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Neurobehavioral effects of exposure to organophosphates and pyrethroid pesticides among Thai children

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A B S T R A C T

The use of pesticides for crop production has grown rapidly in Thailand during the last decade, resulting in significantly greater potential for exposure among children living on farms. Although some previous studies assessed exposures to pesticides in this population, no studies have been conducted to evaluate corresponding health effects. Twenty-four children from a rice farming community (exposed) and 29 from an aquaculture (shrimp) community (control) completed the study. Participants completed a neurobehavioral test battery three times at 6 month intervals: Session I: preliminary orientation; Session II: high pesticide use season; Session III: low pesticide-use season. Only sessions II and III were used in the analyses. High and low pesticide use seasons were determined by pesticide use on rice farms. Urinary metabolites of organophosphates (OPs) and pyrethroids (PYR) were analyzed from first morning void samples collected the day of neurobehavioral testing. Rice farm participants had significantly higher concentrations of dialkylphosphates (DAPs) (common metabolites of OPs) and TCPy (a specific metabolite of chlorpyrifos) than aquaculture farm children during both seasons. But, TCPy was significantly higher during the low rather than the high pesticide use season for both participant groups. Rice farm children had significantly higher DCCA, a metabolite of PYR, than aquaculture participants only during the high exposure season. Otherwise, no significant differences in PYR metabolites were noted between the participant groups or seasons. No significant adverse neurobehavioral effects were observed between participant groups during either the high or low pesticide use season. After controlling for differences in age and the Home Observation for Measurement of the Environment (HOME) scores, DAPs, TCPy, and PYR were not significant predictors of adverse neurobehavioral performance during either season. Increasing DAP and PYR metabolites predicted some relatively small improvement in latency of response. However, due to the small sample size and inability to characterize chronic exposure, any significant differences observed should be regarded with caution. Moreover although not statistically significant, confidence intervals suggest that small to moderate adverse effects of pesticide exposure cannot be ruled out for some indicators of neurobehavioral performance.

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Agriculture accounts for 8.4% of the gross domestic product in Thailand and employs the largest sector of the labor force (39.6%) (Bank of Thailand, 2013). Major crops include rice, cassava, rubber, coconut, cotton, sugar cane and oil palm. Since 2000, Thailand has experienced an approximate four-fold increase in pesticide use (Aiemsupasit, 2005) with organophosphates (OPs) and pyrethroids (PYR) as the major pesticide classes used for crop protection (Panuwet et al., 2012). High levels of OP exposures have been objectively documented in ambient air samples breathed by farmers (Jirachaiyabhas et al., 2004) as well as in their urine (Panuwet et al., 2008). Children who lived in farm areas were also found to be exposed to a significantly higher amount of OPs than non-farm reference children (Panuwet et al., 2009; Petchuay et al., 2008). Unfortunately due to limited resources, the health consequences of these exposures, especially for children, have not been adequately characterized.

OPs and PYR are neurotoxicants known to disrupt neurologic development. For example, even in the absence of acetylcholinesterase (AChE) inhibition, animal studies show loss of hippocampal dopamine particularly if OP exposure occurs during pregnancy (Aldridge et al., 2005). Children may be more vulnerable than adults to the effects of pesticides because of the potential for increased exposure through proportionally higher intake of food, water and air relative to body weight, along with immaturity in neurologic development and detoxification pathways (Costa, 2006; National Research Council, 1993; Eskenazi et al., 1999; Grandjean and Landrigan, 2014). As a result of concerns about neurodevelopmental toxicity, four major US birth cohort studies were initiated to determine the health effects of pre and post-natal exposure to OPs. Thus far, these birth cohort studies have shown a negative association between indices of maternal OP exposure and Bayley mental (MDI) and motor development (PDI) scores among the children at ages 2–3 and measures of intelligence at age 7 (Bouchard et al., 2011; Engel et al., 2011; Rauh et al., 2011). More specifically, maternal indicators of OP exposure, measured in urinary metabolites and cord blood, predicted reductions in tasks of perceptual reasoning and working memory among 6–9 year old children of exposed mothers (Bouchard et al., 2011; Engel et al., 2011; Rauh et al., 2011). Bouchard et al. (2011) also reported reductions in the domains of processing speed and verbal comprehension. Studies of Ecuadorian children (5–8 year old), reported that maternal exposure to OPs was predictive of reduced visuomotor skills, impaired fine motor coordination, and slowed response speed (Grandjean et al., 2006; Handal et al., 2008; Harari et al., 2010).

Numerous cross sectional, descriptive studies have evaluated the effects of childhood pesticide exposure on neurobehavior, but results have been inconsistent due to differences in exposure assessment methods. Unlike organochlorines, OP and PYR pesticides do not persist in human tissue and have a relatively short half-life (Barr et al., 1999). Therefore, measurement of chronic exposure relies on historical reconstruction based on questionnaires and/or measurement of recent exposure using biomarkers such as urinary metabolites and AChE inhibition. Several cross-sectional studies have shown that, relative to unexposed children, OP pesticide exposed children had significant decrements in one or more of the following neurobehavioral functions: latency of response, fine and gross motor skills, visuomotor problem solving, short term memory, and attention (Eckerman et al., 2007; Rohlman et al., 2005; Ruckart et al., 2003). However, exposure was determined either by questionnaire, parental occupation, or was not concurrent with performance measurement. Thus, it is difficult to attribute performance deficits to OP pesticide exposure. Bouchard et al. (2011) found inconsistent or only marginal associations between OP urinary metabolites at age 5 and reduced scores for measures of working memory and perceptual reasoning at age 7. This result may not be surprising given the time frame between biomarker assessment and neurobehavioral evaluation. In contrast, lower acetylcholinesterase (AChE) activity measured at the time of neurobehavioral performance revealed that adolescent male pesticide applicators from Egypt performed significantly worse than controls on tests of visuomotor speed, immediate memory and general information (Abdel Rasoul et al., 2008). Adolescent subjects who worked more days during the pesticide application season performed more poorly on general information, timed math skills, conceptual thinking, visuomotor problem solving, speed of response and memory. Moreover, Lizardi et al. (2008) also reported that higher OP metabolite concentrations at the time of testing were significantly associated with compromised performance on a test of mental flexibility and conceptual thinking among 7-year old children.

Although a number of different neurobehavioral functions have shown significant reductions among pesticide-exposed children, these differences include both lower order functions such as motor speed and higher order cognitive processing involved in problem solving and memory. Increasing evidence from animal and human studies indicates that numerous brain regions may be affected by pre- and post-natal exposure to OPs and that the behavioral consequences of OP exposure depends on the timing as well as the level of exposure (Colborn, 2006; Slotkin, 2004). Moreover, the behavioral manifestations may be not be immediately obvious, but could become detectable as the child develops and is required to perform increasingly complex cognitive tasks.

In contrast to OPs, the neurobehavioral effects of PYR exposure have not been adequately evaluated and are poorly understood. One Canadian study reported a positive association between the PYR metabolite, *cis*-DCCA (3-(2,2-dichlorovinyl-2,2-dimethylcyclopropane carboxylic acid), and increased total difficulties score as reported by parents on the Strengths and Difficulties Questionnaire (Oulhote and Bouchard, 2013), but the authors did not measure behavioral performance. Horton et al. (2011) found that air samples of piperonyl butoxide, a synergist to potentiate the insecticidal action of PYR, collected during the 3rd trimester of pregnancy, was associated with significantly lower Bayley Mental Development Index scores at age 3. However, Bayley mental and psychomotor development were not significantly associated with the specific PYR metabolites, *cis*- or *trans*-permethrin measured in maternal/cord plasma. Therefore, the neurobehavioral effects observed cannot clearly be attributed to PYR.

The purpose of the current study was to evaluate the neurobehavioral effects of OP and PYR exposures among 6–8-year old Thai children living in the central farming region of Thailand where pesticide exposure opportunities significantly exceed those seen in the developed world. In previous studies, we documented that Thai children had higher urinary metabolites of OP and PYR than US children in the National Health and Nutrition Examination Survey (NHANES) (Barr et al., 2010; Panuwet et al., 2009; Rohitrattana et al., 2014a,c). Based on the existing literature and the concentrations of OP and PYR metabolites among our sample, we hypothesized that these exposures would predict decrements in latency of response, motor speed, and higher order cognitive functions of visuomotor coordination, attention, and working memory.

1. Method

1.1. Participants

Fifty-four, 6–8 year old, healthy male and female Thai children were randomly selected from 200 volunteers recruited from rice ($N = 25$) and aquaculture farming (i.e., shrimp farms) ($N = 29$) regions outside of Bangkok, Thailand (hereinafter designated RICE