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# In Utero Exposure to Dichlorodiphenyltrichloroethane (DDT) and Dichlorodiphenyldichloroethylene (DDE) and Neurodevelopment Among Young Mexican American Children

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## ABSTRACT

**OBJECTIVE.** We investigated the relationship between prenatal exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment of Mexican farm-workers' children in California.

**METHODS.** Participants from the Center for the Health Assessment of Mothers and Children of Salinas study, a birth cohort study, included 360 singletons with maternal serum measures of *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDE. Psychomotor development and mental development were assessed with the Bayley Scales of Infant Development at 6, 12, and 24 months.

**RESULTS.** We found a ~2-point decrease in Psychomotor Developmental Index scores with each 10-fold increase in *p,p'*-DDT levels at 6 and 12 months (but not 24 months) and *p,p'*-DDE levels at 6 months only. We found no association with mental development at 6 months but a 2- to 3-point decrease in Mental Developmental Index scores for *p,p'*-DDT and *o,p'*-DDT at 12 and 24 months, corresponding to 7- to 10-point decreases across the exposure range. Even when mothers had substantial exposure, breastfeeding was usually associated positively with Bayley scale scores.

**CONCLUSIONS.** Prenatal exposure to DDT, and to a lesser extent DDE, was associated with neurodevelopmental delays during early childhood, although breastfeeding was found to be beneficial even among women with high levels of exposure. Countries considering the use of DDT should weigh its benefit in eradicating malaria against the negative associations found in this first report on DDT and human neurodevelopment.

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### Key Words

dichlorodiphenyltrichloroethane, dichlorodiphenyldichloroethylene, organochlorine, pesticides, neurodevelopment, Bayley Scales of Infant Development

### Abbreviations

CHAMACOS—Center for the Health Assessment of Mothers and Children of Salinas  
DAP—dialkyl phosphates  
HCB—hexachlorobenzene  
HOME—Home Observation for Measurement of the Environment  
LOD—limit of detection  
MDI—Mental Developmental Index  
DDT—dichlorodiphenyltrichloroethane  
PDI—Psychomotor Developmental Index  
DDE—dichlorodiphenyldichloroethylene  
PCB—polychlorinated biphenyl  
 $\beta$ -HCCH— $\beta$ -hexachlorocyclohexane  
PPVT—Peabody Picture Vocabulary Test  
CI—confidence interval

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**I**N 2001, >90 countries signed the Stockholm Convention on Persistent Organic Pollutants, committing to eliminate the use of 12 persistent organic pollutants of greatest concern to the ecology and health of the global community. These chemicals are highly lipophilic, persist in the environment, and accumulate in the food chain and in fatty tissues of humans.<sup>1,2</sup> The persistent organic pollutant agreement recognized that dichlorodiphenyltrichloroethane (DDT) is an effective and relatively inexpensive means of mosquito control<sup>1</sup> and some countries would need to phase it out gradually. Therefore, DDT continues to be used in some countries, and others are reconsidering its use for malaria control.<sup>1</sup>

Technical grade DDT consists of *p,p'*-DDT, with a number of impurities, including *o,p'*-DDT.<sup>2</sup> DDT and its breakdown product dichlorodiphenyldichloroethylene (DDE) pass into breast milk and cross the placenta.<sup>3</sup> Although in utero exposure may be lower than exposure through lactation because of the low solubility of DDT/DDE in plasma,<sup>4</sup> the fetus may be more vulnerable than the infant to the impact of neurotoxicants.

Studies on animals indicate that DDT is a neurodevelopmental toxicant,<sup>2,5,6</sup> but there are no animal studies on DDE and neurodevelopment. Despite animal evidence, no previous study has investigated the neurodevelopmental toxicity of DDT in humans, although there are a few studies of DDE exposure.

In a large North Carolina birth cohort recruited in the 1980s, Rogan et al<sup>7</sup> demonstrated that levels of DDE in serum and breast milk were dose-dependently related to hyporeflexia, as assessed with the Brazelton Neonatal Behavioral Assessment Scale. However, they reported no adverse association between transplacental or lactational DDE exposure and children's performance on the Bayley Scales of Infant Development at up to 24 months of age,<sup>8,9</sup> on the McCarthy Scales at 3, 4, and 5 years of age, or in school at 8 to 10.5 years of age.<sup>10</sup>

In contrast to the North Carolina study, a more-recent, smaller study from Oswego, New York, with lower exposure levels, found no association of cord blood DDE levels with newborn performance on the Brazelton Neonatal Behavioral Assessment Scale,<sup>11</sup> as well as no association with performance on the Fagan Test of Infant Intelligence at 6 and 12 months of age.<sup>12</sup> However, a Spanish study of 92 infants from a community with high atmospheric hexachlorobenzene (HCB) levels found a significant negative association between relatively low cord serum levels of DDE and cognitive, psychomotor, and social development of 13-month-old children, with no association with HCB levels.<sup>13</sup>

DDT use in the United States was discontinued in 1973, whereas Mexico restricted the use of DDT in 1995 and banned it completely in 2000.<sup>14</sup> Farmworkers who emigrated recently from Mexico might have been exposed there or might continue to be exposed through contaminated soil in the United States (albeit to a lesser

extent). The present study aimed to investigate the effects of in utero exposure to *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDE (DDT/DDE) on the neurodevelopment of infants from primarily Mexican farm-worker families living in California.

## METHODS

### Participants and Recruitment

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) is a longitudinal birth-cohort study of the effects of pesticides and other environmental exposures on the health of pregnant women and their children living in the agricultural Salinas Valley. Methods are described elsewhere.<sup>15</sup> Briefly, pregnant women entering prenatal care at Natividad Medical Center and 5 clinics of Clinica de Salud del Valle de Salinas were screened for eligibility between October 1999 and October 2000. Eligible women were  $\geq 18$  years of age, <20 weeks of gestation, English- or Spanish-speaking, eligible for Medi-Cal (subsidized health care), and planning to deliver at Natividad Medical Center. A total of 601 women were enrolled in this multiyear study, 538 were monitored to delivery, and organochlorine pesticide levels were measured for 426 women. We excluded children if they were not assessed at 6, 12, and/or 24 months ( $n = 63$ ), were not singletons ( $n = 2$ ), had a pertinent medical condition ( $n = 1$ , hydrocephalus), were evaluated by a psychometrician with too few assessments for statistical adjustment ( $n = 4$ , at 6 months), or had raw scores too low to be standardized ( $n = 1$ , at 6 months). A total of 330 infants were included in the analysis at 6 months, 327 infants at 12 months, and 309 infants at 24 months. In 3 instances, the 12-month Bayley Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) score was missing or invalid. Written informed consent was obtained from mothers. The study was approved by the institutional review board at the University of California, Berkeley.

### Procedures

Women were interviewed in English or Spanish, by bilingual bicultural interviewers, during pregnancy, shortly after delivery, and when the child was 6, 12, and 24 months of age. We obtained information on socio-demographic characteristics, habits, housing, and occupation at each interview, as well as information on child care and breastfeeding after birth. Prenatal and delivery medical records were abstracted by a registered nurse. The mother completed the Peabody Picture Vocabulary Test (PPVT)<sup>16</sup> at the 6-month visit and the Center for Epidemiologic Studies Depression Scale<sup>17</sup> at the 12-month visit. The Infant-Toddler Home Observation for Measurement of the Environment (HOME)<sup>18</sup> instrument

was completed at 6 and 12 months and partially completed (32 of 45 items) at 24 months.

### Bayley Scales of Infant Development

The Bayley Scales of Infant Development<sup>19</sup> assess the developmental functioning of infants and young children. The test is age-standardized to a mean of 100 and standard deviation (SD) of 15. The Bayley scales were administered in Spanish and/or English by psychometricians who were blinded to exposure status, either at the CHAMACOS research office or in a recreation vehicle modified as a testing facility. Four psychometricians performed 6-month assessments, and 3 of them performed the assessments at 12 and 24 months. Administration required ~30 to 45 minutes.

### DDT/DDE Exposure Measurement

Blood samples were collected from the mother, through venipuncture, at the time of the second pregnancy interview ( $n = 334$ ; mean  $\pm$  SD:  $26.1 \pm 2.9$  weeks of gestation) or just before delivery ( $n = 26$ ). Serum levels were strongly correlated ( $r \geq 0.98$ ) for 20 women with measurements at both times.

Serum was sent on dry ice to the Centers for Disease Control and Prevention for analysis of *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDE with gas chromatography-high resolution mass spectrometry methods, as described previously.<sup>20</sup> Quality control and blank samples were included in each run. Levels below the limit of detection (LOD) were assigned a value of LOD/2.<sup>21</sup>

DDT and DDE values were adjusted for lipid levels. Total cholesterol and triglyceride levels were determined with standard clinical enzymatic methods (Roche Chemicals, Indianapolis, IN). Total lipid levels were calculated with the summation method described by Phillips et al.<sup>22</sup> The laboratory and analytical methods were certified according to guidelines set forth in the Clinical Laboratory Improvement Amendment of 1988.<sup>23</sup>

### Data Analysis

DDT and DDE levels were transformed to the  $\log_{10}$  scale. We excluded outliers ( $>3$  SD from the mean) for *p,p'*-DDT ( $n = 7$ ), *o,p'*-DDT ( $n = 7$ ), and *p,p'*-DDE ( $n = 5$ ). To assess the relationship between analyte levels and children's neurodevelopment, we constructed separate multivariate regression models for MDI and PDI at each of the time points (6, 12, and 24 months).

Covariates were considered if they were associated with child neurodevelopment in the literature or might have affected the child's assessment. We considered maternal characteristics including age, parity, education, years spent in the United States, any smoking and regular alcohol use during pregnancy, depressive symptoms (Center for Epidemiologic Studies Depression Scale score of  $\geq 16$ ), and PPVT score (continuous). We considered age-specific covariates including breastfeeding duration

(continuous), maternal work status,  $\geq 15$  hours of out-of-home child care per week, father present in home, HOME score (continuous), housing density, and poverty level. Poverty level compares federal poverty thresholds<sup>24</sup> with household income divided by the number of people supported. We also included the child- and assessment-related covariates of gender, age at assessment (corrected for prematurity for 6- and 12-month assessments), psychometrician, season (winter defined as December to February, spring as March to May, summer as June to August, and autumn as September to November), and location of assessment (office or recreation vehicle). Missing covariate values (1%) were imputed.

Adapted backward selection was performed, starting with all main effect terms. Covariates were selected for final models if they were related to the outcome ( $P < .10$ ) or if dropping them changed the coefficient for DDT or DDE by  $\geq 10\%$ . If a covariate was retained for any of the DDT or DDE analytes, then it was included in all models for that outcome/age. All models controlled for psychometrician. Covariates in the final models were categorized as noted in Table 1 unless otherwise specified above.

Although DDT and DDE levels were found to be unrelated to birth weight and gestational age in this population,<sup>25</sup> we recomputed final models controlling for birth weight and gestational age, as well as excluding children born preterm ( $<37$  weeks;  $n = 26$ ) or born small for gestational age ( $<10$ th percentile of national standard;  $n = 13$ ); none of these adjustments changed results for DDT or DDE models appreciably (data not shown). We also investigated interactions with gender, gestational age, and breastfeeding duration and considered potential confounding by additional environmental exposures either thought to be neurotoxic, such as polychlorinated biphenyls (PCBs), lead, and organophosphate pesticides, or found to be at high levels in this population, such as  $\beta$ -hexachlorocyclohexane ( $\beta$ -HCCH) and HCB.<sup>25</sup> Serum  $\beta$ -HCCH, HCB, and PCB levels were measured concurrently with DDT/DDE levels, with the method described above, and were adjusted for lipids. Total PCB levels were generated by summing serum levels of PCB congeners 138, 153, and 180 and multiplying the result by 1.54.<sup>26</sup> With isotope-dilution gas chromatography-tandem mass spectrometry, we measured total dialkyl phosphate (DAP) metabolites of organophosphate pesticides in maternal urine collected twice during pregnancy (mean: 13 and 26 weeks) and averaged the results for data analysis. Details of collection, analysis, and quality control were presented elsewhere.<sup>27</sup> Lead levels were measured in cord blood with the graphite-furnace atomic absorption spectrophotometry method at the California Department of Health Services Environmental Health Laboratory (LOD:  $1.0 \mu\text{g/dL}$ ). These additional exposure measurements were  $\log_{10}$  transformed for data analysis.

**TABLE 1** Demographic Characteristics of the CHAMACOS Study Population, Salinas Valley, California, 2000 to 2001 (n = 360)

	No. (%)			
	Prenatal	6 mo	12 mo	24 mo
Maternal age				
18–24 y	151 (41.9)			
25–29 y	123 (34.2)			
30–34 y	57 (15.8)			
≥35 y	29 (8.1)			
Parity				
0	113 (31.4)			
≥1	247 (68.6)			
Maternal education				
<6th grade	157 (43.6)			
7th to 12th grade	131 (36.4)			
Completed high school	72 (20.0)			
Time in United States				
≤1 y	90 (25.0)			
2–5 y	102 (28.3)			
6–10 y	83 (23.1)			
≥11 y	46 (12.8)			
Born in United States	39 (10.8)			
Married or living as married				
Yes	300 (83.3)			
No	60 (16.7)			
Alcohol use during pregnancy (≥1 time per wk)				
Yes	4 (1.1)			
No	346 (98.9)			
Smoking during pregnancy				
Yes	17 (4.7)			
No	343 (95.3)			
Maternal depressive symptoms (CES-D score of ≥16)				
Yes	167 (51.9)			
No	155 (48.1)			
Child gender				
Female	185 (51.4)			
Male	175 (48.6)			
Breastfeeding at time of assessment <sup>a</sup>				
Yes		181 (54.7)	105 (32.1)	23 (7.4)
No		149 (45.3)	222 (67.1)	286 (92.6)
Maternal work status <sup>a</sup>				
Yes		146 (44.5)	172 (52.6)	211 (68.5)
No		182 (55.5)	155 (47.4)	97 (31.5)
Child care for ≥15 h/wk <sup>a</sup>				
Yes		95 (29.0)	96 (29.4)	138 (45.0)
No		233 (71.0)	231 (70.6)	169 (55.1)
Within 100% of federal poverty limits <sup>a</sup>				
Yes	211 (62.2)	230 (70.8)	213 (65.5)	183 (59.4)
No	128 (37.8)	95 (29.2)	112 (34.5)	125 (40.6)
Housing density <sup>a</sup>				
0.51–1.0 persons per room	82 (24.6)	54 (18.0)	56 (19.0)	59 (20.9)
1.01–1.5 persons per room	130 (39.0)	98 (32.7)	113 (38.3)	112 (39.7)
>1.5 persons per room	121 (36.3)	148 (49.3)	126 (42.7)	111 (39.4)
HOME score <sup>a,b</sup>				
0–25 points		29 (8.8)	1 (0.3)	
26–36 points		271 (82.1)	190 (58.1)	
>36 points		30 (9.1)	136 (41.6)	

Percentages represent percentages of known values. CES-D indicates Center for Epidemiologic Studies Depression Scale.

<sup>a</sup> Values at 6, 12, and 24 months were limited to the population of subjects for whom Bayley assessments were performed at that time.

<sup>b</sup> HOME scores at 24 months were not complete.

We also performed longitudinal analyses evaluating Bayley scale scores at the 3 ages simultaneously in marginal regression models. Estimates were obtained by us-

ing generalized estimating equations,<sup>28</sup> with an independence working correlation. The results were similar to those reported in the cross-sectional multivariate regres-

sion models, with similar levels of precision. For simplicity, only cross-sectional results are presented.

## RESULTS

Women were primarily young and parous and had less than high school education (Table 1). Almost all were born in Mexico and preferred to speak Spanish (91%), with 25% living in the United States for  $\leq 1$  year. One half of the women (50%) were born in coastal Mexican states, where DDT was used until the middle 1990s for domestic food production and until 2000 for malaria control, and another 39% came from regions with medium intensity of historical DDT use, including highland Mexico and Central America. Very few women smoked, and almost none regularly consumed alcohol during pregnancy. Nearly all women lived with the child's father, and two thirds were below the federal poverty line.<sup>24</sup> Almost all women (83%) were from farm-worker households, with 42% working in agriculture during pregnancy. Among exposure-related covariates, we found that time in the United States, country of origin, education, housing density, and having worked in agriculture during pregnancy (which was related strongly to time in the United States) were associated with DDT and/or DDE levels in this sample.

Approximately one third of the children were first-born, 7% were preterm, 4% were small for gestational age, and 3% were low birth weight (<2500 g). By 24 months, 45% of the children were in out-of-home child care and 69% of mothers were working. Almost all children were breastfed initially (97.5%), with 55% and 32% still breastfeeding at the 6- and 12-month assessments, respectively. The mean maternal PPVT score was within the lower range of average (mean  $\pm$  SD: 87  $\pm$  21). Slightly more than one half of mothers were at risk for depression. Few children lived in home environments considered to be of low quality, in terms of stimulation and interaction (HOME scores of <26), at 6 months (8.8%), with even fewer at 12 months (0.3%).

As shown in Table 2, nearly all DDT/DDE levels were above the LOD. Mothers had low total PCB levels (geometric mean: 16.4 ng/g lipid; 95% confidence interval [CI]: 15.2–17.7 ng/g lipid) but relatively high pregnancy DAP levels, compared with national estimates (median: 112.7 and 126.4 nmol/g, respectively).<sup>27,29</sup> Relative to these national estimates,<sup>30</sup> levels of HCB (geometric

mean: 68.2 ng/g lipid; 95% CI: 62.5–74.5 ng/g lipid) and  $\beta$ -HCCH (geometric mean: 32.6 ng/g lipid; 95% CI: 28.7–37.1 ng/g lipid) were also high. Cord lead levels were very low (geometric mean: 0.9  $\mu$ g/dL; 95% CI: 0.8–1.0  $\mu$ g/dL), relative to World Health Organization cutoff values for elevated levels (10  $\mu$ g/dL).

Bayley PDI scores (mean  $\pm$  SD) were 96.4  $\pm$  10.6, 106.7  $\pm$  12.5, and 97.8  $\pm$  10.5 and MDI scores were 95.4  $\pm$  7.0, 100.9  $\pm$  9.0, and 86.0  $\pm$  11.8 at 6, 12, and 24 months, respectively. Table 3 presents the change in Bayley scores associated with a 10-fold increase in DDT/DDE serum levels. After adjusting for covariates, we found 1.73- and 2.14-point decreases in 6-month PDI scores associated with 10-fold increases in serum levels of *p,p'*-DDT ( $P < .05$ ) and *p,p'*-DDE ( $P < .05$ ), respectively. Across the range of exposures in this cohort, this corresponded to reductions of 5.9 and 6.5 points, respectively, in PDI scores. At 12 months, although the coefficient for *p,p'*-DDE was unchanged ( $P = .12$ ), only *p,p'*-DDT levels remained significantly associated with PDI scores ( $P < .05$ ), corresponding to a 7.9-point decrease across the exposure range. We also found a significant negative association between *o,p'*-DDT levels and PDI scores at 12 months among boys ( $\beta = -3.78$ ; 95% CI: -7.47 to -0.09) but not among girls ( $P = .10$  for interaction). By 24 months, there were no associations of PDI scores with any of the 3 analytes.

We found no association between DDT/DDE levels and MDI scores at 6 months. At 12 months, however, we found 1.71- and 2.56-point decreases in MDI scores associated with 10-fold increases in serum levels of *p,p'*-DDT ( $P < .05$ ) and *o,p'*-DDT ( $P < .01$ ), respectively. There was no significant association between 12-month MDI scores and serum levels of *p,p'*-DDE. At 24 months, 10-fold increases in *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDE levels were associated with decreases of 2.12 points ( $P < .05$ ), 3.06 points ( $P < .01$ ), and 2.44 points ( $P < .10$ ), respectively, corresponding to reductions of 7.2, 10.2, and 7.4 points in 24-month MDI scores across the range of exposures in this cohort. Figure 1 presents the adjusted regression lines for serum *p,p'*-DDT levels and MDI and PDI scores at all 3 ages. Fitting nonparametric lowess curves to the data (not shown) supported the conclusion that these associations were approximately linear. In the final models, when we included measurements of exposure to lead, HCB,  $\beta$ -HCCH, PCBs, or

TABLE 2 Prenatal DDT and DDE Measurements

Analyte	No.	LOD Range, ng/g of Lipid <sup>a</sup>	Proportion Above LOD, %	Range, ng/g of Lipid	Geometric Mean (95% CI), ng/g of Lipid <sup>a,b</sup>
<i>p,p'</i> -DDT	360	0.06–4.70	100.0	1.55–33 174.0	22.0 (18.4–26.4)
<i>o,p'</i> -DDT	358	0.04–0.69	95.8	0.07–1878.1	1.8 (1.5–2.1)
<i>p,p'</i> -DDE	360	0.06–4.83	100.0	48.80–159 303.3	1436.9 (1257.4–1642.1)

<sup>a</sup> Values were adjusted for lipid levels.

<sup>b</sup> Measurements below the LOD were assigned a value of LOD/2.

**TABLE 3** Adjusted Coefficients ( $\beta$ ) for Points on the Bayley PDI and MDI Scales for a 1-Log<sub>10</sub> Unit Increase in Serum Levels of *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDE

	$\beta$ (95% CI)		
	6 mo <sup>a</sup>	12 mo <sup>a</sup>	24 mo <sup>a</sup>
PDI			
<i>p,p'</i> -DDT	-1.73 (-3.36 to -0.10) <sup>b,c</sup>	-2.33 (-4.44 to -0.22) <sup>c,d</sup>	0.17 (-1.54 to 1.88) <sup>e</sup>
<i>o,p'</i> -DDT	-1.47 (-3.36 to 0.43) <sup>b</sup>	-1.87 (-4.34 to 0.59) <sup>d</sup>	-0.58 (-2.61 to 1.44) <sup>e</sup>
<i>p,p'</i> -DDE	-2.14 (-4.20 to -0.08) <sup>b,c</sup>	-2.14 (-4.83 to 0.56) <sup>d</sup>	0.59 (-1.58 to 2.77) <sup>e</sup>
MDI			
<i>p,p'</i> -DDT	0.18 (-0.90 to 1.26) <sup>f</sup>	-1.71 (-3.21 to -0.21) <sup>c,g</sup>	-2.12 (-4.03 to -0.21) <sup>c,h</sup>
<i>o,p'</i> -DDT	0.18 (-1.06 to 1.42) <sup>f</sup>	-2.56 (-4.28 to -0.84) <sup>g,i</sup>	-3.06 (-5.30 to -0.83) <sup>h,i</sup>
<i>p,p'</i> -DDE	0.33 (-1.06 to 1.73) <sup>f</sup>	-1.15 (-3.06 to 0.77) <sup>g</sup>	-2.44 (-4.92 to 0.05) <sup>h,j</sup>

<sup>a</sup> Ages at assessments (mean  $\pm$  SD) of 6.6  $\pm$  1.0 months, 12.9  $\pm$  1.5 months, and 24.6  $\pm$  1.1 months.

<sup>b</sup> Controlling for psychometrician, gender, maternal years in the United States, poverty level, and season of assessment.

<sup>c</sup>  $P < .05$ .

<sup>d</sup> Controlling for psychometrician, maternal years in the United States, maternal age, housing density, child's age at assessment, and season of assessment.

<sup>e</sup> Controlling for psychometrician, gender, housing density, maternal education and marital status, maternal depression, child's age at assessment, location at assessment, and season of assessment.

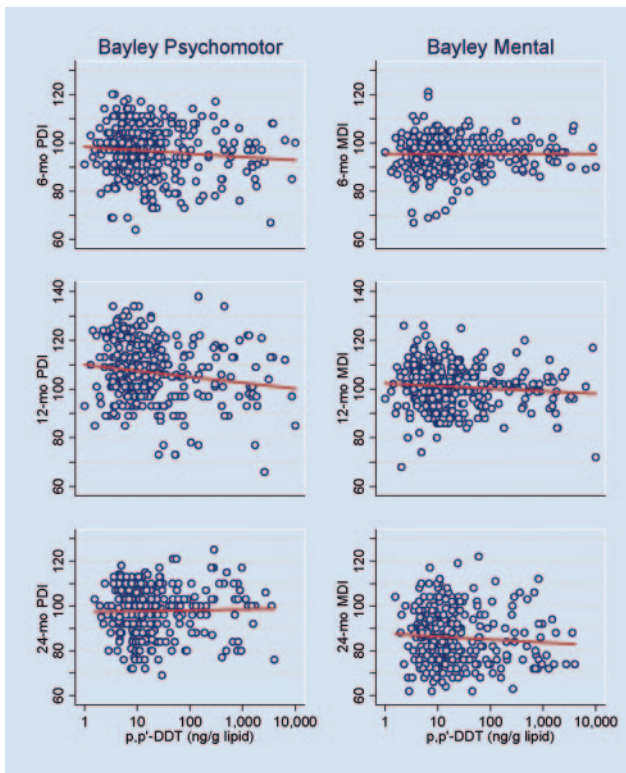
<sup>f</sup> Controlling for psychometrician, gender, and housing density.

<sup>g</sup> Controlling for psychometrician, time breastfed, and maternal years in the United States.

<sup>h</sup> Controlling for psychometrician, time breastfed, gender, maternal education and age, HOME score, and maternal work status.

<sup>i</sup>  $P < .01$ .

<sup>j</sup>  $P < .10$ .



**FIGURE 1**

Association of *p,p'*-DDT levels with Bayley PDI and MDI scores at ages 6, 12, and 24 months for the CHAMACOS study population, Salinas Valley, California. Dots represent observed values. Lines represent the association of DDT exposure with MDI or PDI scores, adjusted for covariates.

DAPs, none of the observed associations of DDT or DDE levels with PDI or MDI scores were diminished.

Breastfeeding was significantly positively associated

with 12- and 24-month MDI scores in the final models. Associations for breastfeeding were similar in multivariate regression models reanalyzed without DDT/DDE levels; each 1 month of breastfeeding was associated with increases of  $\sim 0.20$  points in MDI scores at 12 and 24 months ( $P < .05$ ). Breastfeeding was also positively, although not significantly, associated with 6-month MDI scores and with PDI scores when added to final models.

Within the population with the upper quartile of prenatal DDT/DDE exposure, breastfeeding for longer periods of time was, in most cases, associated positively with MDI or PDI performance; in no case was breastfeeding significantly negatively associated with performance. In only 1 case in which the main effect of DDT/DDE exposure was significant did we find a marginally significant interaction ( $P < .10$ ) with breastfeeding. In that case, we observed that mental development at 12 months was improved by breastfeeding, although less as *o,p'*-DDT exposure increased (data not shown). There was no longer a significant interaction at 24 months.

## DISCUSSION

This study of a predominantly Mexican American population residing in California provides evidence that in utero exposure to DDT and, to a lesser extent, DDE is associated negatively with child neurodevelopment. Specifically, we found that higher maternal serum *o,p'*-DDT and *p,p'*-DDT levels were associated with lower Bayley MDI scores at 12 and 24 months. Exposure to *p,p'*-DDT was associated with lower PDI scores at 6 and 12 months, which was not observed at 24 months. Exposure to *p,p'*-DDE was also associated with lower 6-month PDI scores. We found that, even when mothers

had substantial exposure, breastfeeding was usually positively associated with performance on the Bayley scales.

Serum levels of *o,p'*-DDT, *p,p'*-DDT, and *p,p'*-DDE were correlated strongly with one another ( $r = 0.8-0.9$ ), which made it difficult to separate out their individual effects. However, these chemicals are quite different in their modes of action and properties. For example, *o,p'*-DDT has strong estrogen-like properties, whereas *p,p'*-DDE has antiandrogenic properties.<sup>2</sup> It is well known that these chemicals are hormonally active and, whether affecting estrogenic, androgenic, or thyroid hormones, may result in adverse effects on neurodevelopment.<sup>31</sup>

Although animal studies have demonstrated that DDT is a neurodevelopmental toxicant,<sup>2,5,6</sup> the present study is the first to report on DDT and neurodevelopment in humans. Human studies have focused on the impact of DDE. Although DDE levels in the present study are lower than those in earlier cohorts such as that in North Carolina,<sup>8</sup> they seem higher than those in more-recent studies from Oswego<sup>11</sup> and Spain.<sup>13</sup> Results may also vary because of differences in populations' exposures to other chemicals. Unlike our study, the North Carolina study also reported relatively high levels of PCB exposure, which were found to be associated with poorer neurodevelopment.<sup>8</sup> The Spanish population was relatively small and had high levels of HCB<sup>13</sup>; nevertheless, the authors reported associations of DDE levels with MDI and PDI scores at 13 months, after controlling for PCBs and HCB. Although our population had relatively high levels of HCB and  $\beta$ -HCH, we found no evidence that these levels confounded the relationship between DDT/DDE levels and infant neurodevelopment.

This study has a number of strengths. The CHAMACOS cohort is a longitudinal birth cohort for which considerable information was collected about environmental exposures and potential confounders. Our population had a wide range of and relatively high average serum DDT/DDE levels. Compared with women of reproductive age participating in the National Health and Nutrition Examination Survey of the United States,<sup>32</sup> CHAMACOS women had  $\sim 1.3$ -fold higher median *p,p'*-DDT levels and 8 times higher median *p,p'*-DDE levels. The CHAMACOS population also had relatively low levels of in utero exposure to other known developmental toxicants and neurotoxicants, such as lead, PCBs, cigarette smoke, and alcohol. In addition, although exposure to organophosphate pesticides, measured as DAPs, was relatively high,<sup>27</sup> we were able to control for DAP levels and they did not attenuate the associations we observed for DDT/DDE. Furthermore, our population was homogeneous, which reduced uncontrolled confounding. For example, the mothers had similar diets,<sup>33</sup> and most breastfed, originated in Mexico, and lived in impoverished environments. The fact that most children were raised in poverty may account for the overall low 24-

month MDI scores (sample mean was  $\sim 1$  SD below the standardized mean).

However, this study is limited in that we did not have direct measures of postnatal DDT/DDE exposure for the children. We inferred the level of exposure from breastfeeding duration, but we could not account for other possible sources of postnatal exposure, although they are likely to be minimal. In addition, we did not control for postnatal exposure to other neurotoxicants.

The results of many clinical studies have indicated that breastfed infants score higher on tests of cognitive function.<sup>34</sup> Some have debated whether this is attributable to the medical benefits of breast milk, to the psychosocial benefits (eg, parental stimulation) of breastfeeding, or to uncontrolled confounding of socioeconomic status.<sup>34,35</sup> Our results for a socially and economically homogeneous population support the results of a meta-analysis<sup>34</sup> demonstrating the benefits of breastfeeding on cognitive development after adjustment for socioeconomic factors. Nevertheless, the question arises regarding whether these benefits outweigh the risk to the child when mothers have been heavily exposed to toxicants that accumulate in breast milk. Levels of PCBs, another class of lipophilic endocrine disruptors, have been shown to be related more negatively to cognitive performance among nonbreastfed infants than breastfed infants,<sup>35,36</sup> and the adverse associations of PCBs are likely from prenatal exposure. The present study provides additional evidence that breastfeeding may help to compensate for the subtle perinatal insult associated with DDT/DDE exposure. However, because DDE also may be associated with length of lactation,<sup>37</sup> additional research is needed to distinguish the complex intertwined roles of prenatal exposure, breast milk exposure, and duration of breastfeeding.

## CONCLUSIONS

We report that in utero exposure to DDT and, to a lesser extent, DDE may be associated negatively with the neurodevelopment of young children. Our finding of a beneficial association of breastfeeding suggests that women should be encouraged to breastfeed even in areas with relatively high levels of environmental exposure to DDT. The findings of this study on DDT and DDE levels and human neurodevelopment have important implications for countries that are reconsidering or continuing the use of DDT for malarial control, because DDT persists in the environment and in human bodies, and exposures and their consequences are passed from one generation to the next, even years after cessation of use. In areas such as sub-Saharan Africa, the estimated cost of children's lives lost to malaria is not trivial.<sup>1</sup> However, the benefit of using DDT to control malaria should be balanced carefully against the potential risk to children's neurodevelopment. Whenever possible, alternative antimalarial controls should be considered, especially in



areas where pregnant women and children may be exposed.<sup>1</sup>

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#### INDUSTRY'S ROLE IN HYPERTENSION

“If the American Society for Hypertension hoped to devise an expanded definition of the condition that would be scientifically and ethically defensible, it sure picked the wrong way to do it. Virtually every key step in its efforts to redefine hypertension from mere high blood pressure to a broader syndrome has been financed by pharmaceutical companies that would gain by selling drugs to more people. As described by Stephanie Saul in The Times on May 20, Merck, Novartis and Sankyo gave the small medical society \$75,000 in unrestricted grants that were used to develop a new definition, and \$700,000 more in unrestricted grants that financed dinner lectures to promote the new definition. The drug companies have too much self-interest to be allowed even a peripheral role in defining illness. Hypertension, which is a risk factor for developing cardiovascular disease, is currently defined as a blood pressure reading of 140/90 and above. Some 65 million Americans have high blood pressure by that definition. But 59 million more are considered pre-hypertensive, which means they have blood pressure readings of at least 120/80. The new concept being debated within the society would move about half of these into the hypertension category based on other risk factors. . . . While this approach has merit in principle, some prominent members of the society complain that the new definition is not grounded on solid scientific evidence and inevitably bears the taint of financial ties with the industry. No guidelines produced this way will have much credibility.”

**New York Times. May 30, 2006**

Noted by JFL, MD

**In Utero Exposure to Dichlorodiphenyltrichloroethane (DDT) and  
Dichlorodiphenyldichloroethylene (DDE) and Neurodevelopment Among Young  
Mexican American Children**

Brenda Eskenazi, Amy R. Marks, Asa Bradman, Laura Fenster, Caroline Johnson,  
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