MiniReview

Pesticide Toxicity and the Developing Brain

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Abstract: Organochlorine pesticides are used in some countries for malaria control and organophosphate pesticides are widely used in agriculture and in homes. Previous literature documents children's exposure to these chemicals both in utero and during development. Animal studies suggest that many of these chemicals are neurodevelopmental toxicants even in moderate doses, but there are few studies in human beings. Associations of children's pesticide exposure with neurodevelopment from studies being conducted worldwide are summarized. In addition, we present the work of the CHAMACOS study, a longitudinal birth cohort study of Mexican-American children living in the Salinas Valley of California. In this study, we investigated the relationship of children's neurodevelopment with maternal dichlorodiphenyltrichloroethane and dichlorodiphenyldichloroethylene serum levels, as well as prenatal and child organophosphate urinary metabolite levels. We have examined the association with children's performance on the Brazelton Neonatal Assessment Scales and at 6, 12 and 24 months on the Bayley Scales of Infant Development (mental development and psychomotor development) and mothers report on the Child Behaviour Checklist. We observed a negative association of prenatal dichlorodiphenyltrichloroethane exposure and child mental development. We also observed adverse associations of prenatal but not postnatal organophosphate pesticide exposure with mental development and pervasive developmental disorder at 24 months.

The potential for in utero or early postnatal pesticide exposure to affect human brain development has been shown in numerous animal studies [1]. Studies of acute pesticide poisonings in children have also demonstrated effects on neurological functioning [2]. An emerging literature provides evidence of neurobehavioural consequences resulting from exposure to relatively low levels of organochlorine and organophosphate pesticides in infants and children. In this paper, we summarize the results of research from the CHAMACOS study, from the Center for Children's Environmental Health Research at the University of California, Berkeley, in the context of the existing literature on pesticide exposure and neurodevelopment in infants and children.

The CHAMACOS cohort

CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) is the keystone project of the University of California, Berkeley, Center for Children's Environmental Health Research, which is one of the 11 centers currently funded by the National Institute of Environmental Health Science and the US Environmental Protection Agency. The objectives of the center are to

- estimate sources, pathways and levels of in utero and postnatal pesticide exposures of children living in an agricultural community,
- determine the relationship of pesticide exposure and neurodevelopment, growth and respiratory disease,
- understand the mechanisms of pesticides in human beings, and
- reduce exposure of children to pesticides with interventions and community outreach.

For the CHAMACOS project, pregnant women over 18 years of age who were less than 20 weeks gestation, Medi-Cal eligible, and planning to deliver at the local hospital were recruited in 1999 and 2000 from prenatal care clinics in Salinas, California. Salinas is an agricultural area located approximately 100 m south of the San Francisco Bay Area in a valley known as the 'nation's salad bowl'. Approximately 500,000 pounds of organophosphate pesticides are used annually in the Salinas Valley.

Six hundred and one pregnant women were enrolled in the birth cohort study. The cohort is a largely Mexican immigrant population with almost all women (92%) reporting Spanish as their primary language; 85% were born in Mexico.
and 54% had been in the USA 5 years or less at the time of enrollment. The majority of the women came from agricultural households, with 84% of the women living with at least one agricultural worker and 44% of them reporting working in agriculture during their pregnancy. Approximately 96% of the women are classified as low-income (earning 200% or less of the national poverty level income) and 44% have a sixth grade education or less.

There are four sources of pesticide exposure information that are gathered for the cohort: (i) measurements in biological specimens; (ii) environmental measurements; (iii) information derived from detailed questionnaires and home walkthroughs; and (iv) State of California Pesticide Use Report data. A large biologic repository has been developed with more than 75,000 biologic specimens, including maternal, paternal and child urine; maternal, cord and child blood; breast milk; child saliva; and exfoliated teeth. Urine specimens and blood have been used to measure pesticide levels. We also collected environmental dust samples from participant’s homes and conducted detailed questionnaires and home walkthroughs to assess pesticide exposure. Finally, Pesticide Use Report data are collected by California Department of Pesticide Regulation. These data include reports of the poundage, location, date and time of every pesticide application and, when assessed in conjunction with the geographic position of each home, may be used to predict a participants’ ambient pesticide exposure [3].

This study design presents a number of strengths. The CHAMACOS study is a longitudinal birth cohort study in which we were able to collect information during the prenatal and postnatal periods on environmental exposures from multiple sources and considerable data on potential confounding variables. In addition, it is a relatively homogenous, low-income, Mexican immigration population, which decreases the probability for uncontrolled confounding. Lastly, because the majority of women were originally from Mexico where dichlorodiphenyltrichloroethane (DDT) has been used more recently and either currently worked in agriculture themselves or lived with others who worked in agriculture during pregnancy, they were potentially exposed to relatively high levels of organochlorine and organophosphate pesticides. We were also able to measure exposure to multiple agents in the biologic specimens and to control for these exposures in the analyses. Given that high correlation has been found between biomarkers for different toxicants, which may have similar neurodevelopmental effects [4], controlling for co-exposures is important. At the same time, we confirmed that the population had relatively low levels of in utero exposure to other developmental toxicants and neurotoxicants such as lead, polychlorinated biphenyls, cigarette smoke and alcohol.

Weaknesses of the study design include loss to follow-up and challenges in exposure assessment. The population from which the sample was recruited is a predominantly Mexican immigrant farmworking community and as a result is highly mobile. Despite this, out of the 601 women originally enrolled, 86% were still participating at the delivery visit, 73% were participating a year later when their children were 12 months old and 68% participated at the 2-year visit. We have also faced challenges in exposure assessment, although this is not a weakness particular to this study. Biomarkers, such as urinary organophosphate pesticide metabolites are imperfect measurements of exposure. They may reflect not only exposure to the parent pesticide compound, but also to ambient pesticide metabolites, which may be less toxic [5]. Additionally, urinary organophosphate pesticide metabolites may only reflect recent exposure to pesticides. Direct measures of organophosphate pesticides in blood also only reflect recent exposure levels. However, because we collected several types of biological specimens and information on exposure from other sources, we are not limited to using urinary pesticide metabolites.

Organochlorine pesticides

Organochlorine pesticides, such as DDT, are highly lipophilic organic pollutants that persist in the environment, accumulate in the food chain and are regularly detected in humans. Some countries, such as the USA, banned the use of DDT in the 1970s. In 2001, over 90 countries signed the Stockholm Convention on Persistent Organic Pollutants, committing to eliminate the use of 12 persistent organic pollutants, such as DDT, due to concerns for the environment and human health. However, DDT is an effective and relatively inexpensive form of mosquito control for preventing the spread of malaria. In September 2006, the World Health Organization announced that it would back the use of DDT for malaria control, and as a result some countries are reconsidering its use. Children are exposed to DDT and its breakdown product dichlorodiphenyldichloethylenne (DDE) in utero, through breast milk, and potentially postnatally, through diet and contact with the environment such as through hand-to-mouth behaviour. The foetus’ and infant’s developing nervous system may be particularly vulnerable to exposure of DDT and DDE.

Table 1 summarizes the existing literature on DDT and DDE and neurodevelopment in infants and children. Only studies with biological markers of DDT and DDE were included in the review. Included studies may have analysed levels of o,p'-DDT, p,p'-DDT and/or p,p'-DDE; DDT and DDE are known to have different modes of action and properties but both are potential neurotoxicants. As seen in table 1, the literature on DDT and neurodevelopment is sparse. Most studies have examined the association of DDE and neurodevelopment, although this literature shows inconclusive findings.

Using the CHAMACOS cohort, we investigated whether in utero DDT and DDE exposure were associated with neonatal neurodevelopment using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS). Despite maternal serum DDT and DDE levels that were higher than the National Health and Nutrition Examination Survey US reference population [6], these levels in the mothers were not significantly associated with neonatal performance as
Table 1. Summary of literature on organochlorine pesticide exposure and neurodevelopment in children. Average exposure levels are indicated where available.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogan et al. 1986 [8]</td>
<td>n = 912 neonates ≤1 month old Birth cohort from three health centers in North Carolina</td>
<td>DDE – placenta, maternal and cord serum and milk/colostrums combined into one measure/woman</td>
<td>Brazelton Neonatal Behavioral Assessment Scale (BNBAS)</td>
<td>↑Dose-related number of abnormal reflexes (hyporeflexia) Higher scores on regulation of states with borderline significance</td>
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<td>Gladen et al. 1988 [12]</td>
<td>n = 858 children followed from birth to 1 year Birth cohort from three health centers in North Carolina</td>
<td>DDE – placenta, maternal and cord serum (prenatal exposure) and milk/colostrums (postnatal exposure)</td>
<td>Bayley Scales of Infant Development (BSID-II): Mental Development Index (MDI); Psychomotor Development Index (PDI)</td>
<td>↑MDI/PDI at 6 and 12 months</td>
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<tr>
<td>Rogan et al. 1991 [13]</td>
<td>n = 676–18 months n = 670–24 months Birth cohort from three health centers in North Carolina</td>
<td>DDE – placenta, maternal and cord serum (prenatal exposure) and milk/colostrums (postnatal exposure)</td>
<td>BSID-II: MDI; PDI</td>
<td>↑MDI &amp; PDI</td>
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<tr>
<td>Gladen et al. 1991 [14]</td>
<td>n = 645–3 years n = 628–4 years n = 636–5 years n = 506 (report cards) Birth cohort from three health centers in North Carolina</td>
<td>DDE – placenta, maternal and cord serum (prenatal exposure) and milk/colostrums (postnatal exposure)</td>
<td>• McCarthy Scales of Children's Abilities (MSCA): verbal, quantitative, motor, perceptual, performance, memory, general cognitive • School report cards</td>
<td>Prenatal exposure: • ↑↓Diff in quant. score at 3, 4 and 5 years with the lowest score at 4 years – no dose-response and borderline significance • =for grades Postnatal exposure: • ↑↓Diff in motor score at 3, 4 and 5 years with the lowest score at 4 years and no dose-response • =grades =performance on all clusters</td>
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<td>Stewart et al. 2000 [9]</td>
<td>n = 141 exposed ≤2 days old n = 152 unexposed (Oswego birth cohort) Exposure groups based on maternal report of Lake Ontario lifetime fish consumption ≥40 lbs.</td>
<td>Cord serum levels DDE (median = 0.10 ng/g wet), HCB, Mirex</td>
<td>BNBAS at 12–24 hr and at 25–48 hr after birth</td>
<td>↑↑MDI at 6 months = MDI at 12 months =PDI at 6 months = PDI at 12 months</td>
</tr>
<tr>
<td>Darvill et al. 2000 [15]</td>
<td>Same cohort as in Stewart et al. • 230 at 6 months old • 219 at 12 months old</td>
<td>Cord serum levels DDE, HCB, Mirex; breast milk on a subgroup (the primary exposure was PCB)</td>
<td>Fagan Test of Infant Intelligence</td>
<td>↑MDI and PDI-dose-related 2X dose of DDE ↓3.5 points MDI ↓4.0 points PDI Griffis Scales: locomotor, personal-social, performance and eye-hand coordination (borderline significant) • Associations strongest if shorter period of breastfeeding</td>
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<tr>
<td>Ribas-Fitó et al. 2003 [16]</td>
<td>n = 92 infants 13 months old Birth cohort living near an electrochemical factory in Spain</td>
<td>Cord serum DDE (median = 0.85 ng/mL) and HCB</td>
<td>BSID-II: MDI; PDI</td>
<td>Griffis Scales of Infant Development</td>
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Table 1.

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<tr>
<td>Eskenazi et al. 2006 [11]</td>
<td>n = 330 at 6 months, n = 327 at 12 months, n = 309 at 24 months CHAMACOS birth cohort living in an agricultural community; mostly Latino farmworker families in Salinas Valley California</td>
<td>Maternal serum DDT and DDE at 26 weeks gestation (±2.9 S.D.) for n = 334 or just before delivery for n = 26</td>
<td>BSID-II: • MDI • PDI</td>
<td>• p,p′-DDT (1-log₁₀ increase): ↓PDI at 6 (1.73 points) and 12 mo. (2.33 points) not at 24 months ↓MDI at 12 (1.71 points) and 24 (2.12) months not at 6 months • o,p′-DDT (1-log₁₀ increase): Borderline significant decrease in MDI at 12 (2.56 points) and 24 (3.06 points) months not at 6 months • p,p′-DDE (1-log₁₀ increase): ↓PDI at 6 months (2.14) not at 12 or 24 months =MDI</td>
</tr>
<tr>
<td>Ribas-Fitó et al. 2006 [17]</td>
<td>n = 102 4-year-old children from Ribera d’Ebre cohort, n = 403 4-year-old children from Menorca cohort; Spanish children</td>
<td>Cord serum DDT and DDE Median Ribera d’Ebre, Menorca: DDT: 0.05 ng/ml, 0.08 ng/ml DDE: 0.86 ng/ml, 1.03 ng/ml</td>
<td>MCSA: • General cognitive • Memory</td>
<td>Combination cohorts • DDT: ↓general cognitive (1.99), memory (3.79 borderline significant), verbal (2.63 borderline significant), executive function (2.61), memory span (2.28 borderline significant) and verbal memory (6.1 borderline significant) • DDE: ↓memory (1.93) and in other domains p,p′-DDE (1st trimester): • LPDI at 3 months (10.8), 6 months (1.94) 12 months (5.72) =MDI</td>
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<td>Torres-Sánchez et al. 2007 [18]</td>
<td>n = 225 at 1 month, n = 233 at 3 months, n = 227 at 6 months, n = 191 at 12 months Mexican birth cohort (State of Morelos)</td>
<td>Maternal serum DDE Mean exposure: Prepregnancy 6.8 ng/ml 1st trimester 6.4 ng/ml 2nd trimester 6.8 ng/ml 3rd trimester 7.8 ng/ml</td>
<td>BSID-II: • MDI • PDI</td>
<td>No observed associations between maternal DDT/DDE serum levels and neonatal performance on BNBAS Authors cite that single BNBAS may have limited sensitivity</td>
</tr>
<tr>
<td>Fenster et al. 2007 [7]</td>
<td>n = 419 neonates CHAMACOS birth cohort living in an agricultural community; mostly Latino farmworker families in Salinas Valley California</td>
<td>Maternal serum DDT and DDE at 26 weeks gestation (±2.9 S.D.) for n = 334 or just before delivery for n = 26</td>
<td>BNBAS</td>
<td>No association</td>
</tr>
<tr>
<td>Engel et al. 2007 [10]</td>
<td>n = 151 neonates Mt. Sinai birth cohort in New York City – random subset of whole cohort (404 neonates) for this analysis</td>
<td>Maternal serum DDE Median = 0.6 µg/liter</td>
<td>BNBAS</td>
<td>No association</td>
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</table>

↑↓ signifies a statistically significant effect in the indicated direction (P-value ≤0.05); = signifies no statistically significant effect. DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane.
was associated with lower PDI scores at 12 months and (PDI) at 6 months [11]. We also observed that DDE exposure with lower scores on the Psychomotor Development Index in the North Carolina birth cohort, researches found a 24 months, although the findings were not significant [11].

In the North Carolina birth cohort, researchers found a decrease on the BSID-II MDI at 12 and 24 months, respectively [11]. There was no significant association of serum DDT with the MDI at the 6-month assessment [11]. We did observe a significant inverse association between maternal serum DDT and the psychomotor development scores on the BSID-II at 6 and 12 months but not at 24 months [11]. Besides the CHAMACOS study, only one other study has examined the association between in utero DDT exposure and children's development and results were similar. In the Spanish cohorts from Ribera d'Ebre and Menorca, higher cord serum DDT levels were significantly associated with hyporeflexia on the BNBAS in a birth cohort of 912 infants in North Carolina [8]. However, these findings were not replicated in a similar analysis of the Oswego, New York birth cohort [9]. Although the Oswego cohort study was smaller (n = 293), the BNBAS was administered twice during the first 2 days of life and no association was observed between exposure to DDE and performance on the BNBAS. An analysis of a random subset of infants from the Mt. Sinai Medical Center birth cohort (concurrent with the CHAMACOS cohort) in New York City (n = 151) also found no association between maternal serum DDE and performance on the BNBAS [10]. Thus, the only study that reported association of in utero DDE exposure and neonatal BNAS performance was the earlier North Carolina study conducted in 1986, which may be explained by higher average exposure levels. The median DDE exposure level in the North Carolina birth cohort was 12.06 p.p.b. that was higher than levels in our CHAMACOS cohort at 9.08 p.p.b. However, higher 95th percentile (151.92 p.p.b. versus 34.60 p.p.b.) and maximum values (1219.73 p.p.b. versus 180.00 p.p.b.) were detected in the CHAMACOS cohort compared to the North Carolina cohort. The findings for DDE exposure and neurodevelopment in older infants and children are less consistent than the findings for neonates. In the CHAMACOS study, we evaluated infant neurodevelopment at 6, 12 and 24 months using the Bayley Scales of Infant Development (BSID-II) and found that in utero exposure to DDE was only significantly associated with lower scores on the Psychomotor Development Index (PDI) at 6 months [11]. We also observed that DDE exposure was associated with lower PDI scores at 12 months and lower Mental Development Index (MDI) scores at 12 and 24 months, although the findings were not significant [11]. In the North Carolina birth cohort, researchers found a positive association between prenatal DDE exposure and the MDI on the BSID-II at 6 months of age, but not on subsequent assessments at 12, 18 or 24 months [12,13]. In the same cohort, researchers found that DDE exposure was positively associated with the PDI of the BSID-II at 24 months but not at 6, 12 or 18 months [12,13]. At 3, 4 and 5 years, slight differences in development were detected in association with prenatal and postnatal DDE exposure in the North Carolina cohort using the McCarthy Scales of Children's Abilities (MCSA) [14]. However, there was no apparent dose–response relationship as the lowest scores were observed in the middle exposure category with higher scores in both the low and high exposure categories. A second study of the Oswego birth cohort evaluated infants at 6 and 12 months using the Fagan Test of Infant Intelligence. Similar to the neonatal findings from the Oswego cohort, the authors reported no association between DDE levels in cord serum and development at 6 months [15]. However, at the 12-month evaluation, there was a significant negative correlation between DDE exposure and performance on the Fagan Test of Infant Intelligence [15].

The results of the CHAMACOS study for DDE exposure and neonatal neurodevelopment are largely consistent with other studies with the exception of one earlier study of the CHAMACOS cohort (concurrent with the CHAMACOS cohort) in New York City (n = 151) also found no association between maternal serum DDE and performance on the BNBAS [10]. Thus, the only study that reported association of in utero DDE exposure and neonatal BNAS performance was the earlier North Carolina study conducted in 1986, which may be explained by higher average exposure levels. The median DDE exposure level in the North Carolina birth cohort was 12.06 p.p.b. that was higher than levels in our CHAMACOS cohort at 9.08 p.p.b. However, higher 95th percentile (151.92 p.p.b. versus 34.60 p.p.b.) and maximum values (1219.73 p.p.b. versus 180.00 p.p.b.) were detected in the CHAMACOS cohort compared to the North Carolina cohort.

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We also evaluated children's neurodevelopment at 6, 12 and 24 months in the CHAMACOS cohort in relation to DDT exposure. An increase in maternal serum DDT level on the log scale was associated with a 1.71- and 2.12-point decrease on the BSID-II MDI at 12 and 24 months, respectively [11]. There was no significant association of serum DDT with the MDI at the 6-month assessment [11]. We did observe a significant inverse association between maternal serum DDT and the psychomotor development scores on the BSID-II at 6 and 12 months but not at 24 months [11]. Besides the CHAMACOS study, only one other study has examined the association between in utero DDT exposure and children's development and results were similar. In the Spanish cohorts from Ribera d'Ebre and Menorca, higher cord serum DDT levels were significantly associated with poorer scores in the general cognitive and the executive function domains on the MCSA in 4-year-old children [17].

Organophosphate pesticides

Data are limited on the neurodevelopmental effects resulting from exposure to organophosphate pesticides and exposure assessment remains challenging (table 2). Organophosphate pesticide exposure is commonly assessed by measuring organophosphate dialkylphosphate (DAP) metabolites in
Table 2: Summary of literature on organophosphate pesticide exposure and neurodevelopment in children. Average exposure levels are indicated where available.

<table>
<thead>
<tr>
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</tr>
</thead>
</table>
| Young et al. 2005 [19] | n = 381 ≤2 month olds CHAMACOS birth cohort living in an agricultural community; mostly Latino farmworker families in Salinas Valley California | Maternal urinary dialkylphosphate metabolite levels during pregnancy (M = 14 and 26 weeks) and early postnatal (M = 7 days) | Brazelton Neonatal Behavioral Assessment Scale (BNBAS)                   | • ↑Dose-related number of abnormal reflexes (hyporeflexia) with in utero measure especially in infants >3 days at testing  
• No association with early postnatal exposure measures  
• Linear regression analysis: ↓3.327 points on MDI and 6.46 on PDI at 36 months =at 12 and 24 months  
• Logistic regression analysis: High exposure to chlorpyrifos associated with 2.37 (1.08–5.19) ↑odds of mental delay at 36 months & 4.52 (1.61–12.70) ↑odds of psychomotor delay at 36 months  
• CBCL: ↑in attention problems, attention deficit/hyperactivity disorder and pervasive developmental disorder  
Prenatal exposure:  
• ↓scores on the Stanford-Binet copying test (2.5 points versus 3.3 points)  
• =on the Santa Ana, mean reaction time, Digit Span for prenatal exposure  
Current exposure:  
• ↑in mean reaction time (500 msec. versus 426 msec.)  
• =on the Santa Ana, Digit Span Forward or Stanford-Binet for current exposure  
• Stunting modified results                                                                 |
| Rauh et al. 2006 [21] | n = 254 children 0–3 years Longitudinal birth cohort study of inner-city mothers in New York City | Chlorpyrifos levels in umbilical cord plasma classified as high if >6.17 pg/g plasma | Bayley Scales of Infant Development (BSID-II):  
• Mental Development Index (MDI)  
• Psychomotor Development Index (PDI)  
• Child Behaviour Checklist (CBCL) | • ↑in attention problems, attention deficit/hyperactivity disorder and pervasive developmental disorder                                                                 |
| Grandjean et al. 2006 [23] | n = 72 Ecuadorian children 7 years old 35 exposed (prenatal) children and 37 unexposed children | Prenatal exposure assessed by questionnaire with the mother  
Current exposure assessed by urinary pesticide metabolites (both dimethyl and diethyl metabolites were detected in 31 children) | Santa Ana Pegboard, WISC-R, Stanford-Binet copying subtest and finger tapping, Catsys force plate |  
• ↑in attention problems, attention deficit/hyperactivity disorder and pervasive developmental disorder  
Prenatal exposure:  
• ↓ scores on the Stanford-Binet copying test (2.5 points versus 3.3 points)  
• =on the Santa Ana, mean reaction time, Digit Span for prenatal exposure  
Current exposure:  
• ↑in mean reaction time (500 msec. versus 426 msec.)  
• =on the Santa Ana, Digit Span Forward or Stanford-Binet for current exposure  
• Stunting modified results |
Engel et al. 2007 [10] n = 404 neonates Mt. Sinai birth cohort in New York City Maternal dialkylphosphate metabolites (DAPs) and malathion dicarboxylic acid (MDA) at mean 31.2 weeks (S.D. 3.7 weeks) DAPs: Median diethyl metabolites = 24.7 nm/liter Median dimethyl metabolites = 47.8 nm/liter MDA: median below limit of detection Brazelton Neonatal Behavioral Assessment Scales (BNBAS)

• total diethyl ↑ abnormal reflexes risk ratio 1.49 (95% CI, 1.12, 1.98)
• total dimethyl ↑ abnormal reflexes (non-significant but stronger for infants assessed in first day of life)

Eskenazi et al. 2007 [20] 6 months n = 396 children 12 months n = 372 children 24 months n = 372 children 356 mothers – CBCL at 24 months CHAMACOS birth cohort living in an agricultural community; mostly Latino farmworker families in Salinas Valley California Maternal and child urinary dialkylphosphate metabolites (DAPs) and maternal urinary metabolite of malathion (MDA) and chlorpyrifos (TCPy) Mean maternal DAP: 114.9 nmol/l Mean child DAP: 45.5, 59.5 and 70.9 nmol/l at 6, 12 and 24 months Bayley Scales of Infant Development (BSID-II) at 6, 12 and 24 months:
• MDI
• PDI
Child Behaviour Checklist (CBCL) at 24 months:
• Attention
• Attention deficit/hyperactivity disorder
• Pervasive developmental disorder

• maternal DAPs ↓ Bayley MDI at 24 months = Bayley PDI at any age ↑ CBCL at 24 months
• child DAPs ↑ Bayley MDI at 24 months = Bayley PDI at any age ↑ CBCL, PDD at 24 months
• MDA and TCPy: = Bayley = CBCL

†↓ signifies a statistically significant effect in the indicated direction (P-value ≤ 0.05); = signifies no statistically significant effect.
urine or by measuring the parent compound in blood. In the CHAMACOS cohort, we found that DAPs measured in prenatal maternal urine were associated with the number of abnormal reflexes in neonates as measured by the BNBAS [19]. More than twice the number of neonates born to mothers in the highest exposure group had three abnormal reflexes or more compared to neonates born to mothers in the lower exposure groups. Similar to the results found for CHAMACOS neonates, Engel et al. reported increased numbers of abnormal reflexes in infants born to mothers with higher levels of DAPs in urine during pregnancy in a birth cohort study from Mt. Sinai Medical Center in New York City [10]. Neither the CHAMACOS nor the Mt. Sinai study observed associations between organophosphate pesticide metabolites and other clusters of the BNBAS [6,15].

In the CHAMACOS cohort, maternal DAPs were also associated with decreased mental development scores on the BSID-II at 24 months (adjusted $\beta = -3.54$; 95% CI, $-6.59$, 0.49; $P \leq 0.05$) [20]. However, the observed association between children's concurrent DAP levels and mental development was in the opposite direction. For every 10-fold increase in a child's DAP level, we observed a 2.37 point (95% CI, 0.50, 4.24) increase in the mental development score on the BSID-II at 24 months [20]. Although we have no clear explanation for this discrepancy, it is possible that children with higher mental development scores are also more interactive with their environment and as a result come into contact with more pesticide residues. No associations were observed between maternal or child's DAP and BSID-II mental performance at 6 or 12 months of age or with psychomotor performance at any of the three time points [20]. In a longitudinal birth cohort study from Columbia University in New York City, researchers assessed infants at 12, 24 and 36 months using the BSID-II [21]. Chlorpyrifos (a common organophosphate pesticide) levels in cord plasma were associated with decreases in mental and psychomotor development at 36 months but not at 12 or 24 months. They did not assess the relationship of pesticide exposure during childhood and development.

Results from the Child Behaviour Checklist (CBCL) were similar for both prenatal and postnatal pesticide exposure in the CHAMACOS cohort. The CBCL assesses a range of behaviour problems that produces scales consistent with the Diagnostic and Statistical Manual of Mental Disorders diagnoses [22]. Maternal and child DAP levels were associated with an odds ratio of 2.25 (95% CI, 0.99–5.16) and 1.71 (95% CI, 1.02–2.87), respectively, for maternally reported pervasive developmental disorder (PDD) at 24 months [20]. The PDD scale is made up of items such as ‘avoids eye contact’, ‘rocks head, body’, and ‘unresponsive to affection’. No association was observed between maternal or child's DAPs and CBCL-assessed attention problems at 24 months [20]. Researchers from Columbia also found associations with maternal report of PDD and attention problems with and without hyperactivity at 36 months on the CBCL in their longitudinal birth cohort, similar to the results from the CHAMACOS study [21].

One study from Ecuador examined the relationship of exposure in older children and development. In a study of 7-year-old children, Grandjean et al. found that children's DAP levels were associated with an increase in simple reaction time while prenatal exposure, which was assessed by a maternal occupational questionnaire, was associated with a decrease on the Stanford-Binet copying task [23]. No differences were reported for the Santa Ana Pegboard test or the Digit Span subtest of the Wechsler Intelligence Scale for Children in relation to either prenatal or postnatal pesticide exposure. Currently, no other studies have been published in older children [23].

**Conclusions and next steps**

Previous literature and recent work by the Centers for Children's Environmental Health Research provide evidence of pesticide toxicity to the developing human brain. An important next step in this research endeavour is to pool data from studies with similar methods and outcome and exposure measures. We are currently pooling data and comparing analyses from the Centers for Children's Environmental Health Research at University of California, Berkeley, Mt. Sinai School of Medicine and Columbia University. Another next step is to identify subpopulations that may be more susceptible to pesticide exposure and resulting neurodevelopmental health effects. For example, in the CHAMACOS cohort, we have found that an individual's susceptibility to organophosphate pesticides may vary by age and genotype. Children with a particular variant of the paraoxonase 1 gene had lower levels of the paraoxonase enzyme that metabolizes organophosphate pesticides, which means they may be at higher risk of health effects from organophosphate exposure [24,25]. Future studies should examine the neurodevelopment effects in human beings associated with pesticide mixtures and other classes of pesticides (e.g. carbamates, pyrethroids), and with pesticide mixtures, because there is increasing use of these pesticides in certain communities that are replacing the organophosphate and organochlorine pesticides.

**References**


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