



Contents lists available at ScienceDirect

# International Journal of Hygiene and Environmental Health

journal homepage: [www.elsevier.com/locate/ijheh](http://www.elsevier.com/locate/ijheh)

## Prenatal exposure to organophosphate pesticides and risk of autism spectrum disorders and other non-typical development at 3 years in a high-risk cohort

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### ARTICLE INFO

#### Keywords:

Autism spectrum disorder  
Biomarkers  
Developmental concerns  
Prenatal exposure  
Prospective cohort  
Organophosphate pesticides

### ABSTRACT

**Introduction:** Organophosphates are widely used pesticides that have been shown to affect child neurodevelopment. Previous studies that explored their potential effects on Autism Spectrum Disorder (ASD) relied either on proxies of external exposure or on questionnaires completed by the parents to identify autism-like behaviors but did not provide a clinical diagnosis of ASD.

**Aims:** We studied the associations between prenatal biologic markers for exposure to organophosphate pesticides and the risk of having a child with ASD or other developmental concerns (ODC).

**Method:** We analyzed 203 mother-child pairs of the ongoing MARBLES (*Markers of Autism Risk in Babies – Learning Early Signs*) mother-child cohort, which enrolls mothers who are either pregnant or planning a pregnancy and whose expected child has an elevated risk to develop ASD. Seven metabolites of organophosphate pesticides were assessed in repeated urine samples collected during pregnancy. At 36 months, children were assessed with instruments measuring cognitive function and adaptive behaviors, and with two gold-standard diagnostic instruments for ASD: the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised. Children were classified in one of the following groups: ASD (n = 46), ODC (n = 55) and typically developing (TD, n = 102).

**Results:** After adjustment for potential confounders, organophosphate metabolite concentrations were not associated with an increased risk of ASD or ODC when boys and girls were studied together. After stratification by sex, dimethylthiophosphate (DMTP) pregnancy concentration tended to be associated with an increased ASD risk among girls (OR for a doubling in the DMTP concentration: 1.64 (95%CI, 0.95; 2.82)) but not among boys (OR: 0.84, 95%CI: 0.63; 1.11).

**Discussion:** This is the first study of clinically confirmed diagnoses of ASD that utilized repeated measurements of organophosphate metabolites during pregnancy to explore the associations between these pesticides and ASD risk in children. The association we observed among girls, as well as the lack of association in boys, need to be replicated in further studies with similar design and larger sample size. In light of the higher baseline risk for ASD in this cohort, generalizability to children lacking a first degree relative affected by ASD is unknown.

**Abbreviations:** ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; BMI, Body Mass Index; DEP, diethylphosphate; DETP, diethylthiophosphate; DEDTP, diethylidithiophosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; DMDTP, dimethylidithiophosphate; OP, Organophosphate pesticides; SCQ, Social Communication Questionnaire; ΣDAP, molar sum of DEP, DETP, DMP, DMTP and DMDTP; ΣDEP, molar sum of DEP and DETP; ΣDMP, molar sum of DMP, DMTP, and DMDTP

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<https://doi.org/10.1016/j.ijheh.2018.02.004>

Received 23 January 2018; Received in revised form 8 February 2018; Accepted 9 February 2018  
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## 1. Introduction

Organophosphate (OP) pesticides are a class of insecticides widely used throughout the world. While they were phased out for most residential uses by the U.S. Environmental Protection Agency in the early 2000 s (Clune et al., 2012), they are still applied in agriculture for insect control on food crops (Shelton et al., 2012), on golf courses and some other uses. For the general population, exposure to OP mainly occurs through inhalation from agricultural spray drift and ingestion of residues on food products. An interventional study in 23 children showed that replacing their conventional diet with organic food items for 5 consecutive days led to significant reduction in urinary OP pesticide metabolite concentrations (Lu et al., 2006). OP pesticides were initially developed as nerve gases for chemical warfare and then adapted for insect control at lower doses. They affect mammalian and insect nervous systems by irreversibly inhibiting the enzyme acetyl cholinesterase (AChE) that breaks down the neurotransmitter acetylcholine. Inhibition of AChE leads to accumulation of acetylcholine in the synapses, that can result in acute neurologic symptoms. In addition to high-dose effects on AChE inhibition, toxicological studies have suggested that OP pesticides can down-regulate serotonin receptors, induce oxidative stress and alter calcium and potassium homeostasis (reviewed by Shelton et al., 2012 (Shelton et al., 2012)). In addition, a magnetic resonance imaging study in 40 children aged 5.9–11.2 years found brain morphological changes in the group with high cord blood concentrations of chlorpyrifos (Rauh et al., 2012).

Regarding the effects of OP pesticides on child neurodevelopment, epidemiological studies that measured the parent compounds in blood or their metabolites in urine reported associations with abnormal reflexes in neonates (Engel et al., 2007; Young et al., 2005; Zhang et al., 2014), poorer mental development in toddlers assessed with the Bayley Scales of Infant Development (Eskenazi et al., 2007)), and poorer working memory and intellectual quotient in children (Bouchard et al., 2011; Horton et al., 2012; Rauh et al., 2011). Only a few studies have looked at Autism Spectrum Disorder (ASD), a neurodevelopmental disorder characterized by impairments in social interactions and communication and a pattern of stereotyped behaviors or sensory sensitivities, for which increased prevalence has been observed in the past decades in the United States (Centers for Disease Control and Prevention, 2012). One study did not report an association (Millenson et al., 2017) while the five others reported increased risk of an ASD diagnosis or ASD like symptoms in association with OP pesticide exposure during pregnancy (Eskenazi et al., 2007; Furlong et al., 2014; Rauh et al., 2006; Roberts et al., 2007; Shelton et al., 2014). These studies on ASD were limited by the fact that they relied on 1) mandated reports of commercial pesticide use near the houses of the participants as a surrogate of exposure (Roberts et al., 2007; Shelton et al., 2014) which does not take into account exposures occurring through other sources like food; or 2) by the use of questionnaires completed by the parents to identify autism-like behaviors without clinical confirmation of the ASD diagnosis (Eskenazi et al., 2007; Furlong et al., 2014; Millenson et al., 2017; Rauh et al., 2006).

Our aim was to study prenatal exposure to OP pesticides in relation to children's diagnosis of ASD and other developmental concerns (ODC). We relied on the MARBLES prospective cohort, which obtained repeated urine samples during pregnancy to assess OP exposure and confirmed all diagnoses at 3 years using diagnostic gold-standard assessments for ASD.

## 2. Methods

### 2.1. Population

We analyzed the ongoing MARBLES cohort that started in 2006 and enrolls women at high risk for having a child with ASD. Selection criteria are 1) having a biological child diagnosed with ASD and so being

at elevated risk to have another child with this disorder (close to 20% (Ozonoff et al., 2011) compared to about 1.5% in the general population); 2) being pregnant or planning a pregnancy and being biologically able to become pregnant; 3) living within an approximate 2 h drive to the UC Davis MIND (Medical Investigation of Neurodevelopmental Disorders) Institute clinic; 4) being at least 18 years old. A few women (n = 2) did not match the first criteria of inclusion but were enrolled since they were at high risk of having a child with ASD (e.g., mother had an identical twin with an ASD child). Eligible families are identified using the list of families receiving state-funded services for a child with ASD, provided to us by the California Department of Developmental Services. Some families are also referred by other research studies at the UC Davis MIND Institute or by health and service providers, or learn about the study at outreach events. To confirm the ASD diagnosis of the older sibling, the study psychologist requests the record of an ASD diagnosis, i.e., an evaluation made by a psychologist using the ADOS (Autism Diagnostic Observation Schedule, (Lord et al., 2000)). If neither the parent nor the clinician provides such a record, then the study psychologist administers the ADOS to the child and the Social Communication Questionnaire (SCQ) to the mother (Rutter et al., 2003). Based on these assessments, the older sibling is either deemed to meet criteria for ASD, in which case the mother is enrolled, or not, in which case the mother is ineligible.

For the current study, we included all active MARBLES participants who were born between 2006 and March 2014, for whom pregnancy urine samples were available and who did not drop out before the examination of the child at 3 years of age. A comparison of mother-child pairs included in this analysis versus those not included is provided in the Supplemental Material, Table S3. Those not included lacked urine samples, dropped out before the 3-year visit or had an incomplete exam at 3 years. The MARBLES study has been approved by the institutional review boards for the State of California and the University of California Davis. All participants signed an informed consent before being enrolled in the study.

#### 2.1.1. Collection of urine samples

Beginning at enrollment and throughout pregnancy, mothers of the MARBLES study were asked to collect for each trimester up to three first morning void urine samples (referred as spot samples in this manuscript) and one 24-h urine sample collected on a different day than the spot samples. Mothers collected spot samples, each one week apart, and then stored these spot urine samples in their home freezer until collection by study staff during a home visit. The 24-h urine samples included all urine voids for a 24-h period starting at 8 am the day before the study staff made a home visit. Participants used collection hats that were emptied into the provided 24-h container after each void. Twenty-four hour samples were stored in the mother's home refrigerator. The MARBLES Study personnel picked up urine samples during home visits and transported them to UC Davis for storage at  $-80^{\circ}\text{C}$ . Urine samples were then later thawed and aliquoted as follows: for a given trimester if a woman collected only one or two urine samples (spot or 24 h sample) both samples were analyzed individually (not pooled). If three or more samples (spots and 24 h samples) were available, generally the first sample of that trimester was analyzed as an individual sample and the remaining samples were pooled together (pooled within-trimester, within-subject). Pooling enabled us to take advantage of the repeated measurements per subject to reduce exposure measurement error while keeping the total cost of OP pesticide metabolite measurements reasonable.

#### 2.1.2. Assessments of OP metabolites

In the present study, urine samples (pools, spots and 24-h) from the 2nd and 3rd trimesters of pregnancy were shipped overnight on dry ice to Emory University's Rollins School of Public Health (RSPH) for OP metabolite quantification. Specific gravity was measured on all samples (spot, pools, 24-h) prior to shipment. Dimethylphosphate (DMP),

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