

Developmental exposure to environmental pesticides and autism in children

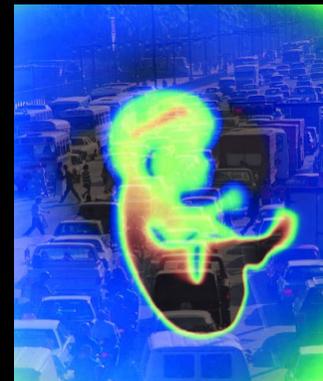
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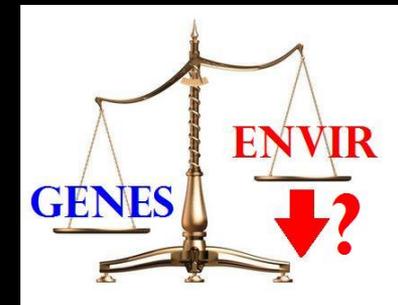
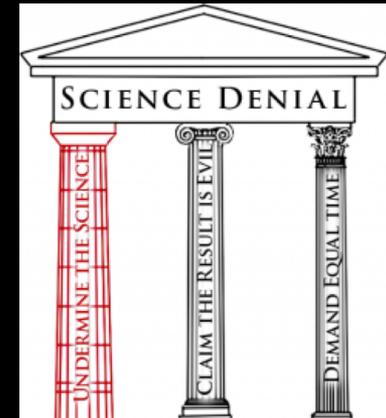
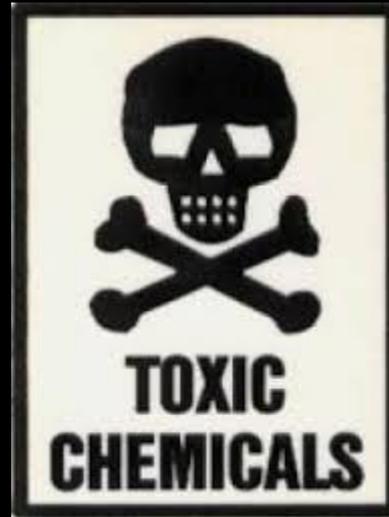
Background



- Autism: severe developmental disorder characterized by atypical socialization and restricted interests and repetitive behaviors
- Prevalence increase not entirely explained by changed diagnostic and ascertainment
- Genes and Environment
- Evidence from twin studies suggest substantial environmental contribution (Hallmeyer et al 2011)
- Still little known on non-genetic factors

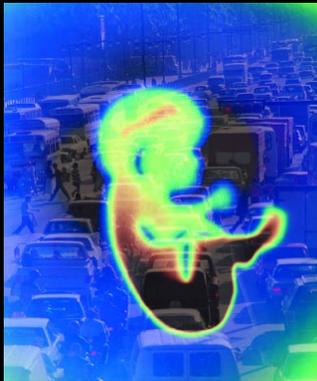


Public concerns ...



Prenatal + early life environment

- Focus on prenatal/perinatal exposure to environmental toxics



What has been done?

Pesticides and neurodevelopment

- Pesticides are designed to be “toxic”
- Over 600 substances and counting ...
- Many can pass the blood/brain and placental barrier
- Accumulating research from different countries and various populations suggested associations of prenatal exposure to pesticides and indicators of neurobehavioral, mental or motor development, low IQ, PDD, ADHD
- Common pesticides in experimental research caused neurodevelopmental impairment



What do we know for ASD?

Developmental exposure suspected to increase risks for autism in children

Limited human research on environmental exposures and ASD to date



What has been done?

Pesticides and ASD

- Major study limitations:
 - small number of cases
 - retrospective exposure assessment (case/control)



Study Objective

- To examine associations between early developmental exposure to ambient pesticides and autism spectrum disorder.

Von Ehrenstein OS, et al. BMJ 2019;364:l962
<http://dx.doi.org/10.1136/bmj.l962>

Study design

- Registry linkage design births 1998-2010
- Autism cases: California Dept. of Developmental Services data records
 - based on the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised* (up to 31 December 2013),
 - additional classification Intellectual disability (“mental retardation”)
 - ~ 80% of all cases captured in CA
 - High specificity (relevant for case/control study)
 - Access to DDS independent of SES, race/ethnicity
 - Linked to birth records (probabilistic based on maternal + child variables, link plus)
- Population controls: birth records
 - Frequency matched 1:10 by sex / birth year

Study population

- Study population in CA Central Valley
“fruit basket”
- ASD cases n= 2,961 (+ID n=445)
- Population controls n= 35,370

Exposure assessment:

GIS-based Residential Ambient Pesticide Estimation System (“GRAPES”)

Pesticide Use Report (PUR) mandatory for agriculture applications in CA

- Pesticide’s active ingredient
- poundage, crop type, and location/date of application

Land Use Survey by CDWR

- County-wide surveys of land use and crop cover

Prenatal / infant exposure estimates

- Exposure estimates based on monthly pounds applied per acre during developmental periods
- 2000 meter buffer of maternal residence
- Exposed: **ever** / never to specific pesticide

Pregnancy / infant pesticide exposure

- Estimates of 3 months pre-pregnancy (captures conception), pregnancy, and first year of life.

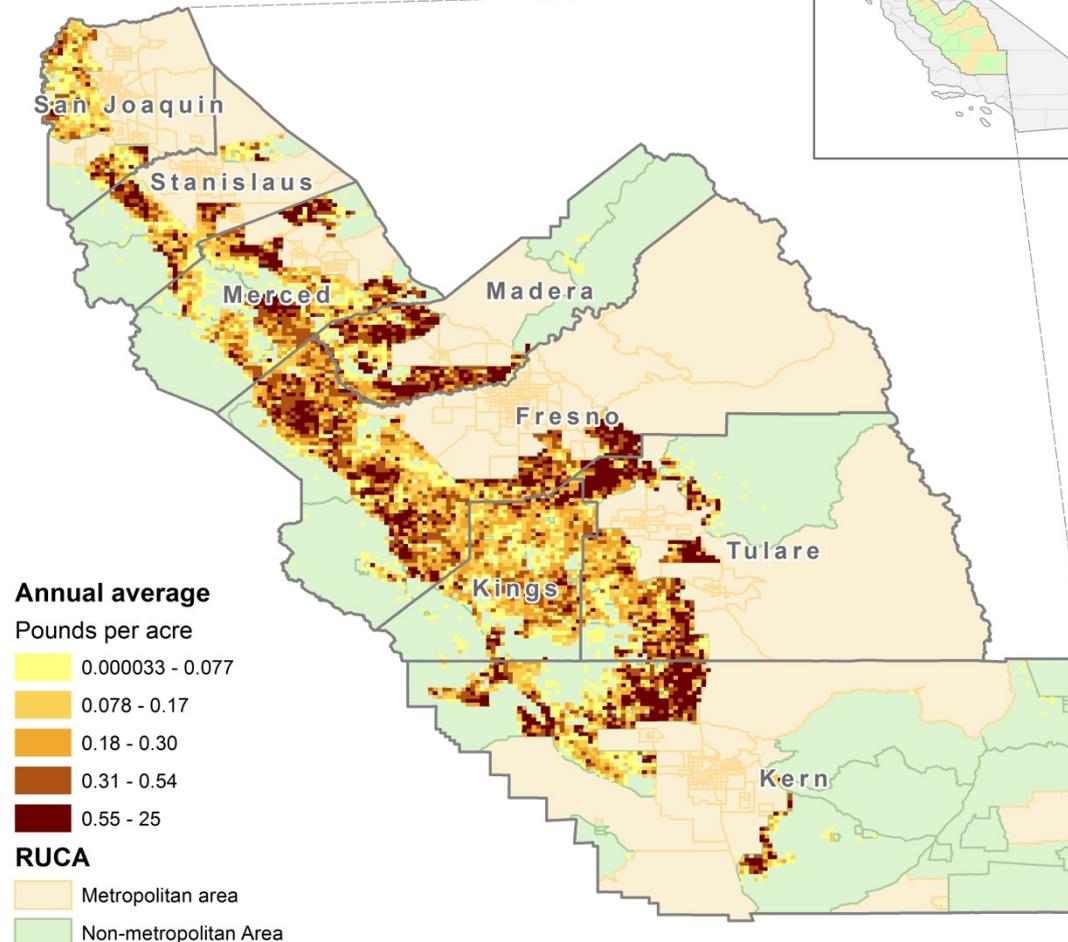
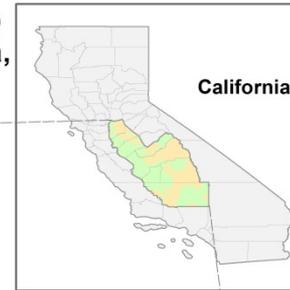
- **A priori decision:**

In our GIS system selection among top 25 used chemicals, select those with previous experimental evidence on neurodevelopmental or neurotoxic effects

11 substances included in analyses

Glyphosate – Central Valley

Chemical Application (Glyphosate, isopropylamine salt)
in San Joaquin Valley Non-metropolitan Area, California,
1998-2010



Analyses

- Multivariable logistic regression
- Adjusted for sex + birth year (matching variables), maternal education, age, regional center, spatial variable for SES (census based index)

RESULTS

Characteristics Study Population by ASD

	ASD (all)		ASD with ID		ASD without ID		Controls	
	N=2,961	%	N=445	%	N=2,516	%	N=35,370	%
Sex								
Males	2,403	81.2	354	79.6	2,049	81.4	29,225	82.6
Females	558	18.8	91	20.4	467	18.6	6,145	17.4
Year of Birth								
1998-2004	1,033	34.9	243	54.6	790	31.4	14,390	40.7
2005-2010	1,928	65.1	202	45.4	1,726	68.6	20,980	59.3
Maternal Age								
19 or less	233	7.9	38	8.5	195	7.8	4,931	13.9
20-24	808	27.3	136	30.6	672	26.7	10,253	29.0
25-29	884	29.9	117	26.3	767	30.5	9,779	27.6
30-34	592	20.0	96	21.6	496	19.7	6,712	19.0
35 and older	443	15.0	58	13.0	385	15.3	3,694	10.4
Missing	1	0.0	.	.	1	0.0	1	0.0

Characteristics Study Population by ASD

	ASD (all)		ASD with ID		ASD without ID		Controls	
	N=	%	N=	%	N=	%	N=	%
Race/Ethnicity	2,961		445		2,516		35,370	
White	1,100	37.1	166	37.3	934	37.1	9,943	28.1
Latinx	1,424	48.1	205	46.1	1,219	48.4	20,802	58.8
Black/AA	149	5.0	33	7.4	116	4.6	1,562	4.4
Asian/PI	214	7.2	35	7.9	179	7.1	2,155	6.1
Others	74	2.5	6	1.3	68	2.7	908	2.6
US Born								
Yes	2,133	72.0	314	70.6	1,819	72.3	22,152	62.6
No	828	28.0	131	29.4	697	27.7	13,209	37.3
Missing	9	0.0
Education								
8th grade	174	5.9	34	7.6	140	5.6	4,518	12.8
9th to 12th grade	435	14.7	69	15.5	366	14.5	7,583	21.4
High school	937	31.6	152	34.2	785	31.2	10,909	30.8
Less than college	923	31.2	131	29.4	792	31.5	7,854	22.2
College or more	455	15.4	48	10.8	407	16.2	3,925	11.1
Missing	37	1.2	11	2.5	26	1.0	581	1.6

ASD all and ASD with ID Comorbidity Co-adjusted for Developmental Period of Exposure (3-Month Pre-pregnancy, Pregnancy, First Year of Life)

	ASD (all)						ASD with ID					
	3-month pre-pregnancy		Pregnancy		First year of life		3-month pre-pregnancy		Pregnancy		First year of life	
Pesticide	OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI	OR ¹	95% CI
Glyphosates²	0.97	(0.9, 1.1)	1.11	(0.96, 1.3)	1.09	(0.9, 1.3)	0.96	(0.74, 1.26)	0.96	(0.66, 1.40)	1.60	(1.09, 2.34)
Chlorpyrifos	0.92	(0.8, 1.0)	1.15	(1.0, 1.3)	1.04	(0.9, 1.2)	0.80	(0.64, 1.00)	1.18	(0.88, 1.59)	1.30	(0.96, 1.76)
Diazinon	0.92	(0.8, 1.1)	1.14	(1.0, 1.3)	0.99	(0.9, 1.1)	0.86	(0.65, 1.13)	1.18	(0.90, 1.54)	1.45	(1.11, 1.89)
Acephate	1.09	(0.9, 1.3)	1.10	(0.95, 1.3)	0.94	(0.8, 1.1)	1.40	(0.97, 2.03)	1.07	(0.77, 1.50)	1.10	(0.80, 1.50)
Malathion	0.94	(0.8, 1.1)	1.08	(0.97, 1.2)	1.09	(0.98, 1.2)	0.72	(0.50, 1.03)	1.05	(0.81, 1.37)	1.29	(1.00, 1.65)
Permethrin	1.07	(0.95, 1.2)	1.04	(0.9, 1.2)	1.04	(0.9, 1.16)	1.07	(0.82, 1.39)	1.24	(0.95, 1.62)	1.23	(0.94, 1.59)
Bifenthrin	1.10	(0.97, 1.3)	0.96	(0.9, 1.1)	1.09	(0.98, 1.2)	1.18	(0.85, 1.64)	0.92	(0.69, 1.22)	1.33	(1.03, 1.72)
Methyl bromide	1.15	(1.0, 1.3)	0.95	(0.9, 1.1)	1.06	(0.9, 1.2)	0.97	(0.72, 1.31)	1.20	(0.92, 1.57)	1.21	(0.94, 1.57)
Imidacloprid	1.09	(0.98, 1.2)	0.92	(0.8, 1.0)	0.97	(0.9, 1.1)	1.02	(0.79, 1.33)	0.88	(0.68, 1.14)	1.08	(0.84, 1.39)
Avermectin	1.03	(0.9, 1.13)	1.14	(1.0, 1.3)	0.97	(0.9, 1.1)	1.08	(0.85, 1.38)	0.98	(0.75, 1.26)	1.08	(0.83, 1.41)
Myclobutanil	0.97	(0.9, 1.1)	1.06	(0.96, 1.1)	0.98	(0.9, 1.1)	1.06	(0.83, 1.35)	1.23	(0.95, 1.58)	1.09	(0.84, 1.41)

Pesticides in pregnancy/infancy and all ASD cases combined

adjusted for year of birth, sex, maternal race/ethnicity, maternal age, maternal education, NOx (CALINE4); pesticide exposure defined as “ever vs. never” (single substance and co-adjusted)

Pesticide	Pregnancy					First year of life				
	Case/Control n*	OR ¹	95% CI	OR ²	95% CI	Case/Control n*	OR ¹	95% CI	OR ²	95% CI
Glyphosate³	2293/26660	1.16	(1.06, 1.27)	1.13	(1.00, 1.27)	2256/26390	1.15	(1.05, 1.26)	1.18	(1.05, 1.33)
Chlorpyrifos	1799/20914	1.13	(1.05, 1.23)	1.06	(0.95, 1.18)	1876/22125	1.10	(1.02, 1.20)	1.02	(0.91, 1.14)
Diazinon	764/9176	1.11	(1.01, 1.21)	1.09	(0.99, 1.21)	787/9890	1.04	(0.95, 1.14)	1.00	(0.90, 1.10)
Acephate	341/4047	1.09	(0.97, 1.23)	1.06	(0.93, 1.19)	381/4783	1.00	(0.90, 1.13)	0.97	(0.86, 1.09)
Malathion	642/7277	1.11	(1.01, 1.22)	1.05	(0.95, 1.16)	784/8911	1.11	(1.02, 1.21)	1.07	(0.97, 1.18)
Permethrin	930/10773	1.10	(1.01, 1.20)	1.04	(0.95, 1.14)	1047/12129	1.10	(1.01, 1.19)	1.05	(0.96, 1.15)
Bifenthrin	638/7300	1.03	(0.94, 1.13)	0.96	(0.87, 1.07)	886/9671	1.09	(1.00, 1.19)	1.06	(0.97, 1.16)
Methyl bromide	657/8085	1.03	(0.94, 1.13)	0.95	(0.86, 1.06)	761/8986	1.08	(0.99, 1.18)	1.05	(0.96, 1.16)
Imidacloprid	1123/14490	0.93	(0.86, 1.00)	0.81	(0.73, 0.88)	1323/16771	0.95	(0.88, 1.02)	0.85	(0.78, 0.94)
Avermectin	1513/17212	1.12	(1.04, 1.22)	1.10	(1.00, 1.21)	1719/20100	1.07	(0.99, 1.15)	1.00	(0.90, 1.11)
Myclobutanil	1254/15222	1.04	(0.96, 1.12)	0.99	(0.90, 1.09)	1375/16871	1.01	(0.93, 1.09)	0.95	(0.86, 1.04)

Pesticides in pregnancy/infancy and ASD with ID

adjusted for year of birth, sex, maternal race/ethnicity, maternal age, maternal education, NOx (CALINE4); pesticide exposure defined as “ever vs. never” (single substance and co-adjusted)

Pesticide	Pregnancy					First year of life				
	Case/ Control n*	OR ¹	95% CI	OR ²	95% CI	Case/ Control n*	OR ¹	95% CI	OR ²	95% CI
Glyphosate³	351/26660	1.33	(1.05, 1.69)	1.13	(0.84, 1.53)	360/26390	1.51	(1.18, 1.92)	1.40	(1.03, 1.90)
Chlorpyrifos	284/20914	1.27	(1.04, 1.56)	1.05	(0.81, 1.36)	301/22125	1.31	(1.07, 1.61)	0.97	(0.74, 1.28)
Diazinon	152/9176	1.41	(1.15, 1.73)	1.22	(0.97, 1.54)	169/9890	1.51	(1.23, 1.85)	1.32	(1.05, 1.67)
Acephate	65/4047	1.26	(0.95, 1.65)	1.20	(0.91, 1.58)	74/4783	1.25	(0.96, 1.62)	1.17	(0.90, 1.52)
Malathion	99/7277	1.12	(0.89, 1.41)	0.95	(0.75, 1.21)	125/8911	1.23	(0.99, 1.52)	1.02	(0.81, 1.28)
Permethrin	175/10773	1.46	(1.20, 1.78)	1.35	(1.08, 1.69)	191/12129	1.44	(1.19, 1.75)	1.25	(1.00, 1.57)
Bifenthrin	91/7300	1.13	(0.89, 1.43)	1.03	(0.81, 1.32)	134/9671	1.33	(1.08, 1.64)	1.23	(0.98, 1.54)
Methyl bromide	133/8085	1.33	(1.07, 1.64)	1.11	(0.88, 1.41)	148/8986	1.33	(1.08, 1.63)	1.12	(0.89, 1.41)
Imidacloprid	163/14490	0.93	(0.76, 1.13)	0.72	(0.58, 0.90)	198/16771	1.01	(0.83, 1.22)	0.77	(0.61, 0.96)
Avermectin	209/17212	1.05	(0.87, 1.28)	0.85	(0.67, 1.08)	247/20100	1.09	(0.90, 1.33)	0.78	(0.61, 1.00)
Myclobutanil	217/15222	1.32	(1.09, 1.60)	1.16	(0.92, 1.46)	232/16871	1.27	(1.05, 1.54)	1.01	(0.80, 1.28)

Summary of results

- small to moderately increased risks for ASD with prenatal exposure to organophosphates chlorpyrifos, diazinon, and malathion, the pyrethroids permethrin and bifenthrin, as well as to glyphosate, avermectin, and methyl bromide
- ASD + ID pronounced risks for exposures during the first year of life.

Strengths & Limitations

Strengths

- GIS tool (not relying on self report)
- Registry based (avoids self selection + large population)
- pesticides selected for analysis a priori based on experimental evidence of neurodevelopmental toxicity.

Limitations

- Exposure misclassification
- Lack of data pesticides from other sources

Conclusions

- Offspring's ASD risk increases following prenatal exposure to common ambient pesticides compared with offspring of women from the same agricultural region without such exposure within 2000m of their residence during pregnancy
- Infant exposure may further increase risks for ASD with comorbid intellectual disability.

Conclusions

- Exposure of pregnant women and infants to ambient pesticides with a potential neurodevelopmental toxicity mode of action should be avoided as a preventive measure against autism spectrum disorder
- Public health risk assessment and regulation should go well beyond a “one disease at a time” approach

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