

Breastfeeding, Exposure to Organochlorine Compounds, and Neurodevelopment in Infants

Núria Ribas-Fitó, MD*; Esther Cardo, MD, PhD*; Maria Sala, MD, PhD*; M. Eulàlia de Muga, MD*;
Carlos Mazón, MD‡; Antoni Verdú, MD§; Manolis Kogevinas, MD, PhD*;
Joan O. Grimalt, PhD||; and Jordi Sunyer, MD, PhD*

ABSTRACT. *Objective.* Exposure to organochlorine compounds (OCs) occurs both in utero and through breastfeeding. Levels of hexachlorobenzene (HCB) found in the cord serum of newborns from a population located in the vicinity of an electrochemical factory in Spain were among the highest ever reported. We studied the association between exposure to OCs and breastfeeding on neurodevelopment in the 1-year-old infants of this population.

Methods. A birth cohort including 92 mother-infant pairs was recruited between 1997 and 1999 in 5 neighboring villages (84% of possible recruits). The mental and psychomotor development of each infant was assessed at 13 months using the Bayley and the Griffiths Scales of Infant Development. OCs were measured in cord serum.

Results. Dichlorodiphenyl dichloroethylene (p,p'DDE) cord serum levels were negatively associated with both mental and psychomotor development. For each doubling of a dose of p,p'DDE, we found a resultant decrease of 3.50 points (standard error: 1.39) on the mental scale and 4.01 points (standard error: 1.37) on the psychomotor scale. Exposure to polychlorinated biphenyls was only marginally associated with psychomotor development. Prenatal exposure to HCB had no effect on child neurodevelopment. Long-term breastfeeding was associated with better performance on both the mental and motor scales. Short-term breastfed infants with higher p,p'DDE levels in cord serum were associated with the lowest scores on both the mental and the psychomotor scales.

Conclusions. Prenatal exposure to p,p'DDE was associated with a delay in mental and psychomotor development at 13 months. No association was found for exposure to HCB. Long-term breastfeeding was found to be beneficial to neurodevelopment, potentially counterbalancing the impact of exposure to these chemicals through breast milk. *Pediatrics* 2003;111:e580–e585. URL: <http://www.pediatrics.org/cgi/content/full/111/5/e580>; hexachlorobenzene, dichlorodiphenyl dichloroethylene, polychlorinated biphenyls, breastfeeding, neurodevelopment.

ABBREVIATIONS. PCB, polychlorinated biphenyl; OC, organochlorine compound; HCB, hexachlorobenzene; MDI, Mental Development Index; PDI, Psychomotor Developmental Index; p,p'DDE, dichlorodiphenyl dichloroethylene; SE, standard error.

Because the brain continues to grow for at least 2 to 3 years after birth, the nervous system is vulnerable during both pre- and postnatal periods.¹ Some environmental chemicals are known to interrupt early-stage neurodevelopmental processes, affecting behavior and cognitive function.² For example, exposure to high levels of polychlorinated biphenyls (PCBs) induces significant neurologic and behavioral dysfunctions in humans and laboratory animals.³ However, existing epidemiologic studies do not allow adequate evaluation of the risk associated with neurodevelopmental effects at current levels of exposure.⁴ Evidence of the neurologic impact of other organochlorine compounds (OCs) is scarce.

Breastfeeding increases organochlorine transfer to infants,⁵ but it has also been associated with improved neurodevelopment. However, the debate regarding the potential benefits of breastfeeding on neurologic development is currently ongoing.^{6,7}

Unusually high atmospheric concentrations of hexachlorobenzene (HCB) were found in the population of a village of 5000 inhabitants in the vicinity of an electrochemical factory (Flix, Catalonia, Spain). The factory, built in 1898, has been producing chlorinated solvents for 4 decades. Production of DDT was ended in 1971, and PCB production was discontinued in 1987. In 1994, adult inhabitants of the area who were studied were found to have the highest serum HCB levels ever measured (mean of 36.7 ng/mL).⁸ In a similar study conducted in 1999, levels of HCB in the cord serum of newborns from this population were among the highest ever reported.⁹ Other OCs in this population were found to be at similar levels described in other general populations. A general population birth cohort was set up to assess the effects of prenatal and postnatal OC exposure on the neurologic development of infants and to understand the interplay between breastfeeding and in utero exposure to OCs.

METHODS

Study Population

A birth cohort was set up of 102 mother-infant pairs including 93% of all singleton children born in the main hospital of the study

From the *Environmental and Respiratory Research Unit, Institut Municipal d'Investigació Mèdica, Barcelona, Spain; †Primary Health Care Center of Flix, Tarragona, Spain; ‡Department of Pediatrics, Hospital de Móra d'Ebre, Tarragona, Spain; and §Department of Environmental Chemistry, CID-CSIC, Barcelona, Spain.

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Address correspondence to Jordi Sunyer, MD, PhD, Respiratory and Environmental Health Research Unit, Institut Municipal d'Investigació Mèdica, C. del Doctor Aiguader, 80, E-08003-Barcelona, Spain. E-mail: jsunyer@imim.es

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area during the period March 1997 to December 1999. The study area included the village of Flix and all other towns of the same administrative health area (12 000 inhabitants). None of the children had major congenital anomalies or other diseases. Ten mother-infant pairs were lost to the 1-year follow-up. This study was approved by the ethics committee of the Institut Municipal d'Investigació Mèdica, and all mothers gave informed written consent.

Neurodevelopmental Tests

The children's mental and psychomotor development was assessed at 13 months (± 6 weeks) using the Bayley Scales of Infant Development¹⁰ and the Griffiths Mental Development Scales.¹¹ The Bayley scales yield 2 indices, the Mental Development Index (MDI) and the Psychomotor Developmental Index (PDI). The Griffiths is divided into 5 subscales (Locomotor, Personal-Social, Hearing and Language, Eye-Hand Coordination, and Performance). The Pearson correlations between the MDI and those mental areas from the Griffiths were 0.76 for Personal-Social, 0.69 for Hearing and Language, 0.73 for Performance, and 0.74 for Eye-Hand Coordination. Correlations between the PDI were 0.84 for Locomotor and 0.60 for Eye-Hand Coordination. All testing was done at the Primary Health Care Centre of Flix in the presence of the mother by the same 2 field workers (E.C. and M.E.d.M.). The field workers were unaware of the child's organochlorine background exposure or place of residence, whether the parents worked in the electrochemical factory, and whether the mother preferred to breastfeed her child.

Organochlorine Exposure

OCs in cord serum were measured by gas chromatography with electron capture detection and gas chromatography coupled to chemical ionization negative-ion mass spectrometry. A Varian Star 3400 coupled to a Finnigan Mat INCOS XL was used for the analyses. Serum samples were stored at -40°C until analysis. All analysis was conducted in the Department of Environmental Chemistry. We present results for the most prevalent compounds found in sera samples: HCB, dichlorodiphenyl dichloroethylene (p,p'DDE), and PCBs are presented as the summation of the individual congeners 28, 52, 101, 118, 138, 153, and 180. Detection limits for HCB and p,p'DDE were 0.03 and 0.09, respectively, and ~ 0.10 for the individual PCB congeners. A value of 0.01 ng/mL was given for nondetectable levels, and a value of 0.05 ng/mL was given for those that were detectable but not quantifiable. The

between-assay coefficient of variation for the assays was 6.4% for HCB, 8.6% for p,p'DDE, and between 6% and 11% for the individual PCB congeners.

Other Variables

Information on socioeconomic background, maternal diseases and obstetric history, parity, gender, fetal exposure to alcohol (at least 2 drinks a week during the entire pregnancy) and cigarette smoking (at least 1 cigarette a day during the last trimester), type and duration of breastfeeding, and maternal intelligence (Raven Progressive Matrices) was obtained through questionnaires administered in person after delivery and at 13 months. Duration of breastfeeding was categorized as formula-fed, short-term breastfed (2–16 weeks), and long-term breastfed (>16 weeks). Sixteen weeks was the median of the duration.

Statistics and Data Analysis

Neurodevelopmental scores followed a normal distribution, whereas cord serum organochlorine levels were skewed to the right and were normalized by base 2 logarithmic transformation. The dependent variable (mental or psychomotor development) was examined in relation to level of organochlorines and the study variables using linear regression models. Both continuous and categorized levels of HCB, p,p'DDE, and total PCBs in cord serum were used in the regression analysis. Study variables were treated as potential confounding factors and were selected on the basis of previous studies.¹² Adjustment of the association between OCs and neurodevelopmental scales for the confounding variables was conducted using multivariate linear regression models after inclusion of variables with $P < .20$. Diagnosis of statistical assumptions of the models was conducted through visual inspection of the standard plots of the residuals. All statistical analysis was conducted with the STATA 6.0 statistical software package. Criteria of statistical significance was $P < .05$.

RESULTS

Table 1 provides a snapshot of study participants according to type and duration of breastfeeding and participation. Nonparticipants had lower education levels and a higher unemployment rate. Mothers whose children were breastfed were younger, had

TABLE 1. Characteristics of the Study Population According to Type and Duration of Breastfeeding, and Participation ($n = 102$)

	Participants			Nonparticipants ($n = 10$)
	Formula-Fed ($n = 27$)	Breastfed 2–16 Weeks ($n = 30$)	Breastfed >16 Weeks ($n = 35$)	
Maternal variables (%)				
Age >30 y	67	43*	54	60
Weight >60 kg†	72	40*	35*	67
Parity: firstborn	41	60	51	30
Smoking in pregnancy	41	43	14*	31
Alcohol in pregnancy	11	20	14	20
Low IQ‡	48	18*	18*	-
Elementary school	58	30	34	86*
Residence in Flix	44	67	54	40
Unemployment	37	40	37	70*
Migration <10 y	42	38	26	25
Paternal variables (%)				
Age >34 y	52	40	40	40
Electrochemical worker	19	20	23	40
Elementary school	50	40	40	71
Child variables (%)				
Female gender	63	40	60	70
Spontaneous delivery	59	63	57	30
Gestational age <37 wk	4	10	6	20
Kindergarten <12 mo	4	3	3	0

* $P < .05$ in comparison with formula-fed.

† Maternal weight measured at first trimester of pregnancy.

‡ Low IQ was defined as a scoring <45 points in the Raven Progressive Matrices.

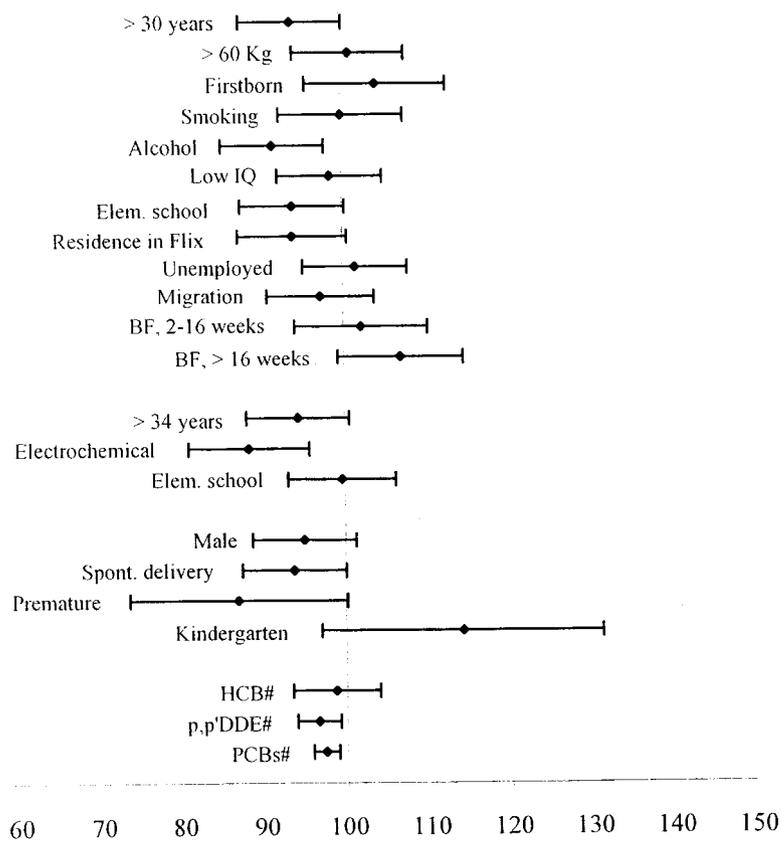


Fig 1. Changes and 95% confidence interval (CI) on the MDI per each study variable and OCs in cord serum. This figure shows how individual components reduce or increase performance on the MDI. Considering the mean of the MDI as 100, each line represents the estimated change (and 95% CI) in the MDI scoring that would accompany each specific variable (ie, a child whose mother was older than 30 years would score -6.00 points [SE: 3.18] less in the MDI than a child whose mother was younger than 30). BF, breastfeeding; #change for a doubling of the concentration in nanograms per milliliter of each OC in cord serum.

higher IQ scores, and were thinner; those with a longer duration of breastfeeding also smoked less.

Figure 1 shows the relationship between MDI, OCs in cord serum, and other study variables. Mothers with low education levels, fathers who worked at the electrochemical plant, and levels of p,p'DDE and PCBs in cord serum were negatively associated to MDI ($P < .05$). Maternal age above 30 (mean in this population), maternal unemployment and migration, paternal age above 34 (mean in this population), and all of the children's variables were also associated with decreased MDI scores, although results were only marginally significant ($P < .1$). Breastfeeding and kindergarten attendance were also associated with better performance, although again, results were only marginally significant ($P < .1$). Figure 2 shows the impact of the same potential stressors on the PDI. The impact of breastfeeding on the PDI was lower than for the MDI, whereas the effects of kindergarten attendance and maternal smoking and drinking were stronger in comparison with MDI. A negative association was found between the PDI scores and exposure to p,p'DDE and PCBs in cord serum. HCB was not associated with either the MDI or the PDI.

The effects of p,p'DDE on both mental and psychomotor development and of PCBs on psychomotor development persisted after adjusting for potential confounding variables such as parents' education levels (for each doubling of a dose of p,p'DDE, there was a decrease of 3.50 points [standard error (SE): 1.39] on the MDI and 4.01 points [SE: 1.37] on the PDI). In addition, a negative dose-response relation-

ship between levels of p,p'DDE in cord serum (measured in tertiles) and MDI and PDI scores was observed. Statistically significant decreased scores were observed for the highest level of exposure, with a coefficient of -12.25 (SE: 4.90; $P = .02$) for the MDI and -12.11 (SE: 4.58; $P = .01$) for the PDI. After including all 3 organochlorines (HCB, p,p'DDE, and PCBs) in the same model, only the negative effect of p,p'DDE persisted (Table 2). Cord serum levels of p,p'DDE had the strongest negative association with the Locomotor, Personal-Social, and Performance areas on the Griffiths Scales. Duration of breastfeeding was positively associated with both the mental and the psychomotor scales (Table 2).

Table 3 depicts performance on the MDI and PDI according to type and duration of breastfeeding and levels of p,p'DDE in cord serum (categorized as above or below the median of 0.85 ng/mL). Infants with lower levels of p,p'DDE exhibited better performance than those with higher levels of exposure (110.88 vs 106.86; $P = NS$). The longer the breastfeeding period, the better the child's performance was (P trend = .04). When we considered infants with the lowest exposure and a longer duration of breastfeeding, only infants who were highly exposed and breastfed short term performed worse in a statistically significant way (Table 3). They also performed worse in the PDI.

DISCUSSION

p,p'DDE cord serum levels were negatively associated with both mental and psychomotor development. Exposure to PCBs was only marginally asso-

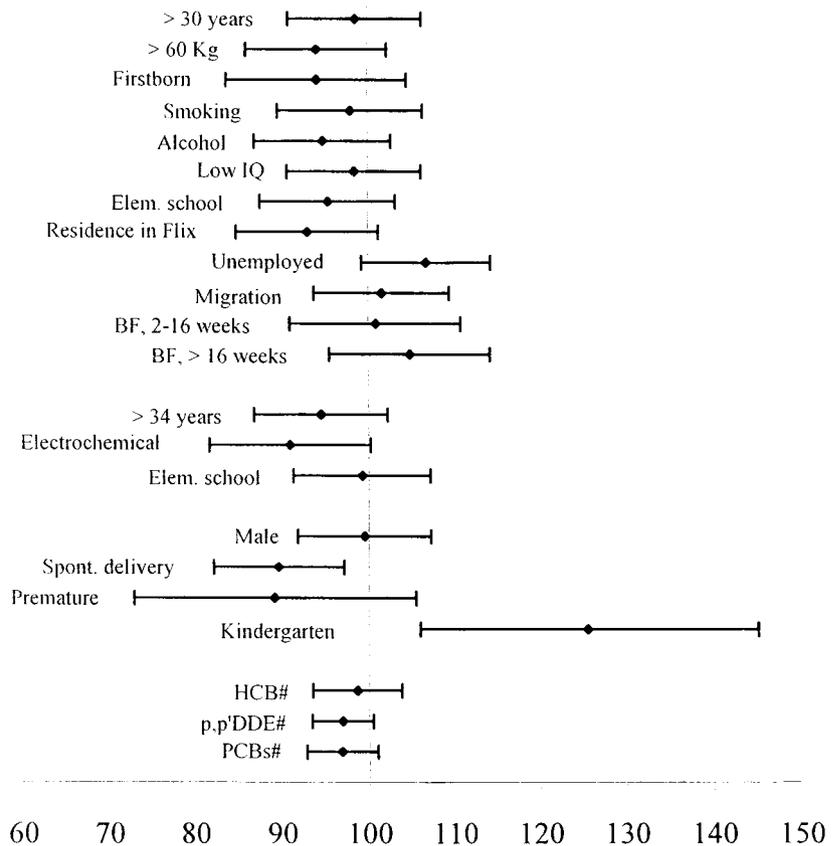


Fig 2. Changes and 95% CI on the PDI per each study variable and OCs in cord serum. This figure shows how individual components reduce or increase performance on the PDI. Considering the mean of the PDI as 100, each line represents the estimated change (and 95% CI) in the PDI scoring that would accompany each specific variable (ie, a child whose mother was older than 30 years would score -1.36 points [SE: 3.92] less in the PDI than a child whose mother was younger than 30). #Change for a doubling of the concentration in nanograms per milliliter of each OC in cord serum.

TABLE 2. Regression Coefficients (and SEs) of Bayley and Griffith Scales on Breastfeeding and OCs in Cord Serum*

	Bayley Scales		Griffiths Scales				
	MDI	PDI	Locomotor	Social	Hearing and Language	Eye-Hand Coordination	Performance
Constant	100.98	82.64	87.23	84.15	113.04	102.69	98.20
Breastfeeding, <16 wk	1.69 (4.82)	-1.76 (5.04)	3.96 (5.75)	9.83 (5.70)	—	0.25 (5.41)	1.49 (5.22)
Breastfeeding, >16 wk	10.71 (4.48)‡	8.97 (4.53)‡	12.43 (5.23)‡	12.73 (5.18)‡	—	9.79 (5.09)§	10.67 (4.74)‡
p,p'DDE (ng/ml)†	-3.44 (1.39)‡	-3.83 (1.46)‡	-4.02 (1.64)‡	-4.66 (1.74)‡	-1.00 (1.34)	-2.88 (1.62)§	-2.78 (1.39)‡
HCB (ng/ml)†	—	—	—	—	—	—	—
ΣPCBs (ng/ml)†	—	-2.84 (1.72)§	-3.45 (2.01)§	—	—	—	—

* OCs were analyzed in the same model. Adjusted by maternal age, tobacco and alcohol exposure during pregnancy, maternal education, migration, paternal occupation, gender, kindergarten, and breastfeeding.

† Each unit change represents a doubling of the concentration in ng/ml of each OC in cord serum.

‡ $P < .05$.

§ $P < .10$.

ciated with psychomotor development. Prenatal exposure to HCB had no effect on child neurodevelopment. Duration of breastfeeding was positively associated with performance on the mental and psychomotor scales, but infants who were breastfed short-term and had higher p,p'DDE levels in cord serum had the lowest scores on the mental and psychomotor scales.

The impact of organochlorine chemicals on neurodevelopment has been studied in a number of cohorts, most of them focusing on PCBs. Existing research suggests that PCBs hinder neurodevelopment among children exposed early in life.⁴ Information about the neurodevelopmental effects of other specific OCs is scarce. In a study conducted in North Carolina, no relationship was observed between prenatal and postnatal exposure to p,p'DDE and mental

or motor development at 12 months.¹³ In a study conducted in Oswego, New York, cord blood levels of DDE failed to predict infant intelligence at 12 months of age.¹⁴ However, in the Oswego study, levels of p,p'DDE were lower than those encountered in our population. PCB levels, alternatively, were higher.¹⁵ We are not aware of any study evaluating the neurotoxic effects of HCB in children.

The present study was conducted in an area where organochlorines are the main pollutant. The population living in this area has the highest levels of HCB ever reported.¹⁶ In addition, the population has been found to have high levels of p,p'DDE as a result of the intensive use of organochlorine chemicals in agriculture in the past. In contrast to the study conducted in 1994, we observed that levels of HCB among women in the present cohort were 61% lower

TABLE 3. Bayley MDI and PDI According to Type and Duration of Feeding and Levels of p,p'DDE in Cord Serum

	Type of Breastfeeding		
	Breastfeeding >16 Weeks	Breastfeeding 2–16 Weeks	Formula Feeding
MDI			
p,p'DDE in cord serum ≤ 0.85 ng/mL	110.94 (6.60)	103.24 (9.25)	101.47 (11.11)
p,p'DDE in cord serum > 0.85 ng/mL	106.79 (9.58)	96.58 (10.66)*	101.37 (9.58)
PDI			
p,p'DDE in cord serum ≤ 0.85 ng/mL	97.26 (5.61)	85.83 (6.61)	91.81 (5.95)
p,p'DDE in cord serum > 0.85 ng/mL	90.57 (4.74)	81.16 (7.25)*	86.85 (6.81)

* $P < .05$. The reference category were those infants who were long breastfed and whose levels in cord serum were low. Adjusted by maternal age, tobacco and alcohol exposure during pregnancy, maternal education, paternal occupation, gender, and kindergarten.

than those observed in women of the same age in the previous study (10.6 vs 4.1 ng/mL). Levels of p,p'DDE also were shown to have decreased in the present cohort, although this diminution was not statistically significant (2.6 vs 2.0 ng/mL). PCB levels were found to have increased in relation to those measured in 1994 (1.4 vs 1.9 ng/mL).¹⁷ It is possible that a neurotoxic co-pollutant such as methyl-mercury could be present in this population,¹⁸ but a recent study among children aged 6 to 16 years from Flix indicated that mercury concentrations in hair were lower than those found in other populations.¹⁹

The effect of these chemicals on brain growth (both pre- and postnatally) is an important issue of concern. Most of the available studies suggest that the prenatal nervous system is more vulnerable to the harmful effects of organochlorine chemicals than the early postnatal nervous system. However, some recent studies support the hypothesis that an additional effect of postnatal exposure through breastfeeding is likely.²⁰ We have observed in the infants of this population that those who breastfed increased their concentrations of organochlorine chemicals during the first weeks of life (N. Ribas-Fitó, submitted for publication). Long-term breastfeeding, however, seems to be beneficial to the infant.

This uncertainty in identifying the susceptible periods for each area of development complicates our understanding of the interrelation between breastfeeding as an exposure pathway and the benefits of breastfeeding itself. A recent study reported that formula-fed infants had significantly lower cognition abilities than breastfed infants and, moreover, that the effects of prenatal PCB exposure were more pronounced in formula-fed than in breastfed infants.²¹ However, this study concluded that the differences in vulnerability of the 2 groups were more likely to be related to parental and home characteristics than to the beneficial effects of breastfeeding per se. Several studies have also attempted to understand the role of breastfeeding on IQ, and although some authors conclude that the observed advantage of breastfeeding on IQ is related only to genetic and socioenvironmental factors, a recent meta-analysis showed that after adjustment for appropriate key co-factors, breastfeeding was associated with significantly higher scores for cognitive development than formula feeding.⁶ Longer duration of breastfeeding has also been positively associated with intelligence

in adulthood.²² We also observed the benefits of long-term breastfeeding on mental indices, along with the indirect benefit of balancing the impact of exposure to p,p'DDE after adjustment for some socioeconomic variables.

Because multiple variables play important roles in the development of the human brain, it is difficult to elucidate the interactions and relations between all variables. The magnitude of the effect of prenatal exposure to organochlorine chemicals seems to be of the same degree as other preventable variables. This is an important concern because environmental exposures are unintentional and the degree of the exposure to these mixtures of chemicals is unknown. We did not assess the home environment with a standardized tool such as the HOME Inventory²³ because of cross-cultural differences. We did include some specific factors, but correlation with maternal education was high. Besides, the correlations between environmental measures and measures of cognitive development have not been shown to be particularly strong until children approach 2 years of age.²⁴

As has been previously reported,²⁵ the scores obtained from the Griffiths Scale were consistently higher than those obtained from the Bayley Scale, although the correlation between the 2 tests was high ($r = 0.881$, $P < .01$). Knowledge of the specific cognitive and motor skills that might be affected after exposure to each individual organochlorine is scarce. It is also not known whether each organochlorine might act on a different site or whether the time window in which humans incorporate them is the same per each chemical. In fact, it is not even clear which of the affected areas might remain affected in later childhood, although possible persistence into school age has been described.²¹ The possible mechanisms of resilience after exposure to these chemicals have not yet been established. Neurotoxic exposures that affect subtle brain functioning manifest themselves only when this functioning is needed, and might never be detected if cognitive or behavioral functioning is within normal limits.²⁶ The effects of environmental pollutants on health are most often subtle, because they usually occur at concentrations that are not expected to result in acute toxic symptoms, but these probable small effects at the individual level might have a large impact at the population level.²⁷

Despite the relatively small size of the cohort, this study reports significant results. This might be explained by the strength of the associations. Although the participation rates in the study were high, there was a significant reduction in participation of children from less-educated and unemployed mothers. This difference could bias our results by underestimating the organochlorine effect. A follow-up is under way, with 1 aim being to evaluate whether the neurodevelopmental effects observed in early life persist later in life.

In conclusion, in this population, prenatal exposure to p,p'DDE was associated with a delay in the mental and psychomotor development at the age of 1 year. No association was found for exposure to HCB. Long-term breastfeeding was found to be beneficial for the neurodevelopment of the child, helping to counterbalance the potential impact of the exposure to these chemicals through breast milk. In clinical terms, practicing pediatricians should be aware of the organochlorine exposure to infants in utero and through breastfeeding. However, they should continue to encourage long-term breastfeeding to balance the potential impact of organochlorine exposure through breast milk.

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