INVESTIGATING HAZARDOUS AIR POLLUTANTS IN RELATION TO AUTISM SPECTRUM DISORDERS

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Background

- Autism is a serious neuro-developmental disorder with long-lasting impacts
- Behaviorally defined along a spectrum of impairments in 3 areas:
  - Social interaction
  - Verbal and non-verbal communication
  - Restricted or repetitive behaviors
- Probably due to disruption *in utero*
- Strong genetic component, but likely multi-factorial, with few causes (or genes) identified

Background, cont.

- Autism reporting appears to be on the rise--
  increase from 1/10,000 to ~1/166 births
- Diagnostic changes, awareness and services
- Exogenous exposures may play a role
  - Medications
  - Smoking
  - Alcohol—case reports
  - Concerns over vaccines, mercury, etc.

Background, cont.

- CA DHS conducted autism surveillance as part of the national CDC ADDM/CADDRE network to establish standardized prevalence rates and monitor trends
- USEPA has modeled concentrations of hazardous air pollutants (HAPs) nationwide

Goal: Link CADDRE autism surveillance data to HAPs data in San Francisco Bay Area

California CADDRE: Multi-source Case Definition

- Birth residence in study area (~80,000 births/year) validated by vital records
- Born in 1994
- Identified through Kaiser or Dept. of Developmental Services (DDS) records (as well as private providers)
- ASD Dx (or MR, no etiology) prior to 9th birthday, then validated by chart review
- Expert review to resolve "suspect" diagnoses

California CADDRE Surveillance Map

Methods—Subject Selection

- Identified 341 potential case records
- Selected 2 controls/case from livebirths, frequency matched by gender and month
- Abstracted birth address from BC
- Geo-coded addresses, assigned census tract
- Linked to HAPs data by census tract
- Excluded known deaths
- Conducted expert review
- Data for 284 ASD cases and 657 controls

HAPs Database

- Lack of monitoring data available on low-level, chronic exposures to air toxics
- EPA model estimates annual average concentrations for each census tract in U.S.
- Based on emission inventories and estimates of general use by area, as well as meteorological data, decay rates, and deposition
- Available for 1990 and 1996; used 1996 as closest to 1994 and considered better data, includes 33 chemicals

HAPs Compound Selection

- Evaluated potential toxicity relevant to autism, e.g. neurotoxin, repro toxin, endocrine disrupter ➡ 25
- Assessed the distribution across 1228 census tracts in the region ➡ 19 reasonable variation

  excl. PCBs, HCB, CCl4, chloroform, etc.
- Examined correlation among chemicals ➡ 10 strongly correlated to others (r >0.85)

HAPs Chemical Correlations

- Aromatic solvents (n=5): r's=0.93-0.99
  - also corr with PAHs
- Chlorinated solvents (n=4): 0.46-0.95
  - vinyl Cl lowest r's (~0.5)
- Metals (n=7): 0.23-0.92
  - Hg-Cd, As-Cd, As-Ni, As-Mn
  - Ni also corr w/ some Cl solvents, diesel PM
- Diesel PM corr w/ metals (0.8)

Analytic Methods

- Individual HAPs
  - Mean levels by case-control status
  - Categorize levels (quartiles, percentiles)
  - Valid to examine individually if highly correlated?
- Group HAPs
  - By function, structure, correlation?
  - Little data available to rank by toxicity (for autism)
  - Sum of concentrations not appropriate so created score

HAPs Class Score

- Calculated quartiles for each chemical within controls
- Assigned score of 1-4, corresponding to low-high quartile level, for each chemical to all subjects
- Grouped chemicals into classes such as metals (7), solvents (9), endocrine disruptors (10) or developmental toxicants (7), with some overlap
- Summed quartile scores across chemicals in a class, e.g. range of 7-28, or 9-36, etc., depending on number of chemicals
- Categorized class score into quartiles – median (50^{th} %) of distribution tended to correspond to mid-points of score range

Analytic Methods, cont.

- Calculate odds ratios (OR) for top 2 quartiles

	Case	Control	
Q 1&2	a	b	OR=ad/bc
Q 3 or 4	c	d	

- When disease is fairly rare, OR estimates Rate Ratio (e.g. a/a+b ÷ c/c+d)
- Control for confounders — birth certificate data
- Calculate adjusted OR using logistic regression

Results—Characteristics (%)

Variable	Case (n=284*)	Control (n=657*)
Male	84.9	81.0
Race		
White	46.1	39.6
Hispanic	18.1	26.3
Other	35.8	34.1
Maternal age		
<25	19.0	25.6
25-35	63.7	59.5
>35	17.3	14.9

* N is less for some variables due to missing data

Characteristics—cont.

Variable	Case (n=284*)	Control (n=657*)
Maternal Educ.		
< HS	9.9	17.7
HS grad	24.0	26.2
Some college	33.9	21.5
College grad	32.2	34.6
Parity		
1	43.0	45.4
2-3	51.0	46.6
>3	6.0	8.1

* N is less for some variables due to missing data

Results: Adjusted Odds Ratios (and 95% CL) by Mechanistic Class of HAPs

Class	Moderate (3^{rd} quartile)	High (4^{th} quartile)
EDs (n=10 chem)	1.33 (0.94, 1.88)	1.28 (0.88, 1.85)
Dev. Tox (n=7 chem)	1.13 (0.79, 1.63)	1.40 (0.98, 2.00)

Adjusted for maternal age and education, and child's race.

Results: Adjusted Odds Ratios by Structural Class of HAPs

Class	3rd Quartile	4th Quartile
Metals (incl. 7 metals)	**1.68 (1.17, 2.41)**	**1.50 (1.05, 2.12)**
Aromatic Solvents (incl 5)	0.84 (0.59, 1.20)	1.15 (0.80, 1.65)
Chlorinated solvs (incl 4)	1.33 (0.93, 1.88)	**1.55 (1.08, 2.23)**

Adjusted for maternal age and education, and child's race.

Results: Odds Ratios Adjusted for Multiple Classes of HAPs

Class	Moderate (3rd quartile)	High (4th quartile)
Metals	1.95 (1.23, 3.09)	1.74 (1.01, 3.01)
Aromatic S	0.59 (0.38, 0.89)	0.59 (0.36, 0.99)
Chlorinated solvents	1.15 (0.76, 1.74)	1.39 (0.81, 2.39)

Adjusted for maternal age and education, child's race, and mutually exclusive chemical classes.

Results: AORs for Selected Metals

Metal	3rd quart	4th quart
Cadmium	1.4 (1.0, 2.0)	1.5 (1.1, 2.2)
Lead	0.75 (0.5, 1.1)	1.1 (0.76, 1.5)
Mercury	1.3 (0.91, 1.9)	1.9 (1.4, 2.7)
Nickel	1.1 (0.77, 1.6)	1.5 (1.0, 2.1)

Arsenic, chromium and manganese not elevated.

Results: AOR of Chlorinated Solvents & Others

HAP	3rd quart	4th quart
Meth Cl	1.5 (1.1, 2.1)	1.4 (0.96, 2.0)
Perc	1.3 (0.93, 1.8)	1.1 (0.78, 1.6)
TCE	1.4 (0.96, 2.0)	1.5 (1.0, 2.1)
Vinyl Cl	1.0 (0.69, 1.5)	1.8 (1.3, 2.4)
Diesel PM	1.0 (0.71, 1.5)	1.4 (1.0, 2.0)
7 PAHs	0.99 (0.69, 1.4)	1.1 (0.76, 1.6)

Results: AOR for Higher Exposure

HAP	51-89th%	≥90th percentile
Chromium	0.78 (0.56, 1.1)	1.7 (1.1, 2.7)
Mercury	1.6 (1.2, 2.2)	1.6 (0.96, 2.5)
Meth Cl	1.4 (1.0, 1.9)	1.5 (0.94, 2.5)
TCE	1.3 (0.98, 1.8)	1.7 (1.1, 2.7)
Vinyl Cl	1.3 (0.97, 1.8)	1.7 (1.1, 2.6)
Styrene	0.92 ((0.67, 1.3)	1.6 (1.0, 2.5)
Diesel PM	1.1 (0.78, 1.5)	1.9 (1.2, 2.9)

Results: AORs for Joint Effects

Category	Hg & Cd	Hg & VCl
Both < med	1.0 (ref)	1.0 (ref)
Hg > med	1.6 (0.96, 2.5)	2.0 (1.3, 3.3)
Other > med	1.3 (0.77, 2.2)	1.6 (0.95, 2.6)
Both > median	1.7 (1.2, 2.4)	1.7 (1.2, 2.5)

N's included 332/347 with both low, 103/115 Hg high, 90/105 other high, and 401/389 both high

Results: Mean Levels in ug/m^3 (&SD) by Case/Control Status

Compound	Cases	Controls
Cadmium	0.0001 (0.0002)	0.00009 (0.00005)
Chromium	0.0044 (0.0057)	0.0039 (0.0049)
Lead	0.0093 (0.012)	0.0082 (0.009)
Mercury	0.0008 (0.002)	0.0006 (0.001)
Nickel	0.0043 (0.006)	0.0037 (0.004)
Benzene	1.71 (0.62)	1.66 (0.50)
Toluene	6.98 (4.1)	6.44 (3.0)
TCE	0.19 (0.11)	0.17 (0.08)
Vinyl Cl	0.02 (0.06)	0.01 (0.02)
Diesel PM	3.37 (3.48)	2.89 (2.35)

Limitations

- Under-ascertainment of cases
  - Moved out of state
  - Clinic-only patients not included (small n)
- Exposure surrogate/misclassification
  - Concentration was modeled, not measured
  - Indoor sources of HAPs not included
  - Exposure at birth residence only, for 1996
- Other sources or exposures not included
- Chemicals highly correlated, difficult to separate
- Limited set of possible confounders on BC

Strengths

- Autism Surveillance System
  - Sources provide confidence in Dx
  - Relatively large numbers
  - Will accrue additional data and biomarkers
- Population-based controls
- Uses existing data, so no recall bias and minimizes drop-out
- Attempt to examine prenatal and early life exposure (vs. current or at diagnosis)

Conclusions

- Ecologic data suggest cases more likely to be born in areas with higher estimated **metals** concentration
  - Biologic plausibility, but low concentrations
- Cases also more likely to be born in areas with higher **chlorinated solvent** concentrations
  - very limited prior data
- **Diesel** particulate matter may also be associated with case status, but less prior plausibility
- Further research is necessary to address limitations described and confirm findings

Follow-up Studies

- Other CADDRE sites will use their 1994 surveillance data and link to HAPs database
- Collaborating with CDHS PHT to examine DDS autism cases in S. CA and central valley in relation to HAPs and CHAPIS data,

  1996-98 births
- CA CADDRE seeking funding to examine 1996 multi-source surveillance data and HAPs
- Etiologic studies to look at various sources of mercury and other exposures