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Prenatal exposure to the organophosphate pesticide chlorpyrifos and childhood tremor

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Abstract

Background—The organophosphate insecticide chlorpyrifos (CPF), widely used for agricultural purposes, has been linked to neurodevelopmental deficits. Possible motor effects at low to moderate levels of exposure have not been evaluated.

Methods—Prenatal exposure to CPF was measured in umbilical cord blood in a sample of 263 inner-city minority children, who were followed prospectively. At approximately 11 years of age (mean age 10.9 ± 0.85 years, range = 9.0–13.9), during a neuropsychological assessment, children were asked to draw Archimedes spirals. These were rated by a senior neurologist specializing in movement disorders who was blind to CPF exposure level.

Results—Compared to all other children, those with prenatal CPF exposure in the upper quartile range ($n = 43$) were more likely to exhibit mild or mild to moderate tremor (1) in either arm ($p = 0.03$), both arms ($p = 0.02$), the dominant arm ($p = 0.01$), and the non-dominant arm ($p = 0.055$).

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Logistic regression analyses showed significant CPF effects on tremor in both arms, either arm, the dominant arm (p -values < 0.05), and the non-dominant arm ($p = 0.06$), after adjustment for sex, age at testing, ethnicity, and medication.

Conclusion—Prenatal CPF exposure is associated with tremor in middle childhood, which may be a sign of the insecticide's effects on nervous system function.

Keywords

Chlorpyrifos; Neurodevelopment; Tremor; Brain; Children

1. Introduction

1.1. Introduction to chlorpyrifos

Chlorpyrifos (CPF) (0,0-diethyl-0-3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide. Prior to regulatory action by the Environmental Protection Agency in 2001, which banned residential use, CPF applications were particularly heavy in urban areas, where the exposed populations included pregnant women (Whyatt et al., 2003; Berkowitz et al., 2003). In a sample of pregnant women in New York City (Perera et al., 2002), detectable levels of CPF were found in 99.7% of personal air samples, 100% of indoor air samples, and 64–70% of blood samples collected from umbilical cord plasma at delivery (Whyatt et al., 2003). Chlorpyrifos is currently used for agricultural purposes across the United States, with the heaviest applications in California, and is one of the most widely used insecticides in the world (Solomon et al., 2014; Grube et al., 2011).

1.2. Adverse developmental effects of early exposure

In animal studies, CPF exposure leads to disruption of neuronal development, neurotransmitter systems (Slotkin, 2004; Aldridge et al., 2005; Slotkin and Seidler, 2005), and synaptic formation in different brain regions (Qiao et al., 2004). These neurodevelopmental effects are associated at a later point with functional impairments in learning, short-term working memory, and long-term reference memory (Levin et al., 2002).

In humans, OPs have been detected in amniotic fluid (Bradman et al., 2003) and are known to cross the placenta, reaching the fetus during a period of rapid brain development (Richardson, 1995; Whyatt et al., 2005). Using urinary metabolites as the biomarker of exposure, several studies have reported that prenatal maternal OP exposure was associated with abnormal neonatal reflexes (Engel et al., 2007; Young et al., 2005), mental deficits and pervasive development disorder at 2 years of age (Eskenazi et al., 2007), and attention problems at 3½–5 years of age (Marks et al., 2010). With a different biomarker of exposure (the parent compound of CPF), sampled in umbilical cord plasma, higher levels of prenatal CPF (greater than 6.17 pg/g) were associated with reduced birth weight and birth length (Whyatt et al., 2005), 3.5- to 6-point adjusted mean decrements on the 3-year Bayley Scales of Infant Development, a 2-fold increased risk of mental delay (< 80 points) and a 5-fold increased risk of motor delay (< 80 points) on the 3-year Bayley Scales of Infant Development (Rauh et al., 2006), and increased number of problems related to attention,

attention deficit hyperactivity disorder, and pervasive developmental disorder as measured by the Child Behavior Checklist at 2–3 years (Rauh et al., 2006). Persistent effects of prenatal OP pesticide exposures on cognitive outcomes have been reported through 7 years of age in both rural (Bouchard et al., 2011) and urban populations (Rauh et al., 2011; Engel et al., 2011). CPF effects on brain structural development has been demonstrated by magnetic resonance imaging (MRI) in a sample of urban children ages 5.9–11.2 years of age, including cortical thinning and regionally specific cortical deformations (Rauh et al., 2012).

1.3. Impact of CPF on motor development and movement

Evidence that low to moderate prenatal exposures to CPF and/or OP chemicals, in general, may disrupt motor processes is limited to the reports of detrimental effects on neonatal reflexes (Engel et al., 2007; Young et al., 2005) and psychomotor development on the Bayley Scales of Infant development at 3 years of age (Rauh et al., 2006). To date, there are no studies evaluating the longer-term consequences of prenatal exposure to CPF on motor development or movement disturbance.

1.4. Tremor

Tremor is a condition that is highly prevalent in human populations, particularly among the elderly (Louis et al., 1998, 2000; Lieberman et al., 1994). Among adults, tremor is associated with exposure to several environmental chemicals, including lead (Louis et al., 2003; Dogu et al., 2007), pesticides (Louis et al., 2006; Jiménez-Jiménez et al., 2007) and harmaline, a beta-carboline alkaloid found in coffee, tobacco smoke, and animal protein (Louis et al., 2002). Less attention has been devoted to the prevalence, clinical features and correlates of tremor among children. A recent report showed that mild tremor is common in children (33.1% of an urban sample with mean age of 11 years), and covaries significantly with several demographic and clinical factors as well as usage of certain medications (Louis et al., 2015).

1.5. Study aims

The present study was undertaken to identify the longer-term motoric consequences of prenatal exposure to CPF in a sample of New York City children at approximately 11–14 years of age, as part of a larger prospective cohort study. Since CPF has been linked to motor problems at high levels of acute exposure, we hypothesized that prenatal CPF exposure would be associated with increased tremor in this sample of children.

2. Materials and methods

2.1. Participants and recruitment

The subjects for this report are participants in an ongoing prospective cohort study of inner-city mothers and their newborn infants (Perera et al., 2002). The cohort study was initiated in 1997 to evaluate the effects of prenatal exposures to ambient pollutants on neurocognitive development in a cohort of mothers and newborns from low-income communities in New York City. Non-smoking women (classified by self-report and validated by blood cotinine levels less than 15 ng/ml), aged 18–35 years, who self-identified as African American or

Dominican, and who registered at New York Presbyterian Medical Center or Harlem Hospital prenatal clinics by the 20th week of pregnancy, were approached for consent. Eligible women were free of diabetes mellitus, hypertension and known human immunodeficiency virus (HIV), documented drug abuse, and had resided in northern Manhattan for at least one year. The study was approved by the Institutional Review Board of Columbia University and informed consent was obtained from all participants.

Of 725 consenting women, 535 were active participants in the ongoing cohort study at the time of this report, and 271 of these children had reached at least 9 years of age with complete data on the following: (1) prenatal maternal interview; (2) biomarkers of prenatal CPF exposure level from maternal and/or cord blood samples at delivery; (3) postnatal covariates, including childhood illnesses and medications; (4) neurodevelopmental assessment including one set of hand-drawn spirals (as described below).

2.2. Maternal and child sociodemographic and biomedical information

From maternal interviews (prenatal and annual thereafter) and medical records, we collected sociodemographic and biomedical information on race/ethnicity, child sex, birthweight, gestational age, maternal education, child medical diagnoses, learning disorders, and medications. This included medications taken for psychiatric or neurological conditions or for medical conditions.

2.3. Biologic samples and pesticide exposure

A 30–60 ml sample of umbilical cord blood was collected at delivery by drawing blood into a heparin-containing syringe to avoid clotting, and a 30–35 ml sample of maternal blood was collected within 2 days postpartum by hospital staff in heparin-containing Vacutainer tubes (Fisher Scientific, Morris Plains, NJ). Aliquots of blood were sent to the Centers for Disease Control and Prevention (Atlanta, GA) for analysis of CPF in plasma, described in detail elsewhere (Whyatt et al., 2003; Perera et al., 2002). Methods for the laboratory assay for CPF, including quality control, reproducibility, and limits of detection (LOD: 0.5–1 pg/g) have also been published previously (Barr et al., 2002). As previously reported, CPF levels in paired maternal and umbilical cord plasma samples were highly inter-correlated ($r = 0.76$; $p < 0.001$, Spearman's rank), indicating that CPF was readily transferred from mother to fetus during pregnancy. In this sample, 52.5% of samples had CPF measurements less than the LOD, and were assigned a value of one half the detection limit concentration. Chlorpyrifos concentrations ranged from 0.25 to 63.00 pg/g in the present sample.

Chlorpyrifos levels were categorized into 4 groups: nondetectable levels ($n = 143$) and 3 tertiles in the detectable range: tertile 1 ($n = 42$), tertile 2 ($n = 43$), and tertile 3 ($n = 43$). Consistent with previous reports (Whyatt et al., 2003, 2005; Rauh et al., 2006), the upper category was used to classify children into high exposure (>6.17 pg/g) or lower exposure (≤ 6.17 pg/g).

2.4. Child neurodevelopmental testing

As part of the follow-up study, the children received a full battery of neurodevelopmental assessment at approximately 11 years of age. Testing was conducted by a trained

neuropsychological tester, who was trained to reliability on all neurodevelopmental measures. For the measure described in the present manuscript (i.e., Archimedes spirals), she was fully trained by a senior neurologist, who is also the senior author on this paper, to instruct the children how to draw the spirals and to then oversee the drawing of complete and properly executed spirals (Louis et al., 2012). As a test of motor function, each child was also asked to draw five spirals: a practice Archimedes spiral with their dominant arm followed by four additional spirals (two with dominant arm followed by two with non-dominant arm). Spirals were drawn on a standard 8.5 × 11 inch sheet of paper using a pen or pencil while the participant was seated at a table. The paper was centered at right angles directly in front of them and held down by their other hand. The drawing hand was not allowed to rest or be supported when the spiral was being drawn. Participants started at the center of the page, without lifting their pen/pencil. The practice spiral was drawn in between the lines of a standardized, pre-drawn, photocopied, spiral. The remaining spirals were drawn free-hand on a blank sheet of paper.

Tremor in these five spiral drawings was rated by a senior neurologist specializing in movement disorders (E.D.L) who was blinded to all clinical information. Tremor ratings, published previously (Louis et al., 2011, 2015) for each spiral were: 0 (no tremor), 0.5 (subtle, low amplitude oscillations are present in a few spots but are not consistently present throughout the spiral), 1.0 (low amplitude oscillations are present in multiple places), 1.5 (low amplitude oscillations are present in multiple places and oscillations can at times reach moderate amplitude), 2 (moderate amplitude oscillations present throughout the spiral) (for examples of rated spirals, see Figs. 2–4 in Louis et al., 2015). During spiral rating, the neurologist was careful to distinguish clear, regular, oscillations from sloppiness, spatial errors, and other irregularities or movement dysfluencies that were not strictly oscillatory. There were two spirals drawn with each hand; the first spiral was considered a practice trial for the spiral task, and the second spiral was used as the tremor measure for the present analyses. Therefore, there was one spiral score for the dominant arm and another spiral score for the non-dominant arm.

2.5. Statistical analysis

The spiral rating scores were not normally distributed (Kolmogorov–Smirnov tests <0.05). A cut-point of 1.0 (low amplitude oscillations are present in multiple places) was considered clinically meaningful, and tremor was classified as present (≥ 1) or absent (<1) for each arm on the spiral task. This resulted in 4 possible scores: tremor present/absent in the dominant arm, tremor present/absent in the non-dominant arm, tremor present/absent in either arm, and tremor present/absent in both arms. Chi-square was used to assess crude associations between high CPF exposure level category and presence/absence of mild to moderate tremor. Binary logistic regression was used to estimate associations between high exposure level and presence of tremor using the above-mentioned cut-point, including covariates and confounders selected on the basis of (1) significant association with both the exposure and binary outcome ($p < 0.05$), (2) significant association with the outcome only and/or (3) impact on the magnitude of the effect size $>10\%$, as described below. All analyses were performed in SPSS (version 21.0).

3. Results

3.1. Descriptive statistics

There were 271 children with all available data (Table 1). Age was inversely, but not significantly, associated with the spiral score in both the dominant (Spearman's $r = -0.09$, $p = 0.13$) and the non-dominant arm (Spearman's $r = -0.04$, $p = 0.55$), such that higher age corresponded weakly with less tremor. Ethnicity was only weakly associated with tremor, such that Dominican children had higher tremor scores than African American children on all four measures. This difference approached significance for presence of clinically meaningful tremor (cut off = 1) in both arms only ($X^2 = 3.35$, $p = 0.07$). Boys were significantly more likely than girls to demonstrate clinically meaningful tremor (dichotomized = 1 versus <1) on all four dichotomous measures of tremor (Table 2).

A total of 21 children had a diagnosis of a neurological, psychiatric, or learning disorder. The most common psychiatric disorder was attention deficit/hyperactivity disorder (ADHD), followed by depression. Although the proportion of children with clinically meaningful tremor was slightly higher among those with any such diagnosis as compared to the proportion in the normal group (38.1% versus 24.4%), the comparison missed statistical significance because of small numbers (Chi-square = 1.915; $p = 0.17$). Table 3 shows the mean tremor scores by medication usage, regardless of formal diagnosis.

3.2. Prenatal chlorpyrifos exposure

Table 4 shows that the more highly exposed groups showed significantly higher proportions with clinically meaningful tremors. Logistic regressions were conducted to estimate the strength of association between prenatal CPF exposure and presence of clinically meaningful tremor, after adjustment for sex, exact age at testing, ethnicity, and medications. Tables 5–8 show the effect sizes for all covariates in the models for each dichotomous outcome. CPF exposure was significantly associated with tremor in the dominant arm ($p = 0.015$), tremor in either arm ($p = 0.028$), and tremor in both arms ($p = 0.027$), and marginally associated with tremor in the non-dominant arm ($p = 0.055$).

4. Discussion

The present findings show that children with high prenatal exposure to chlorpyrifos were significantly more likely to show mild or mild to moderate tremor in one or both arms when assessed between the ages of 9 and 13.9 years of age. The proportion with mild or mild to moderate tremor among the high exposure group ranged from 16.3% to 39.5%, depending on the arm, as compared to 6.1–22.8% in the low exposure group. To our knowledge, this is the first report of tremor resulting from early life exposure to this widely used pesticide.

In a recent study using a larger sample from the same cohort as the present study, we showed that mild tremor (rating of 1) was present in both arms in approximately 1 in 10 children, indicating that there is some measureable tremor in this age group (Louis et al., 2015). Tremor was associated with poorer motor dexterity (i.e., poorer motor hand function), as assessed by the Purdue Pegboard test. Children with psychiatric or neurological disorders had higher tremor scores than those without such comorbidities, regardless of

medication, suggesting that these disorders (e.g., ADHD) might themselves be associated with subtle motor system manifestations. In light of previous reports of CPF associations with ADHD-type symptoms (Rauh et al., 2006; Marks et al., 2010), it is possible that both the tremor and the ADHD-type symptoms may share, at least in part, a common etiology – the CPF exposure itself.

The basis for the tremor we observed is not clear. In general, however, tremors are considered to be the result of nerve dysfunction. These include centrally generated tremors (i.e., tremors that arise from brain dysfunction) and peripherally generated tremors (i.e., tremors that arise from peripheral nerve dysfunction) (Deuschl et al., 1998).

Possible mechanisms to explain the present finding of CPF effects on likelihood of childhood tremor are suggested by the experimental literature showing neurotoxic effects of CPF exposure in rats. Specifically, neonatal CPF exposure was shown to disrupt synaptic proliferation and activity in the midbrain, striatum and the cerebellum (Dam et al., 1999; Slotkin et al., 2002; Slotkin and Seidler, 2005), brain regions (especially the cerebellum) that are highly involved in the control of movement and known to be associated with tremor. In another study, in utero exposure to CPF produced significant sensorimotor deficits in association with loss of cerebellar neurons and glial “scarring” (Abou-Donia et al., 2006).

Tremor, as measured and defined in the present study, may have functional implications for routine motor activities. We recently reported that tremor was associated with poorer motor hand function as assessed using the Purdue Pegboard test (Tiffin, 1968; Louis et al., 2015), indicating either that the tremor itself resulted in some reduction in dexterity or that both the tremor and the loss of dexterity were a result of an underlying perturbed motor state. The possible links between CPF exposure, tremor, and additional measures of motor function remain to be studied.

The use of a clinical scale to assess tremor, rather than accelerometry, in the present study is a limitation. However, prior studies suggest that spiral drawings are a reasonably sensitive measure of tremor, as 97.0% of individuals with mild or greater tremor on a more detailed tremor examination exhibited ratings of 0.5 in one or more arms during spiral drawing (Louis et al., 1998).

Results suggest that early life exposure to CPF increases the likelihood of mild or mild to moderate tremor in a sample of innercity children. This could have adverse effects on daily motor tasks such as handwriting and writing-based school performance – outcomes that need to be assessed in future studies. Further neuropsychological assessment of exposure effects on movement and motor function is indicated by the present findings, including brain-based measures of cortical and subcortical function related to impaired motor control.

A limitation of the study is the lack of postnatal and early childhood biomarkers of CPF exposure. However, mid-way through the larger cohort study, in June of 2000, the U.S. Environmental Protection Agency (EPA) announced a phase-out of the sale of CPF for indoor residential use, with a complete ban effective 12/31/01 (US EPA, 2000, 2002). Following the ban, levels of CPF in personal and indoor air samples among pregnant women in our community, including the larger cohort from which this sample was selected,

decreased at least 3-fold, and plasma blood levels have dropped more than 5-fold (Whyatt et al., 2005), despite some lingering residential residues (Whyatt et al., 2007). For virtually all of the children participating in the present study, the oldest of whom was only 3 years of age when the ban went into effect, postnatal exposures were likely to have been minimal. Although these exposure data are ecological, they do provide some evidence that the very highest levels of exposure in this sample likely occurred during the prenatal period.

Despite the 2001 Environmental Protection Agency ban of CPF for indoor residential use, agricultural applications continue to be widespread, exposing many children who reside in farm communities (Solomon et al., 2014; Grube et al., 2011; Bradman et al., 2007; Accury et al., 2007; Marks et al., 2010). The present study, which reports a link between CPF exposure and tremor, adds to a growing number of reports showing adverse consequences of early exposure to chlorpyrifos across a number of developmental domains, including lower birth weight (Whyatt et al., 2004), deviant neonatal reflexes (Young et al., 2005), neonatal neurological problems (Zhang et al., 2014), cognitive/behavioral deficits from 2 to 7 years of age (Engel et al., 2007, 2011; Rauh et al., 2006, 2011; Marks et al., 2010; Bouchard et al., 2011), social communication/responsiveness problems (Furlong et al., 2014; Shelton et al., 2014), and brain structure anomalies such as frontal and parietal cortical thinning (Rauh et al., 2012). Taken together, growing evidence suggests that prenatal exposure to CPF, at current standard usage levels, is associated with a range of persistent and inter-related developmental problems.

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Table 1

Demographic and clinical characteristics of 271 children in the sample.

| Characteristic | N (%) | Mean±SD; median (range) |
|---|------------|--------------------------------|
| Age in years | | 10.94 ± 0.85; 11.00 (9.0–13.9) |
| Girls | 146 (53.9) | |
| Ethnicity | | |
| Dominican | 169 (62.4) | |
| African American | 102 (37.6) | |
| Right-handed | 242 (89.3) | |
| Current medication usage | | |
| None | 223 (82.3) | |
| Asthma medication | 43 (15.9) | |
| Psychiatric medication ^a | 9 (3.3) | |
| Psychiatric or neurological diagnoses | | |
| None | 250 (92.3) | |
| Learning disorder | 9 (3.3) | |
| Psychiatric or neurologic disorder ^b | 13 (4.8) | |
| Spiral score (dominant hand) | | 0.40 ± 0.32; 0.50 (0–1.5) |
| Spiral score (non-dominant hand) | | 0.48 ± 0.39; 0.50 (0–2.0) |

Values are either numbers (percentage) or mean ± standard deviation; median (range).

^aMedications for ADHD, with the most common medication being methylphenidate ($N = 8$).

^bIncluding ADHD, epilepsy, and bipolar disorder.

Table 2

Dichotomous tremor (≥ 1 versus <1) overall and by sex.

| Tremor | Total (n = 271) N (%) | Boys (n = 125) N (%) | Girls (n = 146) N (%) | Chi-square test, significance |
|------------------|----------------------------------|---------------------------------|----------------------------------|--------------------------------------|
| Dominant arm | 27 (10.0) | 19 (15.2) | 8 (5.5) | $\chi^2 = 7.09, p = 0.008$ |
| Non-dominant arm | 63 (23.2) | 36 (28.8) | 27 (18.5) | $\chi^2 = 4.01, p = 0.045$ |
| Either arm | 69 (25.5) | 40 (32.0) | 29 (19.9) | $\chi^2 = 5.22, p = 0.022$ |
| Both arms | 21 (7.7) | 15 (12.0) | 6 (4.1) | $\chi^2 = 5.86, p = 0.015$ |

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Table 3

Spiral scores by medication status.

| | No medication <i>N</i> = 223 | Asthma medication ^a <i>N</i> = 39 | Psychiatric medication ^b <i>N</i> = 5 | Both types of medications <i>N</i> = 4 | Significance ^c |
|---------------------------------|---------------------------------|---|---|---|---------------------------|
| Spiral score (dominant arm) | 0.39 ± 0.31 | 0.42 ± 0.35 | 0.80 ± 0.45 | 0.50 ± .00 | <i>p</i> = 0.07 |
| Spiral score (non-dominant arm) | 0.48 ± 0.39 | 0.46 ± 0.42 | 0.70 ± 0.27 | 0.75 ± .29 | <i>p</i> = 0.18 |

^a Medications for asthma symptoms and treatment included albuterol (most common), singulair, flovent and advair.

^b Medications for psychiatric disorders included concerta (most common) and few others.

^c Kruskal–Wallis test comparing the four groups to one another.

Table 4

Crure Proportions with tremor (spiral score 1) by CPF exposure level (upper quartile versus all other levels).

| Tremor | High CPF (<i>n</i> = 43) <i>N</i> (%) | Low CPF (<i>n</i> = 228) <i>N</i> (%) | Chi-square test, significance |
|------------------|--|--|--------------------------------------|
| Dominant arm | 9 (20.9) | 18 (7.9) | $\chi^2 = 6.85, p = 0.009$ |
| Non-dominant arm | 15 (34.9) | 48 (21.1) | $\chi^2 = 3.88, p = 0.049$ |
| Either arm | 17 (39.5) | 52 (22.8) | $\chi^2 = 5.33, p = 0.021$ |
| Both arms | 7 (16.3) | 14 (6.1) | $\chi^2 = 5.20, p = 0.023$ |

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Table 5

Estimated associations between prenatal CPF exposure^a and tremor (present versus absent) in either arm, using fully adjusted logistic regression models ($N = 271$).

| Predictor variable | B | SE | Wald | p-Value | OR | 95% CI for OR | |
|---------------------------|-------|-------|-------|---------|-------|---------------|-------|
| | | | | | | Lower | Upper |
| Chlorpyrifos ^a | 0.801 | 0.366 | 4.800 | 0.028 | 2.228 | 1.088 | 4.563 |
| sex | 0.576 | 0.289 | 3.990 | 0.046 | 1.780 | 1.001 | 3.134 |
| Asthma medication | 0.181 | 0.393 | 0.212 | 0.645 | 1.198 | 0.555 | 2.589 |
| Psychiatric medication | 0.638 | 0.707 | 0.816 | 0.366 | 1.894 | 0.474 | 7.570 |
| Race/ethnicity | 0.267 | 0.301 | 0.783 | 0.376 | 1.306 | 0.723 | 2.358 |
| Exact age at testing | 0.075 | 0.172 | 0.191 | 0.662 | 1.078 | 0.770 | 1.510 |

^aDichotomized as upper tertile of detectable values ($n = 43$) versus all lower values ($n = 228$). Cut-point = 6.17 pg/g.

Table 6

Estimated associations between prenatal CPF exposure^a and tremor (present versus absent) in both arms, using fully adjusted logistic regression models ($N = 271$).

| Predictor variable | B | SE | Wald | p-Value | OR | 95% CI for OR | |
|---------------------------|--------|-------|-------|---------|-------|---------------|--------|
| | | | | | | Lower | Upper |
| Chlorpyrifos ^a | 1.189 | 0.536 | 4.916 | 0.027 | 3.284 | 1.148 | 9.397 |
| sex | 1.054 | 0.512 | 4.232 | 0.040 | 2.870 | 1.051 | 7.835 |
| Asthma medication | -0.138 | 0.693 | 0.039 | 0.842 | 0.871 | 0.224 | 3.387 |
| Psychiatric medication | 1.077 | 0.874 | 1.518 | 0.218 | 2.935 | 0.529 | 16.274 |
| Race/ethnicity | 1.164 | 0.591 | 3.876 | 0.049 | 3.202 | 1.005 | 10.200 |
| Exact age at testing | -0.122 | 0.300 | 0.164 | 0.685 | 0.885 | 0.492 | 1.594 |

^aDichotomized as upper tertile of detectable values ($n = 43$) versus all lower values ($n = 228$). Cut-point = 6.17 pg/g.

Table 7

Estimated associations between prenatal CPF exposure^a and tremor (present versus absent) in non-dominant arm, using fully adjusted logistic regression models ($N = 271$).

| Predictor variable | B | SE | Wald | p-Value | OR | 95% CI for OR | |
|---------------------------|-------|-------|-------|---------|-------|---------------|-------|
| | | | | | | Lower | Upper |
| Chlorpyrifos ^a | 0.726 | 0.377 | 3.696 | 0.055 | 2.066 | 0.986 | 4.329 |
| sex | 0.518 | 0.298 | 3.028 | 0.082 | 1.679 | 0.937 | 3.009 |
| Asthma medication | 0.010 | 0.416 | 0.001 | 0.980 | 1.010 | 0.447 | 2.281 |
| Psychiatric medication | 0.826 | 0.710 | 1.352 | 0.245 | 2.284 | 0.568 | 9.193 |
| Race/ethnicity | 0.523 | 0.319 | 2.689 | 0.101 | 1.687 | 0.903 | 3.152 |
| Exact age at testing | 0.049 | 0.177 | 0.077 | 0.782 | 1.050 | 0.743 | 1.484 |

^aDichotomized as upper tertile of detectable values ($n = 43$) versus all lower values ($n = 228$). Cut-point = 6.17 pg/g.

Table 8

Estimated associations between prenatal CPF exposure and tremor (present versus absent) in dominant arm, using fully adjusted logistic regression models ($N = 271$).

| Predictor variable | B | SE | Wald | p-Value | OR | 95% CI for OR | |
|---------------------------|--------|-------|-------|---------|-------|---------------|--------|
| | | | | | | Lower | Upper |
| Chlorpyrifos ^a | 1.155 | 0.475 | 5.902 | 0.015 | 3.175 | 1.250 | 8.062 |
| sex | 1.036 | 0.449 | 5.324 | 0.021 | 2.819 | 1.169 | 6.799 |
| Asthma medication | 0.265 | 0.562 | 0.223 | 0.637 | 1.303 | 0.434 | 3.918 |
| Psychiatric medication | 0.641 | 0.856 | 0.559 | 0.455 | 1.897 | 0.354 | 10.167 |
| Race/ethnicity | 0.336 | 0.445 | 0.570 | 0.450 | 1.400 | 0.585 | 3.351 |
| Exact age at testing | -0.023 | 0.264 | 0.008 | 0.929 | 0.977 | 0.583 | 1.637 |

^a Dichotomized as upper tertile of detectable values ($n = 43$) versus all lower values ($n = 228$). Cut-point = 6.17 pg/g.