Final Report for NIOSH Grant Number R01 OH007400

Entitled

Endocrine Disruptor's and Neurodevelopmental Outcomes

Period of Performance: 9/30/01 through 9/29/06

Submitted on May 17, 2007

by

Principal Investigator: Brenda Eskenazi, PhD
School of Public Health
University of California at Berkeley
2150 Shattuck Avenue, Suite 600
Berkeley, CA 94704-7380

Email: eskenazi@berkeley.edu

Co-Investigators:

Laura Fenster, PhD
Asa Bradman, PhD
Nina Holland, PhD
Tom Boyce, PhD
Abbey Alkon, PhD
Martha Harney, MPH
Alan Hubbard, PhD
Marcy Warner, PhD

Table of Contents

ABBREVIATIONS

BNBAS	=	Brazelton Neonatal Behavioral Assessment Scale
CHAMACOS	=	Center for Health Analysis of Mothers and Children of Salinas
DAP	=	dialkyl phosphates
DE	=	diethyl phosphates
DM	=	dimethyl phosphates
ED	=	endocrine disrupting
HCB	=	hexachlorobenzene
HCCH	=	hexachlorocyclohexane
NHANES	=	National Health & Nutrition Examination Study
o,p'-DDT	=	o,p'–dichlorodiphenyl trichloroethane
p,p'-DDE	=	p,p'–dichlorodiphenyl dichloroethylene
p,p'-DDT	=	p,p'–dichlorodiphenyl trichloroethane
PCBs	=	polychlorinated biphenyls
β-HCCH	=	beta–hexachlorocyclohexane
γ-HCCH	=	gamma–hexachlorocyclohexane
pg/g	=	picograms per gram
ppm	=	parts per million
SD	=	standard deviation
TCP	=	3,5,6-trichloro-2-pyridinol
µg/L	=	micrograms per liter

a. Abstract

Agricultural pesticide use is a significant source of occupational and environmental endocrine disruptor exposure in the United States. Farmworkers and their families are at higher risk of exposure than the general population. Pregnant women in farmworker families may be exposed to high levels of endocrine disrupting pesticides as the result of their work in the fields, contamination of their homes, or both. Over 600,000 pounds of endocrine disrupting (ED) pesticides are used annually in the Salinas Valley. Additionally, women born in Mexico have been found to have elevated levels of DDT and DDE and other persistent ED organochlorine pesticides compared to levels found in U.S.-born participants. Approximately 90% of our study population was born in Mexico.

Although animal studies suggest that ED pesticides potentially affect neurodevelopment, no studies to date have examined these effects in humans. We examined this relationship in approximately 550 children from predominantly low-income Latino farmworker families living in the Salinas Valley of Monterey County, California. These children, whose mothers were enrolled during pregnancy, are participants of Center for Health Assessment of Mothers and Children of Salinas or CHAMACOS, birth cohort study which aims to investigate the effects of pesticides and other environmental exposures on the health of pregnant women and their children living in the Salinas Valley, CA, an agricultural area. We measured biomarkers of exposure to 14 persistent organochlorine pesticides in archived CHAMACOS serum samples. Tests for non-persistent pesticides in urine of pregnant women included fungicides, organophosphates insecticides, pyrethroid, carbamate, and organochlorine insecticides, triazine and choroacetanilide herbicides, naphthalene, and pentachlorphenol, and included development of a new test for ETU, a toxic metabolite of bis-dithiocarbamate fungicides. Prenatal and

delivery medical records were abstracted by a registered nurse. Mothers were interviewed prenatally and postnatally about their sociodemographic characteristics, habits, housing, exposure, work and medical history. We assessed neurodevelopment of neonates ≤ 2 months old using the Brazelton Neonatal Behavioral Assessment Scale. The Bayley Scales of Infant Development, a well-known method for developmental assessments of young children, were used to test the mental and physical skills of the women's babies at six, 12 and 24 months. The Bayley Scales were administered in Spanish or English by study staff who were blind to exposure status.

All women had organochlorine pesticides in their blood, and median levels of DDT and DDE were several times higher than the general U.S. population. For each tenfold increase in DDT levels measured in the mother, we found a corresponding two- to three-point decrease in the children's mental development scores at 12 and 24 months. The highest *in-utero* DDT exposures in children were associated with a seven- to 10-point decrease in Bayley mental scores, compared to the lowest exposures. In the physical skills evaluations – known as psychomotor testing – there were two-point decreases in children's scores at six and 12 months for each tenfold increase in DDT levels in the mothers. No decrease was found at 24 months. When we evaluated the effects of DDE on development, we found associations that were similar to those for DDT, but not as strong. We observed no adverse associations between organochlorine pesticide levels and birth weight or crown-heel length. Higher HCB levels were associated with reduced gestational duration.

Most pesticides in urine had low detection frequencies. For example, ETU was detected in approximately 20% of the matemal urine samples. Nine compounds were detected greater than >50%, with two potentially related to current use pesticides in the Salinas Valley (TCPy, derived from chlorpyrifos, and 1-napthol, derived in part from carbaryl). Malathion and chlorpyrifos urinary metabolites levels were not associated with birth weight, birth length, head circumference, ponderal index and duration of gestation; however, higher levels of total dimethyl organophosphate metabolites in maternal urine were associated with shorter gestational duration. Median levels for five pesticides (2,4-dichlorophenol, 2,5-dichlorophenol, 2-naphthol, para-nitrophenol and 3,4,6-trichloro-2-pyridinol (TCPy)) were higher in our population compared to levels reported for pregnant women in NHANES (n=224). This finding suggests that exposures to the parent compounds of these metabolites were higher in our population of pregnant women compared to the general population of United States pregnant women. Overall, we did not observe associations between agricultural exposure risk factors and levels of non-persistent metabolites in maternal urine, nor did we observe associations between exposure to non-persistent pesticides and child development.

This study provided the first data on in utero exposure and health effects of ED pesticides in a highly exposed population. Our key finding was that prenatal exposure to DDT, and to a lesser extent DDE, was associated with neurodevelopmental delays during early childhood, althoughh breastfeeding was found beneficial, even among women with relatively high exposure. Although use of DDT in agriculture is now banned worldwide, the World Health Organization and the United States Agency for International Development are implementing programs to increase use of DDT internationally for control of mosquitoes carrying malaria. Our results indicate that programs to protect worker health are needed to ensure that workers applying DDT for malaria control are not excessively exposed. Additional research is also needed to assess the specific contribution of Indoor Residual Spraying (IRS) of DDT to general population exposures.

b. Highlights/Significant Findings

This study investigated persistent and non-persistent pesticide exposure to pregnant women living in an agricultural area and birth outcomes and neurodevelopment in their children.

We found an approximately 2-point decrease in psychomotor development (as assessed by the the Bayley Scales of Infant Development) with each 10-fold increase in p,p'-DDT levels at 6 and 12 months (but not at 24 months) and with p,p'-DDE levels at 6 months only ($p<0.05$). We found no association with mental development at 6 months, but a 2- to 3-point decrement in Bayley Mental Development Index scores with p,p'-DDT ($p<0.05$) and o,p'-DDT ($p<0.01$) levels at 12 and 24 months. Even when mothers had substantial exposure, breastfeeding was usually positively associated with Bayley scores. Thus, prenatal exposure to DDT, and to a lesser extent DDE, was associated with neurodevelopmental delays during early childhood, although breastfeeding was found beneficial, even among women with relatively high exposure.

Malathion and chlorpyrifos urinary metabolites in pregnant women were not associated with Bayley mental or motor development scores, although total prenatal organophosphate pesticide exposure was associated with poorer functioning in children at two years. Separately, for 8 additional compounds with detection frequencies >50% (1- and 2-napthol, orthophenylphenol, para-nitrophenol, 2,4- and 2,5-dichlorophenol, and 2,4,5- and 2,4,6-trichlorophenol), we did not observe any consistent relationships between maternal levels and child functioning.

Median levels (ng/g-lipid) of p,p'-DDE (1,052), p,p'-DDT (13), β-HCH (37), and HCB (65) were significantly higher than U.S. population levels. Time spent living outside the United States and birthplace in an area of Mexico with recent use of the organochlorine pesticides for agriculture or malaria control were significant predictors of serum levels of p,p'-DDE, p,p'-DDT, o,p'-DDT, β-HCH and HCB in multivariate models. Our results suggest that most exposure to persistent organochlorine pesticides occurred prior to moving to the United States.

Levels of malathion and chlorpyrifos urinary metabolites in pregnant women were not associated with birth weight, birth length, head circumference, ponderal index and duration of gestation; however, higher levels of total dimethyl organophosphate metabolites in maternal urine were associated with shorter gestational duration. We observed no adverse associations between organochlorine pesticide levels and birth weight or crown-heel length. Higher HCB levels were associated with reduced gestational duration.

Tests for pesticides in urine of pregnant women included fungicides, organophosphates insecticides, pyrethroid, carbamate, and organochlorine insecticides, triazine and choroacetanilide herbicides, naphthalene, and pentachlorphenol. (Including development of a new test for ETU, a toxic metabolite of bis-dithiocarbamate fungicides). Most pesticides had relatively low detection frequencies. For example, ETU was detected in approximately 20% of the maternal urine samples. Nine compounds were detected greater than >50%, with two potentially related to current use pesticides in the Salinas Valley (TCPy, derived from chlorpyrifos, and 1-napthol, derived in part from carbaryl). Overall, we did not observe associations between agricultural exposure risk factors and levels of non-persistent metabolites in maternal urine, nor did we observe associations between exposure to non-persistent pesticides and child development.

Twenty-one of the pesticides were also measured as part of the CDC National Health and Nutrition Examination Study (NHANES). Median levels for five pesticides (2,4-dichlorophenol, 2,5-dichlorophenol, 2-naphthol, para-nitrophenol and 3,4,6-trichloro-2-pyridinol (TCPy)) were

higher in our population compared to levels reported for pregnant women in NHANES (n=224). This finding suggests that exposures to the parent compounds of these metabolites were higher in our population of pregnant women compared to the general population of United States pregnant women.

c. Translation of Findings

We found that prenatal exposure to DDT, and to a lesser extent DDE, was associated with neurodevelopmental delays during early childhood, although breastfeeding was found beneficial, even among women with high exposure. Our findings suggest that countries considering the use of DDT in eradicating malaria should make sure that occupational exposure to DDT is reduced to the extent possible. Additionally, education addressing the need to eliminate or reduce take-home exposure should be distributed to all workers exposed to DDT. The benefit of using DDT to control malaria should be carefully balanced against the potential risk on children's neurodevelopment.

Since the serum DDT/DDE measured body burden, it was not possible to identify the source of the exposure in our populations. In other words, it was not possible to know the proportion of the DDT/DDE levels observed in this population were due to agricultural exposure versus anti-malaria efforts. Women in our study who were born in coastal Mexico had significantly higher levels of DDT and DDE than those who did not, and levels increased with the number of years spent outside of the U.S. DDT was used for both agriculture and malaria control in coastal Mexico. Although widely discussed in non-technical media, surprisingly little data has been published on occupational and environmental exposures to humans from Indoor Residual Spraying (IRS), the dominant DDT application method for malaria control. Our study indicates that exposure monitoring is needed for workers conducting IRS and as well as documenting the specific contribution of IRS to the general populations in affected regions.

Median levels for five pesticides (2,4-dichlorophenol, 2,5-dichlorophenol, 2-naphthol, para-nitrophenol and 3,4,6-trichloro-2-pyridinol (TCPy)) were higher in our population compared to levels reported for pregnant women in NHANES (n=224), suggesting higher exposures compared to the general U.S. population. Additionally, several metabolites, such as ETU, were detected in urine but no reference data were available for comparison. Further, ETU, although detected in only 20% of urine samples, is solely used in agriculture, suggesting that agricultural pesticides are exposing pregnant women. Low detection frequencies for some of these compounds limited the ability of epidemiologic analyses to examine the association between exposures and health effects on the children. Additional risk evaluation of these exposures is needed to augment the epidemiologic analyses. Finally, our population represents a general sample of pregnant women. Research is needed to quantify exposures to pregnant and other farmworkers immediately after reentry to recently sprayed fields.

d. Outcomes/Relevance/Impact

This study is the first to report on the effects of maternal levels of DDT, rather than its breakdown product DDE, on child neurodevelopment. Currently, health authorities around the world, including the United States malaria initiative, have decided to increase use of DDT to combat malaria, increasing the possibility of occupational exposures to public health workers applying DDT. Exposure in human populations should be monitored and potential health consequences should be studied to inform policy.

Overall, exposures to most non-persistent pesticides were low, with detection frequencies in urine below 50%. This finding may in part be due to the difficult task of quantifying transient

exposures to compounds with short half-lives in the body. In future analyses we will conduct risk analyses to aid in the health-interpretation of the observed levels.

e. Scientific Report

BACKGROUND

Pesticide use in agriculture may be one of the most significant sources of endocrine disruptors in the United States. Pregnant women in farmworker families may be exposed to high levels of ED pesticides as the result of their work in the fields, contamination of their homes, or both. Children of farmworkers may be among the highest exposed, *in utero*, as a result of maternal exposure, or as a result of postnatal environmental exposure from drift from nearby agricultural applications, contaminated breast milk from their farmworker mother, playing in the fields, and pesticides tracked into their homes by their parents or other household members working in fields. Neurodevelopmental toxicity resulting from prenatal exposure might be the most important manifestation of endocrine disruption. However, studies examining neurobehavioral development in relation to ED pesticides are lacking. The primary goal of this study was to determine whether *in utero* exposure to ED pesticides was associated with adverse effects on the neurobehavioral development of offspring of exposed women.

This study benefited from biologic specimens and neurobehavioral test results available from an NIEHS- and EPA-funded Center for Children's Environmental Health Research, which is studying pre- and postnatal exposure to organophosphate (OP) pesticides and neurodevelopment in primarily Latino farmworker children in the Salinas Valley of Monterey County, California (Center for Health Assessment of Mothers and Children of Salinas or CHAMACOS). All specific aims were completed as well as some important additional analyses. Primary analyses focused on investigating associations between endocrine disrupting pesticides and neurodevelopmental outcomes.

SPECIFIC AIMS

1. To determine whether exposure to organochlorine pesticides in utero is associated with poorer neurodevelopment as assessed during the neonatal period and at 6, 12, and 24 months.
2. To determine whether exposure to non-persistent pesticides that are known or suspected endocrine disruptors (EDs) (hereafter referred to as non-persistent EDs), *in utero* is associated with poorer neurodevelopment as assessed during the neonatal period and at 6, 12, and 24 months.
3. To identify population-level correlates of exposure to organochlorine and non-persistent ED pesticides.
4. To determine the relationship of exposure to persistent and non-persistent pesticides on fetal growth. Because fetal growth may be related to neurodevelopment, we included this specific aim.

METHODOLOGY

<u>Participants, Interviews and Medical Record Abstraction</u>.

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) project, a component of the Center for Children's Environmental Health Research at the University of California, Berkeley, 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 Salinas Valley, California. Between October 1999 and October 2000, pregnant women entering prenatal care at Natividad Medical Center, a county hospital located in the town of Salinas, or at five centers of Clinica de Salud del Valle de Salinas, were screened for eligibility and then recruited to participate in the longitudinal study. Women were eligible to participate if they were < 20 weeks gestation, ≥ 18 years old, English- or Spanish-speaking, eligible for Medi-Cal, and planning to deliver at Natividad Medical Center. A total of 601 women were eligible and agreed to participate in CHAMACOS. After losses due to miscarriage, moving, or dropping from the study before delivery, birth weight information was available for 538 women and their neonates. Written informed consent was obtained from all participants and the study was approved by the institutional review boards of all collaborating organizations.

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 old. We obtained information on sociodemographic characteristics, habits, housing, and occupation at each interview, as well as on childcare and breastfeeding after birth. The pesticide exposure section of the questionnaire gathered information on: the woman's occupational and residential history, including agricultural work and pesticide exposures; all household residents including their relation to the woman, their age, sex, length of residency, occupation and duties, the storing and changing of their work clothes and shoes, crops worked, and occupational pesticide contact including application; domestic pesticide use and storage during the last 12 months; floor covering, and cleaning methods and frequency; and kinds, numbers and housing of household pets. At each neurodevelopmental assessment the mother was interviewed about her habits, demographic characteristics, migration patterns, pesticide exposures and work and medical history. The mother was also questioned about her child's development and illnesses, breastfeeding, food intake and child care. Medical records were abstracted for prenatal and postnatal medical history, for every pediatric visit, emergency room visit, hospitalization, or laboratory test for children up to age two.

Neuropsychological assessment.

The design for the neurodevelopmental investigation of the effects of ED pesticide exposure was based on other longitudinal studies of the effects of chronic low level exposure to other behavioral teratogens such as lead. The methods are reflected in the Agency for Toxic Substances and Disease Registry (ATSDR) recent monograph Neurobehavioral Test Batteries for Use in Environmental Health Field Studies . The Pediatric Working Group emphasized the importance of prospective studies in assessing the neurobehavioral deficits in children related to toxic exposures. We have followed the outline they provide, that is, we divided the sequence of development into several stages and identified the domains of behavior of greatest relevance at each developmental stage. We selected neurobehavioral tests both to provide a broad overview at each developmental stage such as memory, general cognitive skills, reaction time, sensorimotor, and attention. The Brazelton Neonatal Behavioral Assessment Scale is a valid and reliable instrument and can detect subtle deviations in neonatal performance related to environmental exposures. It is used to evaluate the neonate's capacity to regulate its internal state and to respond to the environment. It consists of a set of 27 behavioral and 18 reflex items used to assess the critical domains of neonatal functioning. We formed seven clusters from the behavioral scores and reflex items following a standard scoring method. The Bayley Scales of Infant Development, Second Edition, assesses the developmental functioning of infants and young children. The Bayley Scales were administered in Spanish and/or English by psychometricians, blind to exposure status, either at the CHAMACOS research office or in a recreation vehicle modified as a testing facility.

Analyses of biological samples.

In prenatal serum we measured dichlorodiphenyltrichloroethane (DDT) (p,p'-DDT, and o,p'-DDT), DDT's primary breakdown product dichlorodiphenyl dichloroethylene (p,p'-DDE), and 8 other organochlorine (OC) compounds: hexachlorobenzene (HCB), β-hexachlorocyclohexane, (β-HCH), γ-HCH, dieldrin, heptachlor epoxide, oxychlordane, trans-nonachlor, and mirex. We also measured 34 congeners of polychlorinated biphenyls (PCBs). Summary PCB measures created for data analysis include a sum based on congeners 138, 153, and 180 (Needham et al. 2005) and the sum of those PCBs reported to induce CYP1A and CYP2B detoxifying enzymes. OC and PCB measures were generally lipid-adjusted and log-transformed for data analysis. Analyses focused on those OC/PCB compounds suspected to be neurotoxicants (DDT, DDE, PCBs) or found to be high in this population (HCB, β-HCH); other OCs were sometimes considered as potential confounders.

We also measured 36 class or pesticide-specific metabolites in maternal urine samples collected twice during pregnancy (~13 weeks and 26 weeks gestation), including tests for fungicides, organophosphate, pyrethroid, carbamate, and organochlorine insecticides, triazine and chloroacetanilide herbicides, naphthalene, and pentachlorphenol. These measurements included the development of a new urine test for the ETU metabolite of bis-dithiocarbamate fungicides (such as maneb).

RESULTS AND DISCUSSION

Aim 1. Organochlorine (OC) pesticides and neonatal neurodevelopmental assessments (Brazelton Outcomes).

We investigated whether decrements in neonatal neurodevelopment, as determined by the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), were associated with *in utero* exposure to p,p'-DDT, o,p'-DDT, and p,p'-DDE. We did not find any detrimental associations between prenatal DDT or DDE and neonatal performance on any of the seven BNBAS clusters (e.g., habituation, motor performance, and reflex) among 303 neonates assessed at ≤2 months old (7).

Aim 1. OC pesticides and PCBs and neurodevelopmental assessments at 6, 12, and 24 months (Bayley Outcomes).

Psychomotor (PDI) and mental (MDI) development were assessed using the Bayley Scales of Infant Development at 6, 12, and 24 months. Controlling for potential confounders, we found an approximately 2-point decrease in PDI with each 10-fold increase in p,p'-DDT levels at 6 and 12 months (but not at 24 months) and with p,p'-DDE levels at 6 months only ($p<0.05$). We found no association with mental development at 6 months, but a 2- to 3-point decrement in MDI with p,p'-DDT ($p<0.05$) and o,p'-DDT ($p<0.01$) levels at 12 and 24 months. Even when mothers had substantial exposure, breastfeeding was usually positively associated with Bayley scores. Thus, prenatal exposure to DDT, and to a lesser extent DDE, was associated with neurodevelopmental delays during early childhood, although breastfeeding was found beneficial, even among women with relatively high exposure (2).

Aim 2. Non-persistent pesticides and neurodevelopmental outcomes at 6, 12, and 24 months (Bayley and Child Behavior Checklist (CBCL) Outcomes).

We examined the association of prenatal urinary MDA and TCPy with performance at 6 (n=396), 12 (n=395), and 24 (n=372) months on the Bayley MDI and PDI and mother's report of

attention-related and pervasive developmental problems on the CBCL at 24 months (n=356). MDA and TCPy were not associated with any of these outcomes (although measures of total prenatal OP exposure were associated with poorer functioning in children at two years) (8). Separately, for 8 additional compounds with detection frequencies >50% (1- and 2-napthol, orthophenylphenol, para-nitrophenol, 2,4- and 2,5-dichlorophenol, and 2,4,5- and 2,4,6-trichlorophenol), we evaluated their association with Bayley mental and motor scores and the CBCL outcomes noted above. We did not observe any consistent patterns associating maternal levels and child functioning.

Aim 3. To identify population correlates of exposure for non-persistent and persistent ED Pesticides.

We investigated the association between exposure risk factors and levels of persistent and non-persistent ED pesticides in serum and urine, respectively. Median levels (ng/g-lipid) of p,p'-DDE (1,052), p,p'-DDT (13), β-HCH (37), and HCB (65) were significantly higher than U.S. population levels. Time spent living outside the United States and birthplace in an area of Mexico with recent use of OC pesticides for agriculture or malaria control were significant predictors of serum levels of p,p'-DDE, p,p'-DDT, o,p'-DDT, β-HCH and HCB in multivariate models. Years spent in the U.S. was also associated with increased serum levels of p,p'-DDE and β-HCH, but to a lesser degree than years lived outside the U.S. There was no difference in HCB levels by time spent in or outside the U.S., suggesting current and thus preventable exposure routes. However, we observed no associations between serum levels of OC compounds and current intake of saturated fat or agricultural take-home exposure risk factors. Lactation history and recent weight gain were negatively associated with serum levels of some, but not all OC compounds studied. Smoking history was borderline associated with elevated HCB levels. We observed no significant associations with body mass index. Although this study suggests that most exposure occurred prior to moving to the United States, the results for HCB indicate the possibility of ongoing exposure in this country (5).

As described above, we measured 36 class or pesticide-specific metabolites in urine samples, including tests for fungicides, organophosphates insecticides, pyrethroid, carbamate, and organochlorine insecticides, triazine and choroacetanilide herbicides, naphthalene, and pentachlorphenol. These measurements included the development of a new urine test for ETU, a toxic metabolite of bis-dithiocarbamate fungicides. Of the 36 compounds, most had relatively low detection frequencies. For example, ETU was detected in approximately 20% of the maternal urine samples. Of the 9 compounds with detection frequencies >50% (3,4,6-trichloro-2-pyridinol (TCPy), 1- and 2-napthol, orthophenylphenol, para-nitrophenol, 2,4- and 2,5-dichlorophenol, and 2,4,5- and 2,4,5-trichlorophenol), only two may be related to current use pesticides in the Salinas Valley (TCPy, derived from chlorpyrifos, and 1-napthol, derived in part from carbaryl, although other sources include smoking and deodorants). Overall, we did not observe associations between agricultural exposure risk factors and levels of non-persistent metabolites in maternal urine. This finding is consistent with the relatively low detection frequencies.

We also compared urinary metabolite concentrations detected in the first prenatal CHAMACOS cohort samples (n=538, ~13 weeks gestation) with U.S. national reference data for 224 pregnant women sampled by NHANES (CDC 2003). Twenty-one of the 36 urinary metabolites measured for the CHAMACOS study were available for comparison with the NHANES data (1999-2002). The same analytical laboratory at the CDC performed the urinary metabolite measurements for both the NHANES and CHAMACOS study, and thus the limits of detection were similar. The CHAMACOS detection frequencies for the metabolites ranged from 0% to 71%, with seven metabolites detected at frequencies over 50%. Median levels for five

(2,4-dichlorophenol, 2,5-dichlorophenol, 2-naphthol, para-nitrophenol and 3,4,6-trichloro-2-pyridinol (TCPy)) of these seven compounds were higher among the CHAMACOS cohort compared to levels reported for pregnant women in NHANES (n=224). This finding suggests that exposures to the parent compounds of the commonly detected metabolites were slightly higher among the CHAMACOS cohort compared to the national reference population.

We are currently preparing a manuscript that will report levels of all non-persistent pesticide metabolites measured in maternal urine. Additionally, we are using a deterministic steady-state model to estimate maternal dose for those compounds that were detected. We will then compare the estimated dose to health-based reference doses derived from EPA databases (e.g., IRIS). This risk assessment will provide a basis to interpret the health significance of the exposure levels (Castorina, In preparation).

Supplemental work: Analysis of household dust samples.

With support from our core Children's Center grant, dust samples from a subsample of participants' homes have been analyzed for several potential ED pesticides, including DDT, DDE, chorpyrifos, dacthal, iprodione, vinclozilin, and several pyrethroids. We have observed positive associations between household agricultural occupational status and levels of persistent, current-use pesticides, including dachtal and iprodione, in these dust samples. We have not observed significant associations between these and several other compounds measured in maternal biological samples and occupational exposure risk-factors. In the future, we will evaluate the association of non-persistent ED exposure in children with occupational status of household members.

Aim 4. Non-persistent and persistent pesticides, PCBs and growth outcomes.

We analyzed the association of prenatal urinary MDA and TCPy with birth weight, birth length, head circumference, ponderal index and duration of gestation. MDA and TCPy were not associated with any parameters of fetal growth or duration of gestation (1).

Although substantial evidence in animals exists for the fetal toxicity of OCs, information on human reproductive effects is conflicting. We investigated whether infants' length of gestation, birth weight, and crown-heel length were associated with maternal serum levels of the 11 OCs measured in maternal serum. We observed no adverse associations between OC levels and birth weight or crown-heel length. We did not find reductions in gestational duration associated with any of the OCs except for HCB. This association does not appear to have had clinical implications for this population, given its relatively low rate of preterm delivery (6.5%). The sum of PCBs reported to induce CYP1A and CYP2B detoxifying enzymes was strongly associated with both decreased birth weight and decreased infant length (3).

Supplemental work: Analysis of maternal thyroid function.

A supplementary grant was obtained from the University of California Institute for Mexico and the United States (UC MEXUS) to analyze TSH, free and total thyroxine (T4) in maternal serum samples. Additionally, neonatal TSH levels were obtained from the California Newborn Screening program. The aim of this supplemental work was to evaluate whether maternal exposure to EDs is associated with increased neonatal TSH levels and higher TSH and lower T4 levels in pregnant women. Certain PCBs induce CYP1A, CYP2B, and uridinediphosphate glucuronosyltransferase (UDP-GT) activity, which are associated with T4 elimination in animals. The sum of these PCBs was positively related to neonatal TSH levels in multivariate models; a 10-fold increase in exposure was associated with a 30% increase (95% CI=2%, 61%) in

neonatal TSH. These results have been recently submitted to Environmental Health Perspectives (Chevrier et al, submitted). In addition, preliminary results suggest that levels of the sum of all PCB congeners is negatively associated with maternal free T4 (adj. β= -0.12, 95% CI=-0.24, -0.01). HCB levels were also negatively associated with both free (adj. β-0.08, 95% CI=-0.15, -0.01) and total T4 (adj. β=0.51, 95% CI=-0.98, -0.05) during pregnancy (Chevrier et al, in preparation).

Supplemental work: Pilot data on Polybrominated Dipheylethers (PBDE) in maternal Serum.

Recent studies have raised concerns about PBDE flame retardant exposures to pregnant women and women of child-bearing age in the U.S. These compounds are structurally similar to PCBs and are known endocrine disruptors. Few studies have measured PBDEs in immigrant populations. CDC completed analyses (at no cost) for PBDEs in a pilot study of 24 maternal serum samples. PBDEs levels in these samples were lower than levels observed in other U.S. populations, although still higher than those observed previously in Europe or Japan. The upper range of exposure is similar to what has been reported in other U.S. populations. PBDEs have been associated with adverse developmental effects in animals. Future studies are needed to determine the sources and pathways of PBDE exposures and whether these exposures have adverse effects on human health. (4)

Community Outreach and Translation:

Our Center grant supports an active Community Outreach and Translation Core (COTC). COTC activities include outreach and presentations to participants, a Community Advisory Board as well as a broad array of community groups. Summary results of all studies related to this grant have been provided to participants and members of the Community Advisory Board.

CONCLUSIONS

CDC recently reported urinary and serum levels of several pesticides in a sample selected to be representative of the U.S. population in 1999-2000 (Second National Report on Human Exposure to Environmental Chemicals, 2003). Our data indicate that OC and OP exposures among our population are higher than in the national sample; this finding remains true even when our data are compared with female or Mexican-American subgroups. In particular, metabolite levels for both malathion and chlorpyrifos are higher than females and Mexican-Americans from the CDC sample. Serum DDE, DDT, HCB and ß-HCH levels were much higher than those reported in the CDC Report. These data support our selection of this population to study the potential neurodevelopmental effects of *in utero* exposure to endocrine disrupting pesticides. The results from our work are especially important given the current paucity of research in humans on *in utero* exposure to ED pesticides and neurodevelopment

This study is the first to report on the effects of maternal levels of DDT, rather than its breakdown product DDE, on child neurodevelopment. At a time when health authorities around the world are considering increasing use of this pesticide to combat malaria, the study is one of the first to suggest that DDT may be harmful to child development. As such, it provides important information for decision makers considering the use of DDT to weigh in gauging its benefit in eradicating malaria against other potential health consequences. An additional study confirming our results has since been published. In this study, inverse associations were observed between DDT in cord serum and verbal, memory, quantitative, and perceptual-performance skills in 475 four-year-olds from Spain (Ribas-Fito N, Torrent M, Carrizo D, Munoz-Ortiz, Julvez J, Grimalt JO, Sunyer. In Utero Exposure to Background Concentrations of DDT

and Cognitive Functioning among Preschoolers. Am J Epidemiol. 2006 164(10):955-62). The children in our study should be followed to determine if our findings persist as the children enter school. Exposure in human populations should be monitored and potential health consequences should be studied to inform policy.

Overall, exposures to most non-persistent pesticides were low, with detection frequencies in urine below 50%. This finding may in part be due to the difficult task of quantifying transient exposures to compounds with short half-lives in the body. In future analyses will conduct risk analyses to aid in the health-interpretation of the observed levels.

Thyroid hormones are essential for the normal development of the brain. Recent studies also suggest that thyroid hormones of maternal origin play an important role in neurodevelopment. Our results suggest that the deleterious effects of PCB exposure on neurodevelopment reported by previous studies may be caused by the disruption of thyroid function even at the very low levels detected in the CHAMACOS cohort. Future analyses supported by UC MEXUS will investigate the association of DDT and DDE exposure with maternal and neonatal thyroid levels.

f. Publications and Presentations

Peer Reviewed Publications:

1. Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell N, Barr D, Furlong C, and Holland N. 2004. Association of *in utero* Organophosphate Pesticide Exposure and Fetal Growth and Length of Gestation in an Agricultural
Population Environ Health Perspect. 2004;112(10):1116–1124.

2. Eskenazi B, Marks AR, Bradman A, Fenster L, Johnson C, Barr DB, Jewell NP. In Utero Exposure to DDT and DDE and Neurodevelopment in Mexican-American Young Children. Pediatrics. 2006;118(1):233-41.

3. Fenster L, Eskenazi B, Anderson M, Bradman A, Harley K, Hernandez H, Hubbard A, Barr DB. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ Health Perspect. 2006;114(4):597-602.

4. Bradman A, Fenster L, Sjödin A, Jones RS, Patterson Jr. DG, Eskenazi B. Polybrominated Diphenyl Ether Levels in the Blood of Pregnant Women Living in an Agricultural Community in California. Environ Health Perspect. Advance online publication, 19 October 2006; doi:10.1289/ehp.8899 (available at http://dx.doi.org/).

5. Bradman A, Schwartz JM, Fenster L, Barr DB, Holland NT, Eskenzai B. Factors predicting organochlorine pesticide levels in pregnant Latina women living in a United States agricultural area. J Expo Sci Environ Epidemiol. Advance online publication, 11 October 2006; doi:10.1038/sj.jes.7500525 (available at http://dx.doi.org/).

6. Montesano MA, Olsson AO, Kuklenyik P, Needham LL, Bradman A, Barr DB. Method for determination of acephate, methamidophos, omethoate, dimethoate, ethylenethiourea and propylenethiourea in human urine using high-performance liquid chromatography-atmospheric pressure chemical ionization mass spectrometry. J Expo Science Environ Epid (in press).

7. Fenster L, Eskenazi B, Anderson M, Bradman A, Hubbard A, Barr DB. In utero exposure to DDT and Performance on the Brazelton Neonatal Behavioral Assessment Scale. NeuroToxicology (in press).

8. Eskenazi B, Marks AR, Bradman A, Harley K, Barr DB, Johnson C, Morga N, Jewell NP. Organophosphate Pesticide Exposure and Neurodevelopment in Young Mexican-American Children. Environ Health Perspect (in press). Advance online publication, 4 January 2007; doi:10.1289/ehp.9828 (available at http://dx.doi.org/).

Letters:
Eskenazi B, Marks AR., Bradman A, Caroline Johnson C, Jewell, NP. Re: Dichlorodiphenyltrichloroethane. Implications of Eskenazi et al study to malaria control in Africa. Pediatrics, (24 August 2006).

Eskenazi B, Marks AR., Bradman A, Caroline Johnson C, Jewell, NP. Re: DDT and neurodevelopment: results inconclusive to effect policy change. Pediatrics, (22 September 2006).

Submitted Peer Reviewed Publications:
Chevrier J, Eskenazi B, Bradman A, Fenster L, Barr D. Associations between prenatal exposure to polychlorinated biphenyls and neonatal thyroid-stimulating hormone levels in a Mexican-American population, Salinas, CA. Environ Health Perspect. Submitted, 2006.

Publications in Preparation:
Chevrier J, Eskenazi B, Bradman A, Fenster L, Barr D. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function in pregnant women. In preparation, submission planned for March 2007.

Castorina R, Bradman A, Fenster L, Barr DB, Bravo R, Hamly ME, McKone TE, Jewell N, Eskenazi B. Non-Persistent Urinary Metabolite Levels during Pregnancy in Women Living in an Agricultural Community. In preparation, submission planned for May 2007.

Award:
Awarded 2nd place for pre-doctoral paper: Chevrier J, Fenster L, Bradman A, Barr D, Eskenazi B. Prenatal exposure to thyroid hormone disruptors in the CHAMACOS cohort, neonatal thyroid hormone levels and neurodevelopment: Preliminary results. 21st International Neurotoxicology Conference, Honolulu, HI. February 2004

Invited Presentations:
- The Endocrine Disruptors and Neurobehavioral Outcome Study. Presented at the California Department of Health Services. Oakland, CA. January 2003.
- CHAMACOS. Presented at the *21st International Neurotoxicology Conference*, Honolulu, HI. February 2004.
- CHAMACOS. Presented at the Monterey County Health Department, Salinas , CA. March 2004.

Presentations and Awards:
Fenster, L. "Endocrine disrupting pesticides and neurodevelopmental outcomes in farmworker children of the Salinas Valley." Presented to the Environmental Health Investigations Branch, California Department of Health Services. Oakland, CA. March, 2002.

Eskenazi, B. "A study of exposures and health of farmworker children living in an agricultural community." Environmental Protection Agency Meeting. Washington, DC. April, 2002.

Bradman, A. "Community/university partnership to investigate children and environmental health in an agricultural community." Office of Environmental Health Hazard Assessment,

California Environmental Protection Agency, Children's Environmental Health – Risk Assessment Symposium. Sacramento, CA. May, 2002.

Castorina, R., Bradman, A., Barr, D., Eskenazi, B. "Using chemical specific urinary metabolites to assess cumulative organophosphate pesticide exposure among pregnant women in the Salinas Valley, CA." Presented at the International Society for Exposure Analysis Conference. Vancouver, BC. August, 2002.

Eskenazi, B., Bradman, A., Fenster, L., Barr, D., Chevrier, J., Hamly, M., McLaughlin, B., Scalf, R., Gladstone, E., Alkon, A., Warner, M. "Endocrine disrupting pesticides and neurodevelopmental outcomes in farmworker children, Salinas Valley." Presented at the Environmental Protection Agency Endocrine Disruptors Workshop. Research Triangle Park, NC. October, 2002.

Chevrier J, Fenster L, Bradman A, Eskenazi B. Effects of in utero exposure to potential endocrine disruptors on the thyroid function in newborns. UC Toxic Substances Research & Teaching Program Symposium. Oakland, CA. April 2003.

Eskenazi, B., Bradman, A., Fenster, L., Barr, D., Chevrier, J., Hamly, M., McLaughlin, B., Scalf, R., Gladstone, E., Alkon, A., Warner, M. "Endocrine disrupting pesticides and neurodevelopmental outcomes in farmworker children, Salinas Valley." Poster presentation at the NIEHS/EPA Children's Centers Meeting. Washington, DC. May, 2003.

Castorina, R., Bradman, A., Barr, D., Eskenazi, B. "Using pesticide specific urinary metabolites to assess cumulative exposure among pregnant women living in the Salinas Valley, CA." Poster presentation at the ISEA Conference. Stresa, Italy. September, 2003.

Eskenazi, B., Fenster, L. "CHAMACOS: A longitudinal birth cohort study of exposures and health of children living in an agricultural community." California Department of Health Services, Occupational Health Branch. Richmond, CA. January, 2004.

Chevrier J, Fenster L, Bradman A, Barr D, Eskenazi B. Prenatal exposure to thyroid hormone disruptors in the CHAMACOS cohort, neonatal thyroid hormone levels and neurodevelopment: Preliminary results. 21st
International Neurotoxicology Conference, Honolulu, HI. February 2004

Bradman, A. "Research activities of the Center for Children's Environmental Health Research." Breast Cancer Fund. San Francisco, CA. April, 2004.

Eskenazi, B. "CHAMACOS: A Cohort of Pregnant Women Living in an Agricultural Community." 2nd Annual UC Berkeley Women's Health Forum: Healthy Women Across Cultures. Berkeley, CA. April 27, 2004.

CHAMACOS Investigators & Field Staff. "The Center for Children's Environmental Health Research: The Last Five Years and the Next 5 Years." Oral Presentation at the Center for Children's Environmental Health Research Science Day. Berkeley, CA. May, 2004.

Chevrier J, Fenster L, Bradman A, Eskenazi B. Prenatal exposure to thyroid hormone disruptors, neonatal thyroid hormone levels and neurodevelopment in an agricultural community. Society for Epidemiologic Research. Salt Lake City, UT. June 2004.

Fenster, L., Bradman, A., Barr, D.B., Eskenazi, B. "Endocrine Disruptors and Neurodevelopmental Outcomes." E.Hormone Conference. New Orleans, LA. October 30, 2004.

Bradman, A., Eskenazi, B., Barr, D., McKone, T., Hamly, M., Castorina, R., Fenster, L. "Center for Children's Environmental Health Research." EPA Task Group on Pesticide Exposure. Washington, DC. April 13, 2005.

Weldon, R, Barr, D., Whitehead, R., Davis, M., Wilson, L., Bradman, A., Holland, N., Eskenazi, B. Measurement of non-persistent and persistent pesticides and other environmental chemicals in human milk. Poster presentation at the UC Toxic Substances Research and Training Program Symposium. Sacramento, CA. April, 2005.

Bradman, A., Fenster, L., Barr, D.B., Anderson, M., Weltzien, E., Schwartz, J., Calderon, N., Holland, N., Eskenazi, B. "Factors predicting DDT and DDE levels in a cohort of pregnant Mexican-American women living in an agricultural area of California." International Society for Environmental Epidemiology. Johannesberg, South Africa. September, 2005.

Fenster, L., Eskenazi, B., Anderson, M., Bradman, A., Hubbard, A., Harley, K., Vargas, G., Barr, D. "Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultrual population." International Society for Environmental Epidemiology. Johannesberg, South Africa. September, 2005.

Bradman, A., Fenster, L., Barr, D.B., Anderson, M., Weltzien, E., Schwartz, J., Calderon, N., Holland, N., Eskenazi, B. "DDT and DDE levels in a cohort of pregnant Mexican-American women living in an agricultural area in California." International Society for Environmental Epidemiology. Johannesberg, South Africa. September, 2005.

Eskenazi, B., Marks, A.R., Fenster, L., Bradman, A., Rodriguez, M.E., Barr, D.B, Jewell, N.P. "In utero DDT and DDE exposure and neurodevelopment in children of farmworkers." International Society for Environmental Epidemiology. Johannesberg, South Africa. September, 2005.

Eskenazi, B., Bradman, A., Holland, N., Barr, D., Tager, I., Lipsett, M., Alkon, A., Johnson, C., Gladstone, E.A. "Health effects of environmental exposures to children living in an agricultural community." International Society for Environmental Epidemiology. Johannesberg, South Africa. September, 2005.

Eskenazi, B. "Birds, Bees, and Business: Are Industrial Exposures Affecting the Health of the Next Generation?" Haas School of Business, UC Berkeley. Berkeley, CA. October, 2005.

Eskenazi, B. "Biomarkers of Pesticide Exposure and their Relation to Health in Children." International Conference of Children's Environmental Health. Buenos Aires, Argentina. November 17, 2005.

Chevrier J, Bradman A, Holland N, Morga N, Eskenazi B. Association between thyroid hormone levels during pregnancy and child neurodevelopment: Preliminary results from a longitudinal study. International Thyroid Congress. Buenos Aires, Argentina. November 2005.

Bradman, A, Fenster, L, Barr, D B., Anderson, M, Weltzien, E, Schwartz, J, Calderon, N, Holland, N, Eskenazi, B. "Factors predicting DDT and DDE levels in a cohort of pregnant Mexican-American women living in an agricultural area of California." ISEA Conference. Tucson, AZ. November, 2005.

Eskenazi, B. "Lessons from the CHAMACOS and Seveso Women's Health Studies." International Symposium on Environmental Endocrine Disrupting Chemicals. Okinawa, Japan. December, 2005.

Eskenazi, B. "Biomarkers of Pesticide Exposure and their Relation to Health in Children Neurodevelopmental Assessment in Children Exposed to Pesticides." Costa Rica. February, 2006

Eskenazi, B. "Center for the Health Assessment of Mothers and Children of Salinas." Presentation at Mills College. February 6, 2006.

Eskenazi, B. "Environmental Chemicals and Women and Children's Health: Lessons from the CHAMACOS and Seveso Women's Health Studies." Grand Rounds at Institut Municipal d'Investigacio Medica (IMIM). Barcelona, Spain. June, 2006.

Eskenazi, B. "Pesticides and Children's Health: Exposure, Effects, and Prevention in Farmworker Children." Presentation at the World Health Organization. Geneva, Switzerland. June, 2006.

Eskenazi, B. "Pesticides and Children's Health: Exposure, Effects, and Prevention in Farmworker Children." "From the Womb to the Tomb" Conference at Hebrew University School of Public Health & Coalition for Public Health. Jerusalem, Israel. July 10, 2006.

Eskenazi B. "Pesticides and Children's Health: Exposure, Effects, and Prevention in Farmworker Children." Presentation to Dr. Ora Kofman & Dr. Andrea Berger's Lab at Ben Gurion University. Beer Sheva, Israel. July 12, 2006.

Eskenazi, B. "Pesticides and Children's Health: Exposure, Effects, and Prevention in Farmworker Children." "Endocrine Disrupting Chemicals: Impact on Human Health" Conference at The Volcani Center, Agricultural Research Organization. Bet Dagan, Israel. July 13, 2006.

Eskenazi, B., Harley, K., Bradman, A., Fenster, L., Wolff, M., Engel, S., Rauh, V., Wyatt, R., Perera, F. "In Utero Pesticide Exposure and Neurodevelopment in Three NIEHS/EPA Children's Center Birth Cohorts." International Society for Environmental Epidemiology. Paris, France. September 3, 2006.

Eskenazi, B., Marks, A.R., Harley, K., Bradman, A., Johnson, C., Barr, D.B., Morga, N., Jewell, N.P. "Organophosphate Pesicides and Neurodevelopment in Young Mexican-American Children." International Society for Environmental Epidemiology. Paris, France. September 3, 2006.

Wolff, M., Eskenazi, B., Whyatt, R., Engel, S., Harley, K., Bradman, A., Perera, F., Rauh, V., Barr, D. "Environmental Exposures and Birth Outcomes in the NIEHS/EPA Children's Center Birth Cohorts." International Society for Environmental Epidemiology. Paris, France. September 6, 2006.

Perera, R., Rauh, V., Whyatt, R., Jedrychowski, W., Lederman, S., Miller, R., Barr, D., Camann, D., Kinney, P., Andrews, H., Orjuela, M., Tang, D., Wolff, M., Engel, S., Gilliland, F., Eskenazi, B., Bradman, A., Holland, N., Harley, K. "In Utero and Childhood Environmental Exposures and Multiple Health Outcomes: NIEHS/EPA Children's Center Cohort Studies." International Society for Environmental Epidemiology. Paris, France. September 6, 2006.

Eskenazi, B. "In Utero Exposure to DDT and DDE and its Potential Health Effects." Presentation to the World Health Organization. Geneva, Switzerland. September, 2006.

Eskenazi, B. "Center for the Health Assessment of Mothers and Children of Salinas." Presentation to Freshman Seminar. UC Berkeley. September, 2006.

Eskenazi, B. "Center for the Health Assessment of Mothers and Children of Salinas." Presentation to Kaiser Permanente Officials. Berkeley, CA. September 28, 2006.

Eskenazi, B. "In Utero Exposure to DDT and DDE and its Potential Health Effects." Presentation to U.S. Environmental Protection Agency Officials. Washington, DC, via telephone. October 17, 2006.

Eskenazi, B. "Center for the Health Assessment of Mothers and Children of Salinas." Presentation to MCH Core Course. UC Berkeley. October 25, 2006.

g. Project-Generated Resources

CDC method development for ETU in urine: A method to measure ethylene thiourea in urine was developed. This assay will prove to be useful not only in this study, but for the evaluation of exposure to ethylene-bis-dithiocarbamates, including maneb and mancozeb, which are fungicides widely used in agriculture and forestry throughout the United States.

h. Inclusion of Gender and Minority Study Subjects

See table on following page.

Principal Investigator/Program Director (Last, First, Middle): Eskenazi, Brenda

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: Endocrine Disruptors and Neurodevelopmental Outcomes

Total Enrollment: 1072 (556 women 258 boy 258 girl) **Protocol Number:** 2003-2-79

Grant Number: RO1 OH007400

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown or Not Reported	Total
Hispanic or Latino	790	248		1,038 **
Not Hispanic or Latino	24	10		34
Unknown (individuals not reporting ethnicity)	0	0		0
Ethnic Category: Total of All Subjects*	814	258		1,072 *
Racial Categories				
American Indian/Alaska Native	1	1		2
Asian	8	6		14
Native Hawaiian or Other Pacific Islander				
Black or African American	0	0		0
White	14	2		16
More Than One Race	3	1		4
Unknown or Not Reported	788	248		1,036
Racial Categories: Total of All Subjects*	814	258		1,072 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Unknown or Not Reported	Total
American Indian or Alaska Native				
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White				
More Than One Race	2	0		
Unknown or Not Reported	788	248		
Racial Categories: Total of Hispanics or Latinos**	790	248		1,038 **

* These totals must agree.
** These totals must agree.

i. Inclusion of Children

This study focused on environmental exposures to pregnant women and potential adverse growth and neurodevelopmental effects on children. A total of 528 live births were recorded during the CHAMACOS study and approximately 425 children were followed through 2 years of age.

j. Human Subjects

All research activities in support of this grant have been conducted under human subject approvals from the UC Berkeley Committee for the Protection of Human Subjects (CPSH # is 2004-2-27, expiration date 3/18/2007)

k. Materials Available for other Investigators

No new specimens were collected for this study. Biological and environmental specimens collected as part of the Center for Children's Environmental Health Research Studies are stored in the UC Berkeley School of Public Health Biorepository. Any use of stored specimens must be reviewed and approved the Center Executive Committee. Researchers interested in possible collaborations with Center investigators can contact the PI or Dr. Asa Bradman at abradman@socrates.berkeley.edu.

FINANCIAL STATUS REPORT

R1OKD7400A

1. FEDERAL AGENCY AND ORGANIZATION ELEMENT TO WHICH REPORT IS SUBMITTED: CENTERS FOR DISEASE CONTROL	2. FEDERAL GRANT OR OTHER IDENTIFYING NUMBER R01-OK007400-04
3. RECIPIENT ORGANIZATION (Name and complete address, including zip code) THE REGENTS OF THE UNIVERSITY OF CALIFORNIA Extramural Fund Accounting 2195 Hearst Ave., Rm 130 - MC 1103 Berkeley, California 94720-1103 PHS#431470	4. EMPLOYER IDENTIFICATION NUMBER 1946002123A1 5. RECIPIENT ACCOUNT NUMBER OR I.D. NUMBER 20646

8. PROJECT/GRANT PERIOD FROM 9/30/2001 TO 9/29/2006	6. FINAL REPORT: YES XXXXX NO 0 9. PERIOD COVERED BY THIS REPORT FROM: 9/30/2004 TO: 9/29/2006	7. BASIS: CASH ACCRUAL

10 STATUS OF FUNDS

A. NET OUTLAYS PREVIOUSLY REPORTED	$ 0 00
B. TOTAL OUTLAYS THIS REPORT PERIOD	909,365 00
C. LESS: PROGRAM INCOME CREDITS	0 00
D. NET OUTLAYS THIS REPORT PERIOD (Line B minus line C)	909,365 00
E. NET OUTLAYS TO DATE (Line A plus line d)	909,365 00
F. LESS: NON-FEDERAL SHARE OF OUTLAYS	0 00
G. TOTAL FEDERAL SHARE OF OUTLAYS (Line E minus line F)	909,365 00
H. TOTAL UNLIQUIDATED OBLIGATIONS	0 00
I. LESS: NON-FEDERAL SHARE OF UNLIQUIDATED OBLIGATIONS SHOWN ON LINE H	0 00
J. FEDERAL SHARE OF UNLIQUIDATED OBLIGATIONS (Line H minus line I)	0 00
K. TOTAL FEDERAL SHARE OF OUTLAYS AND UNLIQUIDATED OBLIGATIONS (LINE G PLUS LINE J)	909,365 00
L. TOTAL CUMULATIVE AMOUNT OF FEDERAL FUNDS AUTHORIZED	909,365 00
M. UNOBLIGATED BALANCE OF FEDERAL FUNDS (Line L minus line K)	0 00

11. INDIRECT EXPENSE

A. TYPE OF RATE (Type "X" in appropriate box) X PROVISIONAL PREDETERMINED FINAL FIXED

B. RATE	C. BASE	D. TOTAL AMOUNT	E. FEDERAL SHARE
26 00%	$21,126 19	135,492 82	135,492 82
	$21,126.19	135,492.82	135,492.82

11 REMARKS

TOTAL CUMULATIVE FEDERAL FUNDS AUTHORIZED INCLUDES $ 309,443.00 CARRYOVER FROM PRIOR PERIOD PER CDC APPROVAL ON FILE

13. CERTIFICATE: I certify to the best of my knowledge and belief that this report is correct and complete and that all outlays and unliquidated obligations are for the purposes set forth in the award documents.	SIGNATURE OF AUTHORIZED CERTIFYING OFFICIAL Loimie Ng TYPED OR PRINTED NAME AND TITLE Wamie Ng Senior Accountant	DATE REPORT SUBMITTED 1/17/2007 TELEPHONE AND FAX 510-643-9481 510-643-8959

Standard Form 269

Form Approved Through 9/30/2007
OMB No. 0925-0001

Department of Health and Human Services

Final Invention Statement and Certification

(For Grant or Award)

DHHS Grant or Award No.: 1 R01 OH007400

A. We hereby certify that, to the best of our knowledge and belief, all inventions are listed below which were conceived and/or first actually reduced to practice during the course of work under the above-referenced DHHS grant or award for the period

09/30/2001 *original effective date* through 09/29/2006 *date of termination*.

B. Inventions (Note: If no inventions have been made under the grant or award, insert the word *"NONE"* under Title below.)

NAME OF INVENTOR	TITLE OF INVENTION	DATE REPORTED TO DHHS
	None	
(Use continuation sheet if necessary)		

C. First Signature —The person responsible for the grant or award is required to sign (in ink). Sign in the block opposite the applicable type of grant or award.

TYPE OF GRANT OR AWARD	WHO MUST SIGN *(title)*	SIGNATURE
Research Grant	Principal Investigator or Project Director Eskenazi, Brenda	
Health Services Grant	Director	
Research Career Program Award	Awardee	
All other types *(specify)*:	Responsible Official	

D. Second Signature — This block *must* be signed by an official authorized to sign on behalf of the institution.

Title	Name and Mailing Address of Institution
Typed Name: Patricia A. Gates Asst. Director, Federal Projects	University of California, Berkeley Sponsored Projects Office 2150 Shattuck Ave., Suite 313 MC5940 Berkeley, CA 94704-5940
Signature: Linda Crnosteno for Patricia Gates — Date: 5/24/07	

HHS 568 (Rev. 9/2004)