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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