Gestational pesticide exposure and autism spectrum disorders: Is there an association?

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What is autism?

Distinguishing characteristics include a lack of social reciprocity, stereotypic movements and or behavior, and language deficit or delay.
Autism in California

Of the approximate 700% increase from 1990 to 2001, approximately 200% is attributable to younger age at diagnosis, inclusion of milder cases, and changes in diagnostic criteria.

Hertz-Picciotto & Delwiche, Epidemiology, 2009
Autism Causation is Multifactorial

= multiple causes...
across the population and within an individual

A
Most rare: one cause

B D
Possible: 2 causes

E B C F
Most common: 3 or more causes
Why pesticides?

- Associations have been reported between prenatal maternal pesticide exposure and:
  - autism spectrum disorders
  - developmental delay
  - attention deficit disorders

- Genetic susceptibility may explain a subclass of cases
Primary modes of action

- Organophosphates & carbamates
  - Inhibition of acetylcholinesterase, the enzyme which allows degradation of the neurotransmitter acetylcholine.

- Organochlorines & pyrethrins
  - Inhibition of GABA, the primary inhibitory neurotransmitter in adults with distinct roles in development of neural network.
Developmental neurotoxicity

Disruption of neuronal excitation / inhibition mechanisms

CHOLINESTERASE INHIBITION

NORMAL REACTION

WITH NERVE AGENT
Other mechanisms of action

- Mitochondrial dysfunction
  - Via oxidative stress
    - apoptosis of neuronal cells (dichlorvos-OP)
    - inhibition of mitochondrial respiration (methoxychlor -OC)

- Immune toxicity
  - Decreased delayed type hypersensitivity and antibody production (atrazine-TZ)

- Maternal hypothyroxinemia
  - Decreased T4 (acetechlor, alachlor-OC)
  - Low T4 associated with dieldrin exposure in adult women
The CHARGE Study

- Population based case-control study of children aged 2-5
  - English, Spanish speaking
  - Born in CA
  - One biological parent in the home

- Aims to shed light on the genetic and environmental etiology of autism and developmental delay

- Battery of cognitive & behavioral tests including confirmation of diagnoses

<table>
<thead>
<tr>
<th>Autism Spectrum Disorders</th>
<th>Developmentally Delayed</th>
<th>Typically Developed</th>
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<tbody>
<tr>
<td>N=478</td>
<td>N=141</td>
<td>N=275</td>
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Preliminary results

Self-reported proximity to an agricultural field or golf course

- DD
- Autism/ASD
- TD

- Residence during gestation within 1/4 mile of an agricultural field or golf course
- Residence of the child within 1/4 mile of an agricultural field or golf course
Residential exposure to agricultural pesticides and the risk of autism spectrum disorders
Maternal Residence Near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley

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- 7.6 (95% CI 3.1-18.6) fold increased risk in highest quartile of exposure to organochlorine pesticides in days post fertilization 26-81.

Roberts et al., Environmental Health Perspectives, 2007
Agricultural exposure

California Department of Pesticide Regulation
Pesticide Use Report Data
Specific aims

- **Specific aim 1:** To estimate the association between agricultural exposure to organochlorine pesticides and the risk of autism.

- **Specific aim 2:** To estimate the association between agricultural exposure to organophosphate & carbamate pesticides and the risk of autism.

- **Specific aim 3:** To estimate the association between agricultural exposure to pyrethroid pesticides and the risk of autism.
Methods

- Using ArcGIS, analyze residential spatial proximity to agricultural pesticide use per township section (1 square mile).

- Create exposure scenarios for trimesters of pregnancy
  - Scenario 1: Distance to quartiles of pesticides assuming circular drift
  - Scenario 2: Approximated pounds of drift taking into account wind direction and application type by modeling exposure in AgDisp

- Analyze the risk of an autism diagnosis by pesticide subclass in multivariate logistic regression models
The industry standard

Figure 2. Example of exposure from residential proximity to parathion applications using the distance-based and narrow and broad zonal exposure definitions, 1988.

Graphic from Rull & Ritz, 2003.
Two exposure scenarios

- Scenario 1: Equivalent drift in all directions
- Scenario 2: Wind, method of application affect probability of exposure
  - Wind roses, AgDISP
AgDisp

Evaporation accounted for during this transit (Figure 3). AGDRN-1/AGDISP are PC-based codes, operating in a Windows environment with a highly capable GUI to guide user operation (Figure 4). Over 1000 copies of these models are in use worldwide.

Figure 2: Droplet trajectories predicted by AGDISP's Lagrangian model in a crosswind.
Export exposure data to SAS

- We aim to analyze the exposure as quartiles of the continuous distribution of lbs per 500m increment.
  - i.e. 4th quartile = max quartile of exposure within 500m

- Outcome will be binary, multivariate logistic regression by pesticide class
PON 1 modification of organophosphate exposure
PON 1 modifies metabolism of organophosphates

- Paroxonase 1 is an enzyme that hydrolyzes organophosphates and nerve gasses

- An Italian linkage study found ASD and PON1 were associated in America but not Italy
  - Those with ASD had a reduced ability to metabolize OPs

- Tokyo subway attack
  - 1995 Sarin gas attack
    - Homozygotes PON1q192 hydrolyzed sarin 10x better than homozygotes for PON1r192
Specific aims

- To measure and report PON1<sub>192</sub> polymorphisms in CHARGE study mothers and children

- To explore effect modification of prenatal exposure to organophosphate exposure by maternal PON1 genotype
Acknowledgements

Major professor: Dr. Irva Hertz-Picciotto, Ph.D., M.P.H.

- CHARGE families and study staff
- Special thanks to Lora Delwiche and Paula Krakowiak, CHARGE study programmers