems. Chlordecone was detected in 56.2% and in 77.3% of cord plasma and breast milk samples, respectively. Correlations of cord chlordecone concentrations with chlordecone in breast milk and postnatal exposure through contaminated food were 0.38 ($p<0.001$) and −0.08 ($p=0.30$), respectively. Mean umbilical cord plasma concentrations of chlordecone was lower than concentration of *p,p′*-DDE, but higher than PCB 153 level. While cord blood levels of chlordecone were unrelated to *p,p′*-DDE ($r=0.02$, $p=0.84$) and Pb ($r=0.02$, $p=0.84$), they were related to PCB 153 ($r=0.16$, $p=0.05$) and Hg ($r=0.34$, $p<0.001$).

The associations between prenatal and/or postnatal exposure to chlordecone with performance on the TAC and the FTII are presented in Table 2. Prenatal and/or postnatal exposures to chlordecone were unrelated to visual acuity, whereas cord DHA concentrations were positively associated with this outcome ($\beta=0.20$, $p=0.02$). In multivariate analysis, cord concentrations of chlordecone above the median were associated with a significant decrease in novelty preference on the FTII. A significant linear negative trend was also found. Because none of the associations between exposure to chlordecone through breastfeeding and the developmental outcomes were significant, results are not presented. Higher postnatal intake of chlordecone through consumption of contaminated food was marginally related to poorer novelty preference score ($p=0.07$). Results did not change when prenatal and postnatal exposures were considered altogether. However, when the only outlier was removed from the analysis, significant associations with postnatal exposure through contaminated food alone (adjusted $\beta=-0.15$, $p=0.05$) and with prenatal exposure (adjusted $\beta=-0.15$, $p=0.04$) were found. Cord chlordecone concentrations were not associated with processing speed on the FTII. Although postnatal chlordecone intake through consumption of contaminated food was marginally significant with processing speed ($p=0.07$), it was no longer significant when the joint exposures during the fetal and postnatal development were considered at the same time. Nor did removal of an outlier change the results.

Crude and adjusted ORs for the association between cord plasma chlordecone and fine and gross motor functions are presented in Table 3. A significant higher risk of obtaining a low score (< 2 items succeeded) on the fine motor scale was found in infants with detectable cord chlordecone levels. Postnatal intake of chlordecone through consumption of contaminated food was not significantly associated with fine motor function (OR=1.86; 95% CI, 0.56–6.17, for an increase of 1 μg/kg body weight/day of chlordecone). The associations with fine motor function remained similar when the joint effects of prenatal and postnatal exposure to chlordecone were considered (data not shown). Cord chlordecone level above LD as well as postnatal chlordecone intake through contaminated food were not related to lower (< 5 items succeeded) gross motor score (OR=0.24; 95% CI, 0.04−1.35, for an increase of 1 μg/kg body weight/day of chlordecone). Again, this result remained the same when prenatal and postnatal exposures were considered altogether (data not shown). Exposure to chlordecone through breast feeding was never related to fine and gross motor functions.

4. Discussion

Findings from this study support the hypothesis that *in utero* and postnatal exposures to environmental levels of chlordecone are associated with less optimal cognitive and motor development during infancy. A linear decrease in novelty preference with increasing cord concentration of chlordecone and with consumption of contaminated food during the first 7 months of life was

Table 1
Characteristics of study participants ($N=153$).

Variables	N	%	Mean ± SD	Range
Family and pregnancy characteristics				
Maternal age (years)	153		31.2 ± 6.2	15–44
Pre-pregnancy BMI (kg/m^2)	149		27.1 ± 1.1	18.1–47.0
Birthplace of mother	153			
French West Indies (Guadeloupe or Martinique)		75.2		
France		16.3		
Others		8.5		
Maternal education	153			
Primary or none		2.6		
Secondary		45.1		
High school		22.9		
Superior education		29.4		
Pre-pregnancy mother working status (% Yes)	153	46.4		
Number of adults living with the infant	153			
1		14.4		
2		72.6		
3 and more		13.1		
Domestic violence (% Yes)	141	21.3		
HOME[a]	153		31 ± 6	13–41
Parity	153			
0		34.0		
1–2		54.9		
3 and more		11.1		
Antibiotics during pregnancy (% Yes)	153	17.7		
Vaginal infection during pregnancy (%Yes)				
	147	57.8		
Type of delivery (% vaginal)	150	80.7		
Birth complications (% Yes)	144	38.2		
Infant characteristics				
Sex (% female)	153	56.2		
Birth weight (g)	153		3279 ± 380	2570–4350
Gestational age (weeks)	153		39.2 ± 1.1	37.0–41.3
Age at visit (days)	153		236.3 ± 15.4	209–300
Breastfed at birth (%)	153	95.4		
Breastfed at 7 months (%)	141	42.6		
Vitamin supplementation (% Yes)	153	88.2		
Pre and postnatal exposures				
Chemicals use during pregnancy at workplace (% Yes)	153	14.4		
Cord chlordecone concentration (μg/L)[b]	153	56.2	0.53 ± 1.97	< LD–22.89
Breast milk chordecone concentration (μg/L)[b]	88	77.3	1.09 ± 1.15	< LD–6.71
Postnatal intake of contaminated food (μg/kg body weight/day)	153		0.09 ± 0.11	0–0.73
Cord Hg (nmol/L)[b]	146	100	30 ± 1[c]	7–230
Cord PCB 153 (μg/L) [b]	147	67.4	0.21 ± 2.02[c]	0.06–0.98
Cord DDE (μg/L) [b]	147	87.8	0.49 ± 3.36[c]	0.06–11.34
Cord Pb (μmol/L) [b]	146	100	0.07 ± 1.57[c]	0.02–2.08
Cord DHA (% total phospholipids)	141		4.1 ± 1.5	1.7–8.9
Cord Se (μmol/L)	146		1.63 ± 0.32	1.1–2.7
Postnatal tobacco use (% Yes)	153	13.1		
Neurodevelopmental outcomes				
Fagan tests of infant intelligence				
Novelty preference (%)	153		58 ± 7	37–77
Processing speed (s)	153		1.82 ± 0.49	0.95–3.82
Teller acuity cards				
Visual acuity	151		8.59 ± 3.62	0.43–19.00
Brunet-Lezine				
Fine motor	135			
0–1 items (succeeded %)		27.4		
2–3 items (succeeded %)		72.6		
Gross motor	139			
1–5 items (succeeded %)		54.7		
6 items (succeeded %)		45.3		

BMI: Body mass index; HOME: Home Observation for Measurement of the Environment; Hg: Mercury; PCB 153: Polychlorinated biphenyl congener 153; DDE: *p,p′*-dichlorodiphenyl dichloroethylene; Pb: lead; DHA: Docosahexaenoic acids; Se: Selenium.

[a] Two items were removed from the original scale because the evaluation was not made at home (Bradley and Caldwell, 1979).
[b] Percentage detected.
[c] Geometric mean among individuals with detected concentration of contaminants.

found. Additionally, we observed a tendency for longer processing time to encode visual stimuli into memory with increasing intake of contaminated foodstuffs. By contrast, visual acuity was unrelated to chlordecone exposure during infancy. Finally, infants with a detectable level of chlordecone in cord were at greater risk of lower score on fine motor, without gross motor effects.

Table 2
Association between chlordecone exposure and cognitive and visual development at 7 months.

	Teller acuity cards			Fagan tests of infant intelligence					
	Visual acuity[b] ($N=135$)			Novelty preference[c] ($N=153$)			Processing speed[d] ($N=130$)		
	N	Adjusted		*N*	Adjusted		*N*	Adjusted	
Prenatal exposure alone		β (95% CI)	*p*-value		β (95% CI)	*p*-value		β (95% CI)	*p*-value
Cord blood (μg/L)									
LD[a]	58	1		67	1		55	1	
> LD, ≤ median,	38	−0.11(−0.29–0.06)	0.197	43	−0.10(−0.26–0.06)	0.234	35	0.15(−0.04–0.35)	0.111
> median	39	−0.08(−0.26–0.10)	0.377	43	−0.19(−0.35 – −0.03)	0.022	40	0.05(−0.14–0.24)	0.597
p-value for trend			0.294			0.019			0.474
Postnatal exposure alone									
Postnatal intake of contaminated food (μg/kg body weight/day)	135	−0.08(−0.31–0.10)	0.308	153	−0.14(−0.29–0.01)	0.071	130	0.16(−0.01–0.41)	0.066
Prenatal and postnatal exposures									
Cord blood (μg/L)									
LD[a]		1			1			1	
> LD, ≤ median,		−0.10(−0.27–0.07)	0.283		−0.09(−0.25–0.07)	0.284		0.12(−0.07–0.32)	0.212
> median		−0.08(−0.25–0.10)	0.382		−0.19(−0.35 – −0.04)	0.017		0.04(−0.14–0.23)	0.668
p-value for trend			0.318			0.016			0.578
Postnatal intake of contaminated food (μg/kg body weight/day)		−0.06(−0.28–0.14)	0.500		−0.14(−0.28–0.01)	0.072		0.12(−0.06–0.34)	0.173

Abbreviations: LD, limit of detection.

[a] Prenatal exposure to chlordecone is divided into 3 groups: LD = 0.06 μg/L; > LD, ≤ median correspond to > 0.06 to 0.31 μg/L; > median correspond to > 0.31 μg/L.
[b] All models adjusted for pre-pregnancy body mass index, maternal vaginal infection, cord DHA concentrations, plasma lipid concentrations, sex of infant, HOME total score, child examiner.
[c] All models adjusted for pre-pregnancy maternal employment status, cord plasma lipid concentrations, infant vitamin supplementation, postnatal exposure to maternal tobacco smoke, number of adults living with the infant, child examiner.
[d] All models adjusted for pre-pregnancy body mass index, maternal vaginal infection, medications and chemicals use during pregnancy, type of delivery, plasma lipid concentrations, sex of infant, maternal education, number of adults living with the infant, domestic violence, HOME total score.

Table 3
Association between prenatal chlordecone exposure and motor function with the Brunet-Lezine.

Cord chlordecone concentrations (μg/L)					
Fine motor score[b]	< LD[a]	≥ LD	Crude OR (95% CI)	Adjusted OR (95% CI)	*p*-value
≥ 2 items succeeded	10	27	1.00	1.00	
< 2 items succeeded	50	42	1.25(1.07–1.45)	1.26(1.09–1.47)	0.002
Gross motor score[c]					
≥ 5 items succeeded	24	30	1.00	1.00	
< 5 items succeeded	33	42	0.94(0.82–1.09)	0.96(0.81–1.13)	0.603

Abbreviations: OR, odds ratio; LD, limit of detection.

[a] LD for cord chlordecone = 0.06 μg/L.
[b] Logistic regression model adjusted for plasma lipid concentrations, age of infant at testing, birthplace of mother, domestic violence.
[c] Logistic regression model adjusted for birth complications, cord Hg concentrations, plasma lipid concentrations, age of infant at testing, infant vitamin supplementation, birthplace of mother, postnatal exposure to maternal smoking.

Visual impairment was the third most reported symptom in the neurological syndrome associated with chlordecone intoxication (Cannon et al., 1978). This deficit was characterized by incapacities to fixate and focus and the presence of a nystagmus. Visual acuity was unaffected, although blurred vision and visual hallucinations have been reported (Taylor, 1982). In our study, we did not find association between infant visual acuity and prenatal or postnatal exposure to chlordecone. Lack of association may be explained by the lower level of exposure in our population. Nevertheless, it is worth noting that the significant associations between chlordecone, short-term recognition memory and processing speed are not mediated by visual impairments that could have impacted on the test performance.

In our population based-study, we observed a dose-dependent decrease in novelty preference in 7-month-old infants with higher cord chlordecone concentrations. Furthermore, we observed that higher postnatal intake of contaminated food also tended to be associated with poorer novelty preference and slower processing speed. The preference for novelty task provide an indicator of short-term visual memory in infants (Fagan and Singer, 1983), while processing speed represent the time necessary to process the information into memory or impaired attention (Colombo and Mitchell, 1990). Our results are consistent with reports of poorer short-term memory among workers, and the dose-response relation observed between blood chlordecone concentrations and severity of neurological symptoms (Cannon et al., 1978). Although mean chlordecone cord plasma concentration in our study was a thousand times lower than the one measured among the plan workers' (Guzelian, 1982), the observed effects could result from the greater vulnerability of the developing brain to neurotoxicants and the resulting permanent organisational deficits (Grandjean and Landrigan, 2006; Rice and Barone, 2000). In rodent models, pre-weaning rats exposed to chlordecone during the neonatal period exhibited memory impairment, particularly in early learning and information retention in passive avoidance tests (Mactutus and Tilson, 1984; Mactutus et al., 1982). Early studies have shown that

chlordecone increases 5-hydroxyindoleacetic acid levels in the rat hippocampus (Tilson et al., 1986), a brain area involved in learning and memory process. In addition, estrogen modulates memory-related synaptic plasticity in the hippocampus. Some estrogenic chemicals have been shown to modulate synaptic plasticity of hippocampal neurons (Ogiue-Ikeda et al., 2008). Then it is reasonable to postulate that the estrogen-like properties of chlordecone might also affect synaptic plasticity and be involved in memory deficits.

The observed effects of prenatal chlordecone exposure on fine motor development are in accordance with the observation of intention tremors (triggered by aiming for a target) in the Hopewell employees. Presence of tremors in the upper limbs was the main complaint, characterised as interfering in daily activities (Cannon et al., 1978). Although infants were evaluated with a limited number of items aimed to document fine motor function in the Brunet-Lezine, those with detectable cord level of chlordecone obtained lower scores then those with undetectable level. Alternatively, gross motor development was unrelated to *in utero* or postnatal exposure to chlordecone at these levels. In rats, chlordecone exposure during neonatal development induced fine body tremors and depressed undifferentiated motor activities (Mactutus and Tilson, 1984). In this animal study, reasons for a reduction in motor activities were unclear and were attributed to tremor interference with locomotion. Several mechanisms have been proposed to explain the mode of action of chlordecone on tremors induction such as Na^+-K^+ATPases inhibition, decline of brain dopamine and alteration of calcium regulation in the synaptosomes (Desaiah, 1982).

In this study, no impact of breastfeeding was found, with or without taking into account concentration of chlordecone in breast milk and/or breastfeeding duration. Several reasons can account for these results. First, because breast milk samples were taken 3 months after delivery, chlordecone concentrations may have been underestimated due to depuration. Also, the toxicocinetic of chlordecone is unique compared to other organochlorines. This molecule was shown to bind to serum albumin and high-density lipoproteins, to have a partitioning coefficient lipid:-blood of 7 (instead of 100 to 600 for other organochlorines), and to be mainly eliminated by biliary excretion (Faroon et al., 1995). In the absence of knowledge of the kinetic of excretion of chlordecone in breast milk (where the lipids derived from high-density lipoproteins is very low), it was difficult to predict the exposure of breastfed infants with only one measurement at 3 months. Together these methodological problems may have introduced an undifferential exposure classification bias, which underestimated the strength of the association. Additionnaly, several studies have shown that breastfeeding is beneficial for cognitive and neurological developments, despite infants exposure to environmental contaminants (Jacobson and Jacobson, 2003; Koopman-Esseboom et al., 1996; Patandin et al., 1999; Ribas-Fito et al., 2007). Nutrients in breast milk, such as DHA and immunoglobins or maternal stimulation may account for the positive effect of breastfeeding on infant development (Anderson et al., 1999; Der et al., 2006; Jacobson et al., 2008).

This study has several strengths and limits. First, pre- and postnatal exposures to chlordecone have been estimated from several sources of exposure (transplacental transfer, consumption of contaminated water and food, and breast milk), for which the independent and joint effects on infant development were evaluated. The estimation of postnatal food chlordecone intake was benefit by recent survey (French Agency for Food Safety) on contamination level of foodstuff in Guadeloupe. Although several participants were excluded for medical purposes or were lost to follow-up, they were no statistical difference between excluded and included participants with regard to maternal and newborns characteristics. Confounding effects of a large number of socio-economic and medical covariates, including other recognized neurotoxicants (Hg, Pb, DDE and PCB) and beneficial nutrients (DHA) were examined in the analyses. Nevertheless, we cannot completely exclude residual confounding. Nondifferential postnatal exposure misclassification is likely, which might have underestimated the strength of the association with the developmental outcomes. Finally, because of time constraints, we were unable to perform the whole Brunet-Lezine test. Therefore, results with motor function should be interpreted with caution.

5. Conclusions

The present study was undertaken to evaluate early cognitive, visual, and motor impairments on infants exposed to chlordecone *in utero* and during postnatal development. The findings indicate that prenatal exposure was associated with reduced visual recognition memory and an increasing risk of non-optimal fine motor development. Furthermore, postnatal exposure was related to poorer visual recognition memory and longer time to process visual information. In light of these results and considering that these infants will be chronically exposed to chlordecone through consumption of contaminated foodstuffs, it is essential to investigate long-term developmental deficits and evaluate if these early impairments are predictive of poorer neurobehavioral development at school age.

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Ethics

The participation of human subjects did occur after informed consent was obtained. The research procedures were approved by the Guadeloupean Ethics Committee for biomedical studies involving human subjects.

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Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2012.07.006.

References

AFSSA, Actualisation de l'exposition alimentaire au chlordécone de la population antillaise. Évaluation de l'impact de mesures de maitrise des risques. Avalaible: 〈http://www.anses.fr/Documents/RCCP-Ra-ChlAQR2007.pdf〉 (accessed 22 March 2012). Document technique AQR/FH/2007-219, 2007, pp. 79.

Anderson, J.W., Johnstone, B.M., Remley, D.T., 1999. Breast-feeding and cognitive development: a meta-analysis. Am. J. Clin. Nutr. 70, 525–535.
Bradley, R.H., Caldwell, B.M., 1979. Home observation for measurement of the environment: a revision of the preschool scale. Am. J. Ment. Defic. 84, 235–244.
Cabidoche, Y., Achard, R., Cattan, P., Clermont Dauphin, C., Massat, F., Sansoulet, J., 2009. Long-term pollution by chlordecone of tropical volcanic soils in the French West Indies: a simple leaching model account for current residue. Environ. Pollut. 157, 1697–1705.
Cannon, S.B., Veazey Jr., J.M., Jackson, R.S., Burse, V.W., Hayes, C., Straub, W.E., Landrigan, P.J., Liddle, J.A., 1978. Epidemic kepone poisoning in chemical workers. Am. J. Epidemiol. 107, 529–537.
Cellule interrégionale d'épidemiologie Antilles Guyane, 2005. Pesticides organochlorés et santé publique aux Antilles françaises. Bull. Alerte Surveillance Antilles Guyane. 8, 13.
Cohn, W.J., Boylan, J.J., Blanke, R.V., Fariss, M.W., Howell, J.R., Guzelian, P.S., 1978. Treatment of chlordecone (Kepone) toxicity with cholestyramine. Results of a controlled clinical trial. N. Engl. J. Med. 298, 243–248.
Colombo, J., Mitchell, D.W., 1990. Individual differences in early visual attention: fixation time and information processing. In: Colombo, J., Fagen, J. (Eds.), Individual Differences in Infancy: Reliability, Stability, Prediction. Lawrence Erlbaum Associates, Hillsdale, NJ, pp. 193–227.
Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br. J. Psychiatry. 150, 782–786.
Der, G., Batty, G.D., Deary, I.J., 2006. Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis. BMJ 333, 945.
Desaiah, D., 1982. Biochemical mechanisms of chlordecone neurotoxicity: a review. Neurotoxicology 3, 103–110.
Dubuisson, C., Heraud, F., Leblanc, J.C., Gallotti, S., Flamand, C., Blateau, A., Quenel, P., Volatier, J.L., 2007. Impact of subsistence production on the management options to reduce the food exposure of the Martinican population to Chlordecone. Regul. Toxicol. Pharm. 49, 5–16.
Fagan, J., Singer, L., 1983. Infant Recognition Memory as A Measure of Intelligence. In: Lipsitt, L., Rovee-Collier, C. (Eds.), Advances in infancy research, Norwood, NJ, pp. 31–78.
FAO/WHO, Food Consumption and Exposure Assessment of Chemicals. WHO/FSF/FOS/97.5. Report of a FAO/WHO Consultation. World Health Organization, 10–14 February 1997, Geneva, Switzerland 1997, pp. 69.
FAO/WHO, Proceedings of the Joint FAO/WHO Workshop on Methodology for Exposure Assessment of Contaminants and Toxins in Food. WHO/SDE/PHE/FOS/00.5. World Health Organization, 7–8 June 2000, Geneva, Switzerland, 2000, pp. 20.
Faroon, O., Kueberuwa, S., Smith, L., DeRosa, C., 1995. ATSDR evaluation of health effects of chemicals. II. Mirex and chlordecone: health effects, toxicokinetics, human exposure, and environmental fate. Toxicol. Ind. Health 11, 1–203.
Grandjean, P., Landrigan, P.J., 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368, 2167–2178.
Guldner, L., Multigner, L., Heraud, F., Monfort, C., Thome, J.P., Giusti, A., Kadhel, P., Cordier, S., 2010. Pesticide exposure of pregnant women in Guadeloupe: ability of a food frequency questionnaire to estimate blood concentration of chlordecone. Environ. Res. 110, 146–151.
Guzelian, P.S., 1982. Comparative toxicology of chlordecone (Kepone) in humans and experimental animals. Annu. Rev. Pharmacol. Toxicol. 22, 89–113.
Hammond, B., Katzenellenbogen, B.S., Krauthammer, N., McConnell, J., 1979. Estrogenic activity of the insecticide chlordecone (Kepone) and interaction with uterine estrogen receptors. Proc. Nat. Acad. Sci. U.S.A. 76, 6641–6645.
Hudson, P.M., Yoshikawa, K., Ali, S.F., Lamb, J.C.T., Reel, J.R., Hong, J.S., 1984. Estrogen-like activity of chlordecone (kepone) on the hypothalamo-pituitary axis: effects on the pituitary enkephalin system. Toxicol. Appl. Pharmacol. 74, 383–389.
Jacobson, J.L., Jacobson, S.W., 2003. Prenatal exposure to polychlorinated biphenyls and attention at school age. J. Pediatr. 143, 780–788.
Jacobson, J.L., Jacobson, S.W., Muckle, G., Kaplan-Estrin, M., Ayotte, P., Dewailly, E., 2008. Beneficial effects of a polyunsaturated fatty acid on infant development: evidence from the inuit of arctic Quebec. J. Pediatr. 152, 356–364.
Jacobson, S.W., Fein, G.G., Jacobson, J.L., Schwartz, P.M., Dowler, J.K., 1985. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev. 56, 853–860.
Jacobson, S.W., Jacobson, J.L., O'Neill, J.M., Padgett, R.J., Frankowski, J.J., Bihun, J.T., 1992. Visual expectation and dimensions of infant information processing. Child Dev. 63, 711–724.
Jacobson, S.W., Jacobson, J.L., Sokol, R.J., Martier, S.S., Ager, J.W., 1993. Prenatal alcohol exposure and infant information processing ability. Child Dev. 64, 1706–1721.
Josse, D., 1997. Brunet-Lezine Révisé: Échelle de Développement Psychomoteur de la Première Enfance. Établissement d'Applications Psychotechniques, Paris, France.
Koopman-Esseboom, C., Weisglas-Kuperus, N., de Ridder, M.A., Van der Paauw, C.G., Tuinstra, L.G., Sauer, P.J., 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97, 700–706.
Mactutus, C., Tilson, H.A., 1985. Evaluation of long-term consequences in behavioural and/or neural function following neonatal chlordecone exposure. Teratology 31, 177–186.
Mactutus, C.F., Tilson, H.A., 1984. Neonatal chlordecone exposure impairs early learning and retention of active avoidance in the rat. Neurobehav. Toxicol. Teratol. 6, 75–83.
Mactutus, C.F., Unger, K.L., Tilson, H.A., 1982. Neonatal chlordecone exposure impairs early learning and memory in the rat on a multiple measure passive avoidance task. Neurotoxicology 3, 27–44.
McCall, R.B., Carriger, M.S., 1993. A meta-analysis of infant habituation and recognition memory performance as predictors of later IQ. Child Dev. 64, 57–79.
McGrath, E., Wypij, D., Rappaport, L.A., Newburger, J.W., Bellinger, D.C., 2004. Prediction of IQ and achievement at age 8 years from neurodevelopmental status at age 1 year in children with D-transposition of the great arteries. Pediatrics 114, e572–e576.
Multigner, L., 2006. Pesticides organochlorés aux Antilles: États d'avancement des études épidemiologiques. Bull. Alerte Surveillance Antilles Guyane, 9.
Multigner, L., Ndong, J.R., Giusti, A., Romana, M., Delacroix-Maillard, H., Cordier, S., Jegou, B., Thome, J.P., Blanchet, P., 2010. Chlordecone exposure and risk of prostate cancer. J. Clin. Oncol. 28, 3457–3462.
Ogiue-Ikeda, M., Tanabe, N., Mukai, H., Hojo, Y., Murakami, G., Tsurugizawa, T., Takata, N., Kimoto, T., Kawato, S., 2008. Rapid modulation of synaptic plasticity by estrogens as well as endocrine disrupters in hippocampal neurons. Brain Res. Rev. 57, 363–375.
Patandin, S., Lanting, C.I., Mulder, P.G., Boersma, E.R., Sauer, P.J., Weisglas-Kuperus, N., 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J. Pediatr. 134, 33–41.
Raven, J.C., Court, J.H., Raven, J., 1992. Manual for Raven's Progressive Matrices and Vocabulary Scales: Standard Progressive Matrices. Psychologists, Oxford.
Ribas-Fito, N., Julvez, J., Torrent, M., Grimalt, J.O., Sunyer, J., 2007. Beneficial effects of breastfeeding on cognition regardless of DDT concentrations at birth. Am. J. Epidemiol. 166, 1198–1202.
Rice, D., Barone Jr., S., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. 108 (Suppl 3), 511–533.
Schisterman, E.F., Whitcomb, B.W., Louis, G.M., Louis, T.A., 2005. Lipid adjustment in the analysis of environmental contaminants and human health risks. Environ. Health Perspect. 113, 853–857.
Soine, P.J., Blanke, R.V., Guzelian, P.S., Schwartz, C.C., 1982. Preferential binding of chlordecone to the protein and high density lipoprotein fractions of plasma from humans and other species. J. Toxicol. Environ. Health 9, 107–118.
Taylor, J.R., 1982. Neurological manifestations in humans exposed to chlordecone and follow-up results. Neurotoxicology 3, 9–16.
Tilson, H.A., Hudson, P.M., Hong, J.S., 1986. 5,5-diphenylhydantoin antagonizes neurochemical and behavioral effects of p,p′-DDT but not of chlordecone. J. Neurochem. 47, 1870–1878.