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Neurodevelopmental Impacts of Pesticide Exposures

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Assessing impacts of pesticides on the developing brain

- Cell culture preparations
- Animal testing—prenatal; neonatal period
(in rodents corresponds to third trimester in humans)
- Human studies: epidemiologic
 - Importance of accurate exposure assessment
 - Controlling for other variables; confounders
 - Various tests for neonatal and childhood cognitive and motor function

Brazelton Neonatal Behavioral Assessment Scale (BNBAS)

- 17 reflexes and a range of behaviors including muscle tone, activity level, attention and orientation, and arousal.
- Transitory and not predictive of later neurological function

Bayley Scales of Infant Development

- Mental Development Index (MDI); Psychomotor Development Index (PDI)
- Focuses on the rate at which the infant attains age-appropriate developmental skills (attention, memory, learning, motor skills)
- Predictive validity for school-age cognitive function is poor for children who perform within the normal range; abnormalities are predictive of later performance
- Apical; sensitive; not specific for brain regions

Fagan visual recognition memory test

- Assesses recognition memory and visual discrimination
- Specific for those functions
- Moderately predictive of intellectual function in childhood

Several tests of IQ

- McCarthy Scales of Children's Abilities
- Wechsler Pre-school and Primary Intelligence
- Stanford-Binet
- Kaufman Assessment Battery for Children

Organophosphate pesticides

- A family of chemicals
- Exposures often estimated by measuring urinary metabolites
- Urinary metabolites are generally not specific for a single family member except for chlorpyrifos, malathion

Organophosphate pesticides

- Rodent studies: neonatal exposures > hyperactivity; changes in neurochemistry (Slotkin et al. EHP; 2006)
- Neurodevelopmental impacts are NOT exclusively due to cholinesterase inhibition
- Impacts on brain chemistry and architecture differ among OPs.

Organophosphates—human studies

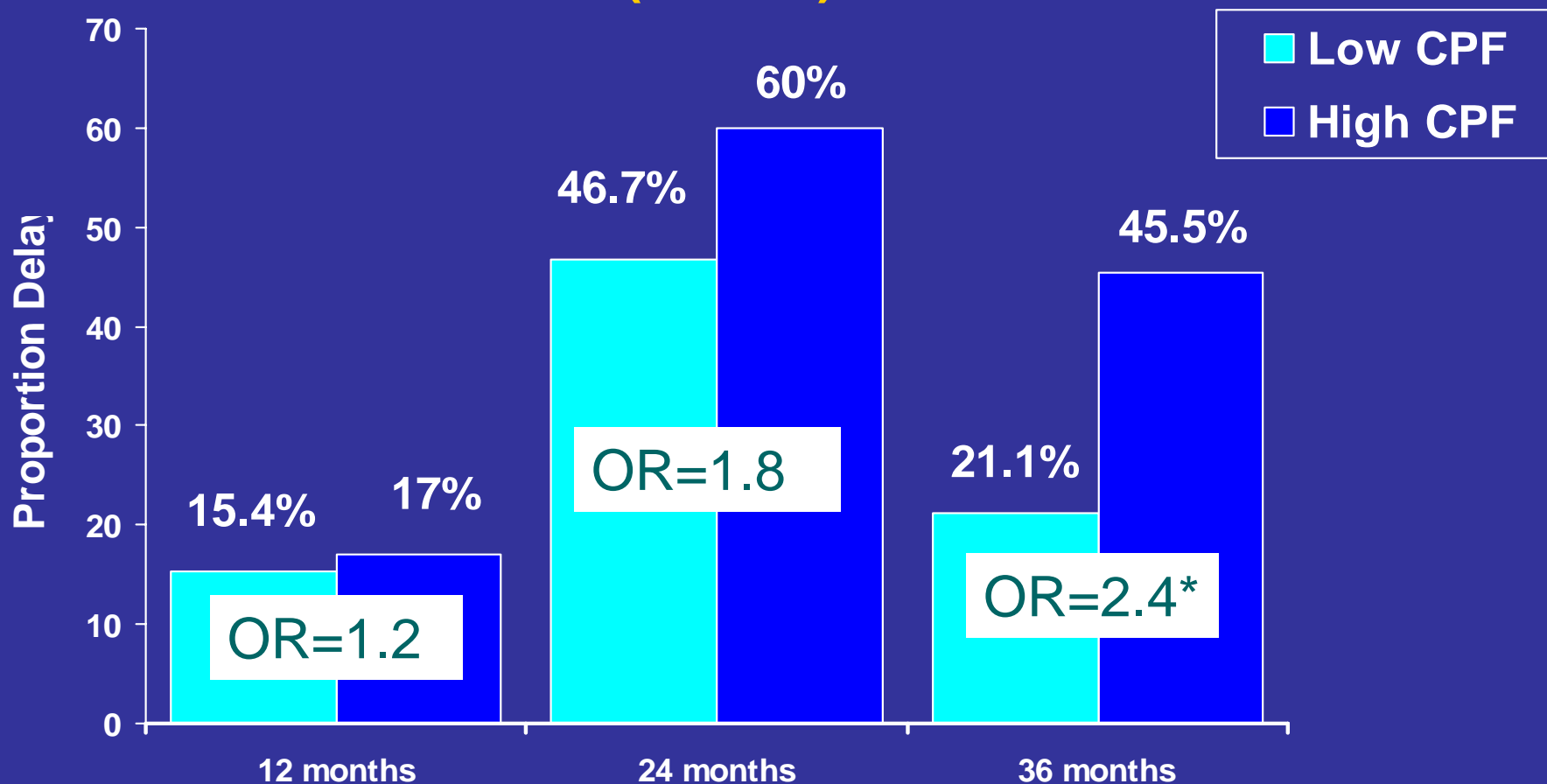
- New York City—urban
- Salinas Valley—agricultural
- Ecuador

Summary of effects of prenatal chlorpyrifos exposure—New York

- Prenatal chlorpyrifos exposure was associated with a 3.5 to 6-point adjusted mean decrement in 36-month development scores (Bayley MDI and PDI)
- This decrement resulted in a 2-fold inc. risk of developmental delay (< 80) on the Bayley MDI, and a 5-fold risk of delay on the PDI
- Prenatal pesticide exposure was associated with significantly increased risk for diagnosis of ADHD and Pervasive Developmental Disorder

Rauh, et al. Pediatrics, 2006

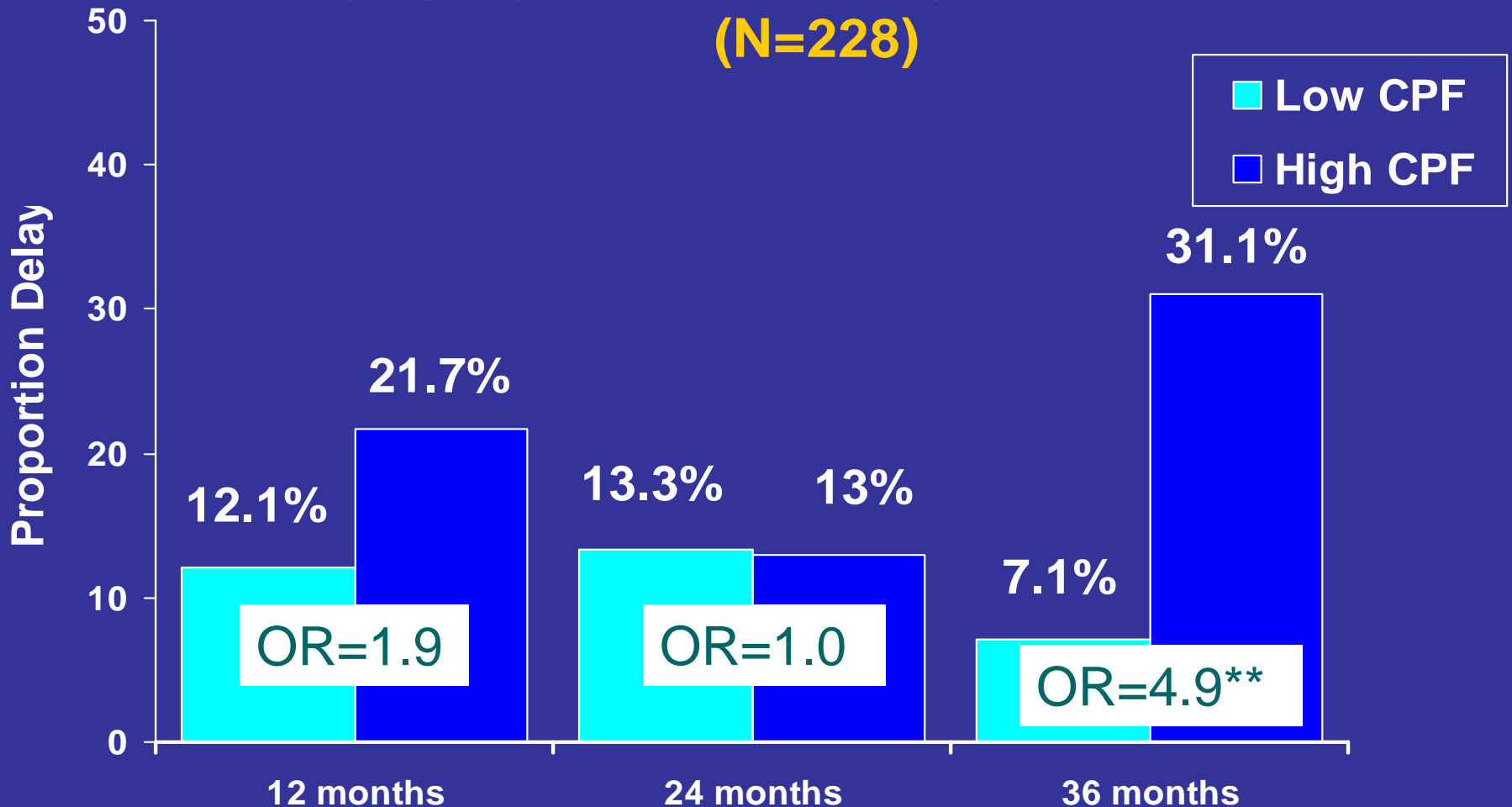
Cognitive Delay (< 85) at 12, 24 & 36 months on the Bayley, by level of chlorpyrifos exposure (N=228)



Logistic regression adjusted for race/ethnicity, sex, gestational age, ETS, maternal IQ, maternal education, HOME Inventory

*p<.01

Motor Delay (< 85) at 12, 24 & 36 months on the Bayley, by level of chlorpyrifos exposure (N=228)



Logistic regression adjusted for race/ethnicity, sex, gestational age, ETS, maternal IQ, maternal education, HOME Inventory

**p<.001

CHAMACOS birth cohort; agricultural workers; Salinas Valley

- Prenatal organophosphate exposures (as measured by DAP metabolites) associated with:
 - Decreased gestation time and poorer neonatal reflexes
 - Decreased Bayley MDI at 24 mos.
 - [childhood exposure associated with increased MDI]
 - Did not see effect of chlorpyrifos or malathion specifically

Eskenazi, et al. EHP, 2007

Organochlorine pesticides (DDT/DDE)

- Four prospective studies: North Carolina, Salinas Valley, Spain, Mexico
- Prenatal maternal serum or cord blood levels
- Mental development was found to be positively associated with DDE exposure only in the early North Carolina study at 6 months
- All other studies found either no association or a negative association.

Pesticides and autism spectrum disorder (ASD)

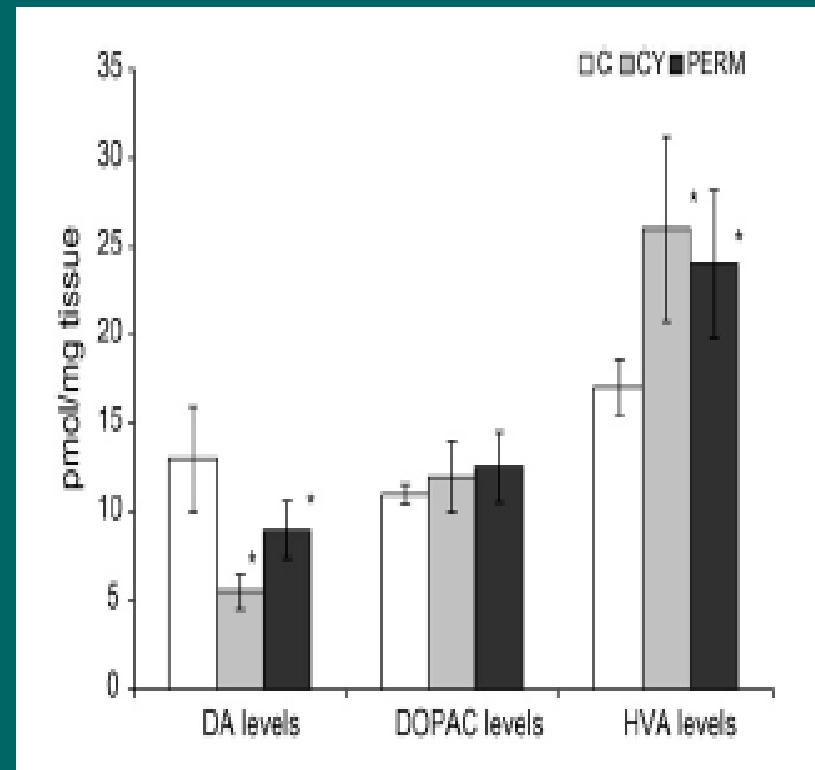
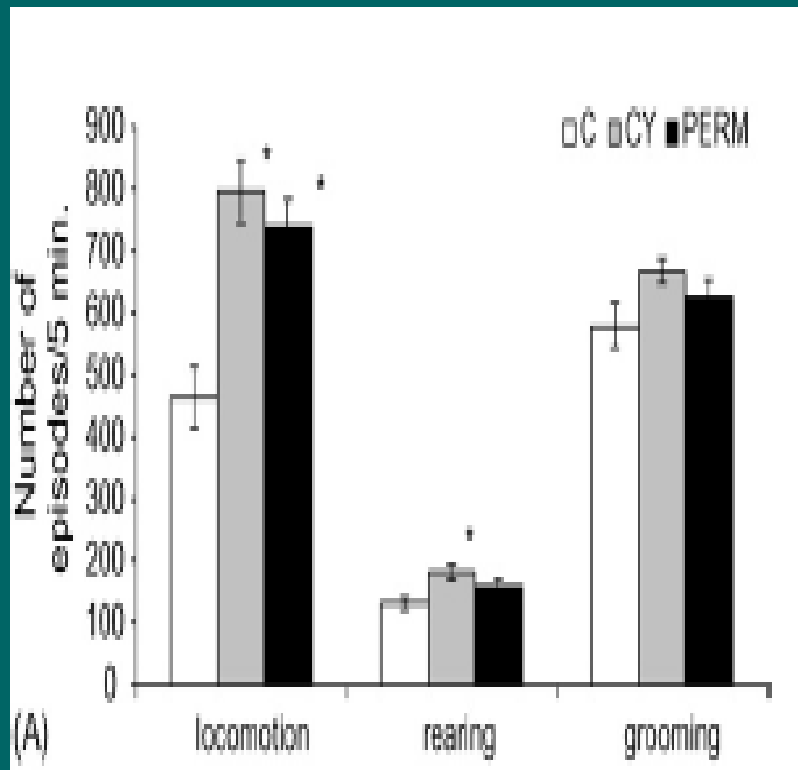
- Hypothesis: residential proximity to agricultural pesticide applications during pregnancy could be associated with ASD in offspring.
- Retrospective, case-control study
- Cases identified CA Dept of Developmental Services
- Pesticide use from CA Dept Pesticide Regulation

(Roberts, et al; EHP; 2007)

Pesticides and autism spectrum disorder (ASD)

- Risk for ASD was associated with residential proximity to organochlorine pesticide applications occurring around the period of CNS embryogenesis (endosulfan, dicofol)
- This association increased with dose and was attenuated with increasing distance of residence from the field site.
- Limits: misclassification of exposure; confounders or effect modifiers

Effect of neonatal cypermethrin and permethrin (1/10 LD50; postnatal day 6-15) on adult behavior— Wistar rats



Nasuti, et al. Toxicology; 2007

Summary

- Prenatal exposure to OP pesticides can have long term impacts on brain development,
- Increased risk of cognitive, motor delays; increased risk of ADHD, PDD
- Prenatal exposure to organochlorines may be associated with increased risk of autism spectrum disorder (needs further study and confirmation)
- Animal studies: neonatal pyrethroids/pyrethrins alter behavior and neurotransmitter levels in adulthood; may also increase risk of adult disease; human data lacking