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ORIGINAL ARTICLE

Prenatal β-Hexachlorocyclohexane (β-HCH) Exposure and 7-Year Child IQ in the CHAMACOS Birth Cohort

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Abstract

Fetal and infant exposures to β-hexachlorocyclohexane (β-HCH) occur through placental and breastmilk transfers. No studies have examined the relationship between β-HCH and child intelligence quotient (IQ). This study examined associations between in utero β-HCH exposure and cognitive development in 7-year-old children. Data from women and children ($n = 256$) participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth cohort study were evaluated. We assessed exposure to β-HCH by measuring maternal serum concentration during pregnancy. We administered the Wechsler Intelligence Scale for Children (WISC), Fourth Edition, to children at age 7. Analyses were adjusted for maternal age, country of birth, work status, parity, and other pesticide exposures, language used for child cognitive assessment, and duration of breastfeeding. Higher serum β-HCH concentrations were associated with higher cognitive scores across all unadjusted models for the full-scale and sub-scale cognitive tests. In the adjusted models, a 10-fold increase in serum β-HCH concentration was associated with a 4.5-point increase in Working Memory IQ score (95% CI, 0.6 to 8.3; $p = 0.02$). We observed no significant interaction by length of breastfeeding or sex on associations. Our findings suggest that prenatal exposure to β-HCH is not adversely related to IQ at age 7 in a cohort of Mexican American children with fairly high exposure in utero as measured by maternal serum levels. Future research must replicate these findings in other study cohorts of women and children.

Keywords beta-Hexachlorocyclohexane · Children · Cognitive development · In utero exposure · Neurodevelopment · Organochlorine pesticide

Introduction

Hexachlorocyclohexane (HCH), an organochlorine pesticide, was used extensively around the world until the latter half of the twentieth century when concerns about human health and environmental effects emerged, leading to decreased production and use (Agency for Toxic Substances and Disease Registry 2005; Nayyar et al. 2014; Vijgen et al. 2011). The commercial form of the pesticide, γ-HCH (lindane), and the α-HCH and β-HCH isomers, which are formed during manufacturing of γ-HCH, were listed as persistent organic pollutants during the 2009 Stockholm Convention (Nayyar et al. 2014; Vijgen et al. 2011) leading to use restrictions and elimination as well as requirements for environmental decontamination. HCH isomers are lipophilic and known to bioaccumulate in animal and human tissue (Agency for Toxic Substances and Disease Registry 2005; World Health Organization & International Programme on Chemical Safety 1991).

The USA, the only producer of HCH in North America, ceased all production of γ-HCH in 1976 and voluntarily canceled its agricultural uses in 2006 after a similar Canadian ban passed in 2005 (Agency for Toxic Substances and Disease Registry 2005; Commission for Environmental Cooperation 2013; United States Environmental Protection Agency 2006). In the USA, γ-HCH is currently approved by prescription only for second-line treatment of lice and scabies (Agency for Toxic Substances and Disease Registry 2005; United

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States Environmental Protection Agency 2006) and comes with a black box warning outlining potential neurotoxicity including seizure, dizziness, headache, and paresthesias (FDA 2015). However, despite these changes in the USA and Canada, as of 2013, four authorizations for lindane-based products for agricultural use remained in effect in Mexico (Commission for Environmental Cooperation 2013).

Although HCH use has been largely discontinued in agriculture, human exposure to HCH persists due to environmental contaminations. Human exposure can occur through environmental contamination of soil from previously applied pesticides or historical unregulated chemical waste production dumping practices (Jayaraj et al. 2016; Nayyar et al. 2014; Vijgen et al. 2011). Countries known to have HCH-contaminated environmental sites include Albania, Argentina, Austria, Azerbaijan, Brazil, China, Croatia, Czech Republic, France, Germany, Hungary, India, Italy, Japan, Macedonia, Nigeria, Poland, Romania, Russia, Slovakia, South Africa, Spain, Switzerland, Turkey, The Netherlands, UK, Ukraine, and the USA (Vijgen et al. 2019). Agricultural workers in countries which lacked legislation and regulation can experience high levels of occupational chemical exposure via contact with contaminated soil (Jayaraj et al. 2016) while non-agriculture workers can come in contact with contaminated ground and drinking water near these contaminated sites (Vijgen et al. 2019).

The β-HCH isomer has been used in human biomonitoring of γ-HCH exposures because the calculated median half-life is long (7.2 to 7.6 years) (Jung et al. 1997) and high levels of the β-HCH isomer are found in serum and adipose tissue after γ-HCH exposures (Baumann et al. 1980; Jung et al. 1997). Though numerous studies have documented a decline in β-HCH levels in the general US population (Agency for Toxic Substances and Disease Registry 2005; Kutz et al. 1991), National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004 reveal that detectable levels of β-HCH persist, particularly in older, and Mexican American populations (Centers for Disease Control and Prevention 2009), likely due to exposures pre-regulation in Mexico. Mexican women of childbearing age have been shown to have higher serum concentrations of β-HCH. A 2014 Canadian study showed that Mexican primiparous women have a significantly higher serum concentration of β-HCH compared with Canadian primiparous women likely reflecting higher exposure of β-HCH in Mexico compared with other Northern American countries (Adlard et al. 2014).

Pre- and perinatal chemical exposures are particularly concerning because developing fetuses and neonates may be more susceptible to chemical exposures and these effects could be long lasting (Mitro et al. 2015; Weselak et al. 2007). Fetuses and neonates are at risk of β-HCH exposure through placental and breastmilk transfers (Fytianos et al. 1985; Saxena et al. 1981; Zhang et al. 2018). Studies document a correlation between maternal β-HCH serum and breastmilk concentrations and neonatal and infant β-HCH cord blood and serum concentrations (Choi et al. 2018; Dorea et al. 2001; Sala et al. 2001; Zhang et al. 2018). In utero β-HCH exposure has been associated with increased risk of birth defects (Pathak et al. 2009; Ren et al. 2011), stillbirth (Saxena et al. 1983), preterm birth and low birth weight (Callan et al. 2016; Dewan et al. 2013; Guo et al. 2014; Pathak et al. 2009; Tyagi et al. 2015), and thyroid dysfunction (Alvarez-Pedrerol et al. 2008; Li et al. 2014; Lopez-Espinosa et al. 2010).

HCH has been shown to be neurotoxic in animal studies. For example, one study found in utero γ-HCH exposure significantly reduced radioligand binding to $GABA_A$ receptors in the rat fetal brainstem compared with controls (Brannen et al. 1998). Another reported that repeat γ-HCH exposure in rat pups led to significant increases in micromolecular tracer uptake in the brain indicating neonatal exposure has an effect on blood–brain barrier permeability (Gupta et al. 1999). The authors of both studies concluded that these effects could lead to disruptions in postnatal neurological functions and behavior later in life (Brannen et al. 1998; Gupta et al. 1999). Another study found that rats with gastrointestinal exposure to γ-HCH starting 1 day after birth had dose-dependent myelin deficits in specific brain regions (Serrano et al. 1990).

Data from human studies, however, are limited and inconclusive. A study of a Spanish cohort of 40 newborns found that β-HCH in cord blood was negatively associated with cord blood levels of glutamate, a neurotransmitter in the central nervous system important for normal growth and development, and concluded that this could alter human neurodevelopment (Palou-Serra et al. 2014). In contrast, a sub-analysis of a Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort study ($n = 303$), which examined in utero exposure to organochlorine pesticides, found no association between maternal β-HCH and the Bayley Scales of Infant Development at 6, 12, or 24 months of age (Fenster et al. 2007). None of these studies has specifically examined in utero β-HCH exposure and cognitive performance as measured by IQ testing. However, other organochlorine pesticides with similar properties to β-HCH have been associated with adverse childhood cognitive function and lower IQ scores in other studies (Eskenazi et al. 2013; Eskenazi et al. 2006; Gaspar et al. 2015; Gunier et al. 2017; Jurewicz et al. 2013; Stewart et al. 2008).

In this study, we examined associations between in utero β-HCH exposure and cognitive development in a population of 256 7-year-old children participating in the CHAMACOS birth cohort study. We hypothesized that in utero exposure to β-HCH is negatively associated with cognitive development as measured by the Wechsler Intelligence Scale for Children (WISC), Fourth Edition. To our knowledge, no other studies have examined this relationship in pregnant women and their offspring.

Materials and Methods

Study Population

Study participants were mothers and children in the CHAMACOS study. The CHAMACOS study is a longitudinal birth cohort that enrolled 601 pregnant women, mostly of Mexican descent, living in the Salinas Valley of California between October 1999 and October 2000. Prior publications discuss recruitment and study methods in detail (Eskenazi et al. 2004; Eskenazi et al. 2006; Gaspar et al. 2015; Gunier et al. 2017). In short, pregnant women were recruited when entering prenatal care at the county hospital or one of five community clinics and were eligible if they were ≥ 18 years old, < 20 weeks gestation, Spanish or English speaking, eligible for low-income health insurance (MediCal), and planning to deliver in the county hospital.

Of the 601 women enrolled, 537 stayed in the study through a live birth. For this analysis, we excluded twins ($n = 10$), children with medical conditions that might affect neurodevelopmental testing ($n = 1$ with Down syndrome, $n = 1$ with deafness, $n = 1$ with hydrocephalus, and $n = 1$ with autism), children whose mothers did not have a serum β-HCH measurement during pregnancy ($n = 122$), and children missing neurodevelopmental testing at age 7 ($n = 145$–172, depending on the sub-scale).

The children who were included in this analysis ($n = 256$) did not differ significantly on maternal demographic characteristics compared with the children who were excluded from this analysis due to missing maternal serum β-HCH levels or neurodevelopmental testing at the 7-year study visit. However, children included in this analysis were significantly more likely to be girls ($p = 0.02$), to have breastfed for > 6 months ($p = 0.001$), to have attended preschool ($p < 0.01$), and to have mothers with depression ($p < 0.01$), higher maternal PPVT scores ($p = 0.05$), and higher cumulative average household income by age 7 ($p < 0.01$) than those excluded from this analysis (Table S1). There was no significant difference in maternal serum β-HCH levels between the two groups ($p > 0.05$).

The University of California, Berkeley Committee for the Protection of Human subjects approved this study and written informed consent was obtained from all women and oral assent was obtained from all children at 7 years of age included in this study.

β-HCH Collection and Measurement

Maternal blood samples were collected by venipuncture at the time of the second pregnancy interview (mean ± SD = 25.7 ± 2.2 weeks gestation) or at delivery if pregnancy levels were missing (Bradman et al. 2007). These samples were analyzed for β-HCH using gas chromatography–high-resolution mass spectrometry (GC/MS). Details of sample handling as well as laboratory methods and quality control have been published previously (Barr et al. 2003; Bradman et al. 2007). Isotopically labeled analogues of the target analytes were added to 1 g of serum and all water removed via lyophilization. Accelerated solvent extraction (10% dichloromethane in hexane) was used to extract β-HCH, which was then cleaned with Florisil®, purified with gel permeation chromatography and concentrated. GC/MS was used to analyze β-HCH by isotope dilution calibration for quantification. Each run included quality-control materials and blank samples. The limit of detection (LOD) for β-HCH levels averaged 1.6 pg/g-serum (SD 0.7), and values below this level were assigned the value of LOD/2 (Fenster et al. 2006; Hornung and Reed 1990). Total cholesterol and triglycerides were measured by standard clinical enzymatic methods (Roche Chemicals, Indianapolis, IN) and used to calculate total lipids. β-HCH concentrations were expressed on a serum lipid basis (ng/g of lipids) (Phillips et al. 1989). This method was chosen based on the assumption that lipid-adjusted serum concentrations are a marker for β-HCH in adipose tissue (Schisterman et al. 2005).

Cognitive Assessment

Child cognitive ability at age 7 was measured by the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (Wechsler 2003). A single bilingual psychometrician who was trained and supervised by a pediatric neuropsychologist and blinded to exposure status assessed all children. The majority of assessments occurred in the CHAMACOS field office and a review of videotaped assessments was conducted for quality assurance. Assessments were performed in the dominant language of the child, which was determined at the beginning of the assessment using the oral vocabulary subtest of the Woodcock-Johnson/Woodcock-Munoz Tests of Cognitive Ability in both English and Spanish (Woodcock and Munoz-Sandoval 1990). Four domains of cognitive ability were assessed on the WISC-IV: Verbal Comprehension (composed of Vocabulary and Similarities subtests), Perceptual Reasoning (Block Design and Matrix Reasoning subtests), Working Memory (Digit Span and Letter-Number Sequencing subtests), and Processing Speed (Coding and Symbol Search subtests). US population–based norms for English- and Spanish-speaking children were used to standardize WISC-IV scores (mean = 100, SD = 15) (Wechsler 2003). The relationship between prenatal serum β-HCH level and cognitive ability was assessed for the WISC-IV Full-Scale intelligence quotient (IQ) (FSIQ) and for each of four IQ sub-scales. The Letter-Number Sequencing or Symbol Search subtests were not administered for the first 3 months of assessments resulting in 26 and 27 participants lacking scores for the Processing Speed and Working Memory sub-scales, respectively. Children were

included in each analysis if their standardized score was available. Final populations for each full and sub-scale analysis are as follows: $n = 229$ for FSIQ and Working Memory IQ (WMIQ) analyses, $n = 230$ for Processing speed IQ (PSIQ) analysis, and $n = 256$ for Perceptual Reasoning IQ (PRIQ) and Verbal Comprehension IQ (VCIQ) analyses.

Maternal Interviews and Assessments

Maternal interviews were conducted in Spanish or English by bilingual interviewers and occurred twice during pregnancy (median 13 and 26 weeks gestation), after delivery, and throughout childhood (at 6 months and 1, 2, 3.5, 5, and 7 years). Lifestyle behaviors and demographic information were collected including maternal age, education, country of birth, number of years lived in the USA, marital status, paternal education, and family income. The 6-month visit included maternal verbal intelligence assessment using the Peabody Picture Vocabulary Test (PPVT) for English speakers or the Test de Vocabulario en Imagenes Peabody (TVIP) for Spanish speakers (Dunn and Dunn 1981). The 7-year visits included an assessment of the home learning environment using the Home Observation for Measurement of the Environment (HOME), which includes maternal responses to parenting questions and observed parent–child interactions (Caldwell and Bradley 2003), as well as maternal depression using Center for Epidemiological Studies Depression scale (CES-D) (Lewinsohn et al. 1997; Radloff 1977).

Statistical Analysis

Serum β-HCH concentrations were log10-transformed to stabilize variance and reduce influence of outliers and modeled as a continuous exposure. WISC-IV full and sub-scale scores were approximately normally distributed and modeled as continuous outcomes. A directed acyclic graph (DAG) (Fig. S1) was used a priori to identify covariates that could potentially confound the association between in utero β-HCH exposure and cognitive abilities. Covariates were defined as categorical or continuous variables, as shown in Table 1. These included maternal age (categorical), maternal country of birth (binary), maternal work status (categorical), maternal parity (binary), language of child cognitive assessment (binary), duration of breastfeeding (binary), and other chemical exposures including pregnancy urinary concentrations of dialkyl phosphate (DAP) metabolites (continuous), a marker of organophosphate pesticide exposure, and serum dichlorodiphenyldichloroethylene (DDE) concentration (continuous), which is a metabolite of the pesticide dichlorodiphenyltrichloroethane (DDT). Maternal pregnancy urine DAPs have been shown to be associated with poorer cognitive abilities in prior studies of this and other cohorts (Bouchard et al. 2011; Gonzalez-Alzaga et al. 2015). Maternal serum concentrations of DDE and DDT were also previously associated with neurodevelopment in this cohort (Eskenazi et al. 2006; Gaspar et al. 2015) and, because analysis showed they were highly correlated, only maternal DDE levels (with higher percent detected) were included in our analysis. Maternal country of birth, maternal years in the USA, and maternal preferred language were all significantly correlated to each other so maternal country of birth was chosen to represent immigration status in the primary regression model. Maternal pregnancy urinary DAP and pregnancy serum DDE concentrations were considered as log10-transformed continuous variables.

Bivariate tests of association were conducted for each potential confounder with prenatal serum β-HCH concentration and full and sub-scale IQ scores using *T* tests for categorical covariates with 2 levels, analysis of variance (ANOVA) for covariates with ≥ 3 levels, and Pearson coefficients for continuous covariates. Unadjusted and adjusted linear regressions were conducted between the exposure and WISC-IV full or sub-scale outcomes. We retained covariates in the final multivariate regression models that were significant ($p < 0.2$) or caused a greater than 10% change in beta-coefficient in any of the full or sub-scale adjusted regression models when removed. All multivariate regression models were adjusted for maternal age, country of birth, work status, parity, and pregnancy urine DAPs and serum DDE concentrations as well as language used for child cognitive assessment and duration of breastfeeding. Separate sensitivity analyses were performed with maternal years in the USA (categorical) instead of maternal country of birth, with maternal age as a continuous variable instead of categorical and both maternal years in the USA and maternal age as a continuous variable to account for possible residual confounding. The associations between maternal serum β-HCH level and full and sub-scale IQ score were then assessed for interaction by child sex and duration of breastfeeding. We assessed for interaction for duration of breastfeeding to try to explore effects of lactational exposure to β-HCH. Because β-HCH exposure continues during the postnatal period via breastmilk, we hypothesized that effects on cognitive functioning might be greater in children who were breastfed for a long time versus a short time. In a separate sensitivity analysis, we also controlled for covariates occurring after the exposure of interest, including 7-year HOME score (continuous), maternal PPVT score (continuous), maternal depression (dichotomized as CES-D score ≥ or below 16), and maternal poverty status measured as cumulative average household income at 7 years (continuous). These variables have been found to be associated with cognitive abilities in other studies (Bouchard et al. 2011; Ellis and Hennelly 1980; Gunier et al. 2017; Lewinsohn et al. 1997; Luster and Dubow 1992; Neisser et al. 1996; Petterson and Albers 2001; Yeates et al. 1983). The covariates occurring after the exposure were included because they may be proxies for confounders that impact in utero exposure to β-HCH. Missing data for

Table 1 Study cohort characteristics and maternal serum β-HCH concentration (ng/g lipid), CHAMACOS, Salinas Valley, CA, 1999–2008 ($n = 256$)

Characteristic	*N*	(%)	Geometric mean serum β-HCH (ng/g lipid)	(95% CI)	*p* Value
Maternal age (years)					
18–24	108	(42.2)	25.4	(19.6,33.0)	0.03
25–29	91	(35.6)	38.6	(30.2,49.3)	
30–34	35	(13.7)	37.4	(22.2,63.0)	
35–45	22	(8.6)	55.4	(30.9,99.3)	
Maternal country of birth					
USA/other	39	(15.2)	6.2	(4.3,9.0)	< 0.001
Mexico	217	(84.8)	45.0	(38.7, 52.3)	
Maternal years in the USA					
≤ 1	58	(22.7)	48.7	(36.5,65.0)	< 0.001
2–5	72	(28.1)	50.4	(38.1,66.5)	
6–10	59	(23.1)	48.0	(36.0,63.9)	
≥ 11	39	(15.2)	21.7	(15.3,30.7)	
Entire life	28	(10.9)	4.3	(3.1,6.0)	
Maternal education					
≤ 6th grade	113	(44.1)	43.3	(34.8,53.8)	< 0.001
7–12th grade	83	(32.4)	37.1	(28.5,48.3)	
≥ High school graduate	60	(23.4)	17.4	(11.6,26.1)	
Maternal marital status					
Not married	46	(18.0)	22.7	(15.4,33.6)	0.03
Married/living as married	210	(82.0)	36.1	(30.2,43.3)	
Maternal work status					
Did not work	93	(36.3)	29.5	(22.6,38.6)	< 0.001
Some field or agriculture work	104	(40.6)	48.6	(38.5,61.2)	
Other work only	57	(22.3)	19.5	(13.3,28.6)	
Family income at baseline					
At or below poverty level	158	(61.7)	36.5	(30.1,44.3)	0.15
Above poverty level	98	(38.3)	28.6	(21.3,38.4)	
Maternal parity prior to index child					
0	88	(34.4)	44.5	(34.1,58.0)	0.01
≥ 1	168	(65.6)	28.6	(23.2,35.1)	
Child sex					
Boy	115	(44.9)	32.0	(25.5,40.1)	0.68
Girl	141	(55.1)	34.3	(27.1,43.5)	
Language of child neurodevelopment testing					
Spanish	169	(66.0)	47.3	(39.7,56.4)	< 0.001
English	87	(34.0)	16.8	(12.5,22.5)	
Maternal depression at 7 years					
No	201	(78.5)	31.1	(25.8,37.5)	0.13
Yes	55	(21.5)	42.4	(30.1,59.8)	
Breastfeeding duration of index child (months)					
≤ 6 months	131	(51.2)	33.0	(26.2,41.6)	0.93
> 6 months	125	(48.8)	33.5	(26.5,42.4)	
Pregnancy log10 urine (DAPs) (nmol/g Cr)	256				0.91
Pregnancy log10 serum (DDE) (ng/g lipid)	256				< 0.001
Maternal 6-month PPVT score	256				0.15
NSLY79 HOME SF total score at 7 years	256				0.94
Age at neurodevelopment testing (years)	256				0.14

Missing covariates: $N = 2$ maternal work status during pregnancy

Abbreviations: *β-HCH*, beta-hexachlorocyclohexane; *CI*, confidence interval; *DAPs*, dialkyl phosphate; *DDE*, dichlorodiphenyl-dichloroethylene; *PPVT*, Peabody Picture Vocabulary Test; *HOME SF*, Home Observation for Measurement of the Environment

covariates were not imputed, as only two or fewer cases were omitted using complete case analysis.

Statistical significance for main effects was considered if $p < 0.05$ based on two-tailed tests and for interactions if $p < 0.10$. All statistical analyses were performed using STATA, version 15.1 (Stata Corporation, College Station, TX).

Results

Demographic Characteristics

Table 1 presents detailed maternal and child characteristics for the cohort included in this analysis ($n = 256$). Most mothers were born in Mexico (84.8%) with about half having been in the USA for less than 5 years (50.8%). Mothers averaged (SD) 26.3 (5.0) years old and 40.9% worked in agriculture during pregnancy. The majority of mothers reported their family income during pregnancy to be at or below the federal poverty level (61.7%). About half of the children were girls (55.1%) and 66.0% completed the neurodevelopmental testing in Spanish.

Prenatal Serum β-HCH Levels

The geometric mean (GM) serum β-HCH concentrations (confidence interval) for all mothers of children included in this analysis was 33.3 ng/g lipid (28.2 to 39.2), nearly twice as high as the GM serum β-HCH levels found in the Mexican-American general US population (Centers for Disease Control and Prevention 2009). A comparison of the GM of serum β-HCH concentrations from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) study for the U.S. population (Centers for Disease Control and Prevention 2009) and this CHAMACOS study cohort is shown in Fig. 1. In this CHAMACOS study sample, serum β-HCH concentrations ranged from 0.93 to 2206.23 ng/g lipid.

Table 1 shows the association between maternal serum β-HCH concentrations and cohort characteristics. Higher maternal serum β-HCH concentrations were significantly associated ($p < 0.001$) with mothers born in Mexico, fewer years in the USA, less than a high school education, field or agricultural work, higher pregnancy serum DDE levels, and child neurodevelopmental testing in Spanish. Older maternal age, nulliparity, and being married or living as married were also significantly associated ($p < 0.05$) with higher maternal serum β-HCH concentrations. Maternal serum β-HCH levels were not significantly associated with pregnancy urine DAPs ($p = 0.91$).

Child 7-Year-Old WISC-IV Scores

For children included in this analysis, the mean (SD) child FSIQ score at 7 years was 105.2 (13.9) and ranged from 64 to 140 ($n = 229$) (Table S2). The mean (SD) scores for each child WISC-IV at 7 years sub-scale analyses are as follows: 100.2 (14.2) for WMIQ ($n = 229$); 108.5 (13.1) for PSIQ ($n = 230$); 102.0 (16.0) for PRIQ ($n = 256$); 105.1 (14.6) for VCIQ ($n = 256$) (Table S2). Complete ranges for the sub-test scores can be found in Table S2.

Prenatal β-HCH Exposure and Cognitive Function

In crude analyses, higher serum β-HCH concentration was associated with higher cognitive scores, in general, across all the full-scale and sub-scale cognitive tests (Table 2). Significant associations in the unadjusted models were seen

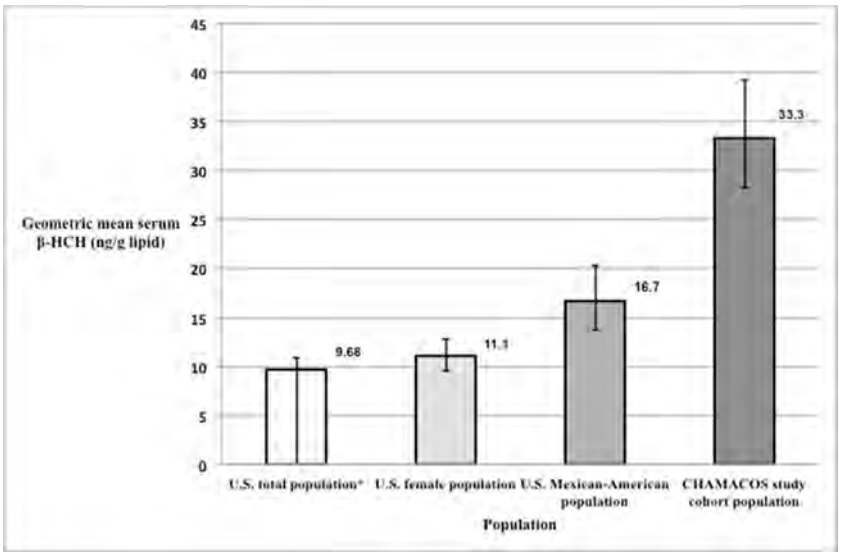

Fig. 1 Geometric mean serum β-HCH concentrations (ng/g lipid) for US populations from the National Health and Nutrition Examination Survey (NHANES) (1999–2000) (Centers for Disease Control and Prevention 2009) compared with CHAMACOS cohort population (1999–2000). Bars = 95% confidence interval. Asterisk indicates lower confidence interval for US total population is below the level of detection (LOD)

Table 2 Unadjusted and adjusted change in cognitive scores in children tested at 7 years of age for a 10-fold increase in maternal serum beta-hexachlorocyclohexane (β-HCH) concentration (ng/g lipid), CHAMACOS study, Salinas Valley, California, 1999–2008

Cognitive test	*N*	Unadjusted model			*N*	Adjusted model[a]			Sensitivity analysis adjusted model[b]		
		β	(95% CI)	*p* Value		*β*	(95% CI)	*p* Value	*β*	(95% CI)	*p* Value
Full-Scale IQ	229	4.2	(1.2,7.2)	< 0.01	228	1.7	(− 1.9,5.4)	0.35	1.4	(− 2.2, 5.0)	0.44
WISC-IV sub-scales											
Working Memory IQ	229	4.5	(1.5,7.6)	< 0.01	228	4.5	(0.6, 8.3)	0.02	4.1	(0.2,7.9)	0.04
Processing Speed IQ	230	2.5	(− 0.3,5.4)	0.08	229	2.8	(− 0.9,6.5)	0.14	2.6	(− 1.1,6.3)	0.17
Perceptual Reasoning IQ	256	0.7	(− 2.8,4.1)	0.70	254	0.5	(− 3.9,4.9)	0.82	0.4	(− 4.0,4.7)	0.87
Verbal Comprehension IQ	256	5.9	(2.8,8.9)	< 0.01	254	0.2	(− 3.1,3.5)	0.90	0.1	(− 3.2,3.4)	0.94

Abbreviations: *β*, beta-coefficient on regression models; *CI*, confidence interval; *WISC-IV*, Wechsler Intelligence Scale for Children, Fourth Edition

[a] All models adjusted for maternal covariates including age, country of birth, work status, parity, pregnancy urine DAP and serum DDE levels, and child covariates including length of breast feeding (months) and language of neurodevelopmental testing.

[b] Sensitivity analysis adjusted models additionally controlled for maternal 6-month PPVT score and maternal depression, HOME score at age 7, and cumulative average household income at 7 years

for Full-Scale IQ score ($\beta = 4.2$; 95% confidence interval (CI), 1.2 to 7.2), Working Memory IQ score ($\beta = 4.5$; 95% CI, 1.5 to 7.6), and Verbal Comprehension IQ score ($\beta = 5.9$; 95% CI, 2.8 to 8.9). The Processing Speed and Perceptual Reasoning sub-scale IQ scores were not significantly associated with serum β-HCH concentrations.

After adjusting for covariates, the significant associations seen for Verbal Comprehension and Full-Scale IQ scores did not persist (Table 2). However, even after adjusting for covariates, a 10-fold increase in serum β-HCH concentration was associated with a 4.5-point increase in Working Memory IQ score (95% CI, 0.6 to 8.3) (Table 2). Results were similar in the sensitivity analysis models with additional covariates including 7-year HOME score, maternal PPVT score, and depression, and cumulative average household income at 7 years (Table 2). This significant finding persisted in separate sensitivity analyses when adjusting for maternal years in the USA instead of maternal country of birth, maternal age as a continuous variable instead of a categorical variable, and both maternal years in the USA and maternal age as a continuous variable (Tables S3–5) though the positive association between Working Memory IQ score and β-HCH became insignificant when adjusting for maternal years in the USA in the sensitivity analysis also adjusting for maternal 6-month PPVT score and maternal depression, HOME score at age 7, and cumulative average household income at 7 years (Table S4).

We observed no significant interaction by length of breastfeeding on associations between maternal serum β-HCH concentrations and cognitive test scores (Table 3). We also observed no interaction by sex; although associations with β-HCH concentration tended in the direction of reduced IQ in boys and increased IQ in girls, none of the associations was statistically significant (Table 4).

Discussion

We found no evidence that prenatal exposure to β-HCH is adversely related to IQ at age 7 years in a cohort of Mexican-American children with fairly high in utero exposure as measured by maternal prenatal serum levels. In fact, we found that prenatal exposure to β-HCH was positively associated with Working Memory IQ score after adjusting for potential confounding covariates. The 4.5-point increase in working memory score for a 10-fold increase in serum β-HCH is about one-third of a standard deviation for the IQ test (SD 15). The range of β-HCH was 0.93–2206.23 ng/g lipid, which encompasses four 10-fold increases. This relationship persisted in sensitivity analysis after further adjustment for covariates known to impact child cognitive scores as well as in additional sensitivity analyses to account for choice of variable and type of variable (i.e., continuous versus continuous) used in the primary regression models. We also found that, among those children who were breastfed longer (> 6 months), higher maternal serum levels of β-HCH did not result in worse IQ scores than those who were breastfed for a shorter time, suggesting that postnatal exposure from breastmilk did not pose any additional risk to cognitive outcomes.

These results are not consistent with findings from studies on other organochlorine pesticides, like DDT, and child IQ (Eskenazi et al. 2013; Eskenazi et al. 2006; Gaspar et al. 2015; Gunier et al. 2017; Jurewicz et al. 2013; Stewart et al. 2008). However, the findings are consistent with prior findings from the CHAMACOS cohort of 303 infants at 6, 12, or 24 months of age that found no association between maternal β-HCH and the Bayley Scales of Infant Development, another proxy for neurodevelopmental outcomes (Fenster et al. 2007).

The statistically significant positive relationship between in utero β-HCH exposure and Working Memory IQ is unusual, contrary to our hypothesis, and not consistent with prior

Table 3 Change in 7-year cognitive scores for breastfeeding ≤ 6 months vs. breastfeeding > 6 months for a 10-fold increase in maternal serum beta-hexachlorocyclohexane (β-HCH) concentration (ng/g lipid), CHAMACOS study, Salinas Valley, CA, 1999–2008

Cognitive test	*N*	Breastfed ≤ 6 months adjusted model[a]		Breastfed > 6 months adjusted model[a]		*p* Value$_{int}$	*N*	Breastfed ≤ 6 months sensitivity analysis adjusted model[b]		Breastfed > 6 months sensitivity analysis model[b]		*p* Value$_{int}$
		β	(95% CI)	*β*	(95% CI)			*β*	(95% CI)	*β*	(95% CI)	
Full-Scale IQ	228	0.2	(− 5.0,5.4)	2.7	(− 1.6,7.1)	0.42	228	− 0.4	(− 5.5,4.8)	2.6	(− 1.7,6.9)	0.33
WISC-IV sub-scales												
Working Memory IQ	228	3.8	(− 1.7,9.2)	4.9	(0.3,9.5)	0.73	228	3.2	(− 2.3,8.7)	4.6	(0.01,9.2)	0.67
Processing Speed IQ	229	0.6	(− 4.6,5.9)	4.2	(− 0.2,8.6)	0.26	229	0.4	(− 4.8,5.6)	4.0	(− 0.4,8.5)	0.25
Perceptual Reasoning IQ	254	0.4	(− 5.7,6.5)	0.6	(− 4.7,5.9)	0.96	254	− 0.4	(− 6.4,5.7)	0.9	(− 4.4,6.2)	0.73
Verbal Comprehension IQ	254	− 0.7	(− 5.4,3.9)	0.9	(− 3.1,4.9)	0.56	254	− 1.0	(− 5.6,3.6)	0.9	(− 3.1,4.9)	0.50

Abbreviations: *β*, beta-coefficient on regression models; *CI*, confidence interval; *WISC-IV*, Wechsler Intelligence Scale for Children, Fourth Edition

[a] All models adjusted for maternal covariates including age, country of birth, work status, parity, pregnancy urine DAP and serum DDE levels, and child covariates including length of breast feeding (months) and language of neurodevelopmental testing

[b] Sensitivity analysis adjusted models additionally controlled for maternal 6-month PPVT score and maternal depression, HOME score at age 7, and cumulative average household income at 7 years

research on organochlorine pesticide exposures and IQ. The reason for this remains unclear; it is possible that an unknown variable not controlled for in regression models is conferring some advantage for the Working Memory sub-scale or that the association is due to chance. One possible explanation for our positive findings is that we experienced bias from conditioning on live birth (Liew et al. 2015), whereby women with very high levels of β-HCH were more likely to experience a miscarriage, thereby eliminating fetuses with the greatest potential for developmental problems.

Despite these largely null findings with childhood IQ, other negative cognitive or behavioral outcomes associated with β-HCH exposure could occur. In fact, there is strong evidence of association between serum β-HCH level and diseases of cognitive decline, like Parkinson and Alzheimer diseases, among adults in other study cohorts (Corrigan et al. 2000; Kim et al. 2015; Richardson et al. 2011; Saeedi Saravi and Dehpour 2016; Singh et al. 2013). Animal studies suggest HCH isomers induce oxidative stress in neuronal cells, which could be a mechanism for this cognitive decline (Sharma et al. 2010). Similarly, higher levels of placental mitochondrial DNA, which is a marker of oxidative damage, have been shown in placental tissue from newborns in a Belgian cohort (Vriens et al. 2017). It is possible that, unlike other organochlorine

Table 4 Change in 7-year cognitive scores for boys vs. girls for a 10-fold increase in maternal serum beta-hexachlorocyclohexane (β-HCH) concentration (ng/g lipid), CHAMACOS study, Salinas Valley, CA, 1999–2008

Cognitive test	*N*	Boys adjusted model[a]		Girls adjusted model[a]			*N*	Boys sensitivity analysis adjusted model[b]		Girls sensitivity analysis adjusted model[b]		
		β	(95% CI)	*β*	(95% CI)	*p* Value$_{int}$		*β*	(95% CI)	*β*	(95% CI)	*p* Value$_{int}$
Full-Scale IQ	228	0.1	(− 5.3,5.4)	2.7	(− 1.6,6.9)	0.39	228	− 0.5	(− 5.8,4.7)	2.5	(− 1.6,6.7)	0.31
WISC-IV sub-scales												
Working Memory IQ	228	5.2	(− 0.4,10.8)	4.1	(− 0.3,8.5)	0.72	228	4.7	(− 0.9,10.3)	3.8	(− 0.6,8.2)	0.78
Processing Speed IQ	229	0.2	(− 5.1,5.6)	4.2	(− 0.0,8.4)	0.19	229	− 0.02	(− 5.3,5.3)	4.1	(− 0.1,8.3)	0.18
Perceptual Reasoning IQ	254	− 1.3	(− 7.7,5.0)	1.5	(− 3.6,6.5)	0.44	254	− 1.9	(− 8.2,4.4)	1.5	(− 3.5,6.5)	0.35
Verbal Comprehension IQ	254	− 1.3	(− 6.2,3.5)	1.1	(− 2.8,4.9)	0.39	254	− 1.7	(− 6.5,3.1)	1.1	(− 2.7,5.0)	0.30

Abbreviations: *β*, beta-coefficient on regression models; *CI*, confidence interval; *WISC-IV*, Wechsler Intelligence Scale for Children, Fourth Edition

[a] All models adjusted for maternal covariates including age, country of birth, work status, parity, pregnancy urine DAP and serum DDE levels, and child covariates including length of breast feeding (months) and language of neurodevelopmental testing.

[b] Sensitivity analysis adjusted models additionally controlled for maternal 6-month PPVT score and maternal depression, HOME score at age 7, and cumulative average household income at 7 years

pesticides, in utero β-HCH does not affect early neurodevelopment but may instead affect cognition later in life. More research is needed to clarify the relationship between β-HCH and effects on neurodevelopment. This is especially relevant given known higher serum β-HCH concentrations in Mexican populations and the potential for continued exposure to contaminated sites in the future.

This study design and analysis has strengths. First, the longitudinal study design allowed for measurement of lipid-adjusted serum β-HCH concentrations during pregnancy in association with cognitive abilities using a well-established standardized test when the children were at school age. Potential confounders, including other pesticides, were controlled for during statistical analysis, as well as covariates with known impact on child IQ. The exposure and the outcomes were modeled as continuous variables, which allowed for stronger statistical analysis and power despite missing data for some covariates and a moderate sample size. Additionally, this cohort had a wide range of exposure levels and was conducted in a fairly homogenous, highly exposed population. The long half-life of β-HCH makes it an ideal marker for ongoing exposure through pregnancy. Lastly, all neurodevelopmental testing was conducted by a single psychometrician who was blinded to exposure status, which diminished bias and measurement error in testing.

However, this study also has some limitations. Early life exposure to β-HCH occurs both in utero and through breastfeeding. Although breastmilk samples in this study were not analyzed for β-HCH concentration, we did examine interaction by length of breastfeeding and found no differences in associations of maternal prenatal serum β-HCH concentrations and cognitive test scores by breastfeeding duration. This suggests that β-HCH exposure through longer duration of breastfeeding does not have an effect on neurodevelopment. Due to limited serum volume, not all women participating in the CHAMACOS study had serum β-HCH concentrations measured, which limited the sample size of this analysis. Lastly, the results of this study may have limited generalizability to the public as the level of β-HCH in the general US population is declining (Centers for Disease Control and Prevention 2009).

This study is the first to examine in utero maternal serum β-HCH concentration and child IQ. The results of this study expand upon the dearth of information concerning the potential impacts of hexachlorocyclohexane and developmental neurotoxicity, and provide some evidence that in utero β-HCH is not inversely correlated with child IQ at age 7. However, future research must replicate this analysis in other study cohorts of women and children. Studies should then focus on assessing whether associations between maternal serum β-HCH concentration and child IQ emerge earlier in childhood with resolution by age 7 or later in childhood or adolescence, and whether there is an association between in utero β-HCH exposure and other health and developmental outcomes in older children. Lastly, because epidemiologic studies have demonstrated associations between adult β-HCH exposures and diseases of cognitive decline, future studies should look at whether in utero or earlier exposure to β-HCH confers higher or earlier risk of cognitive decline in adulthood.

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Conflict of Interest The authors declare that they have no conflict of interest.

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