Time to act: chlorpyrifos and autism

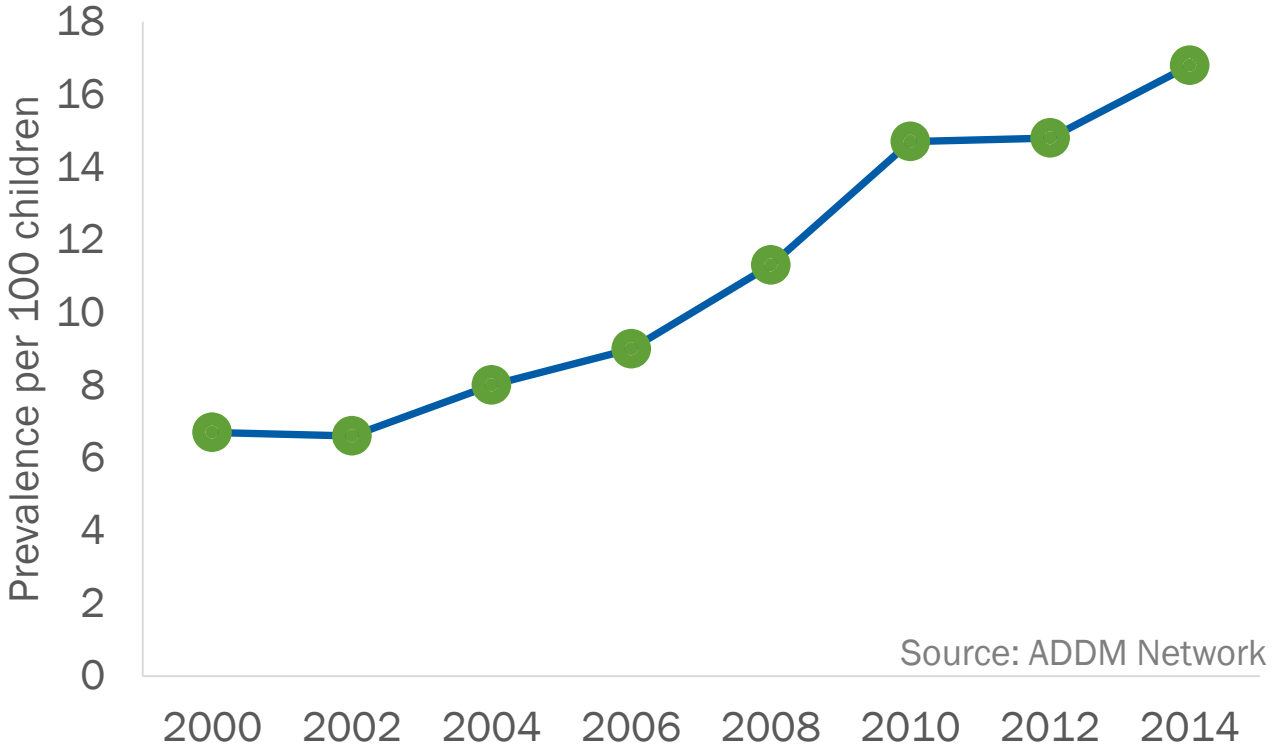
Katherine Pelch, PhD

TEDX THE ENDOCRINE DISRUPTION EXCHANGE

May 14, 2019

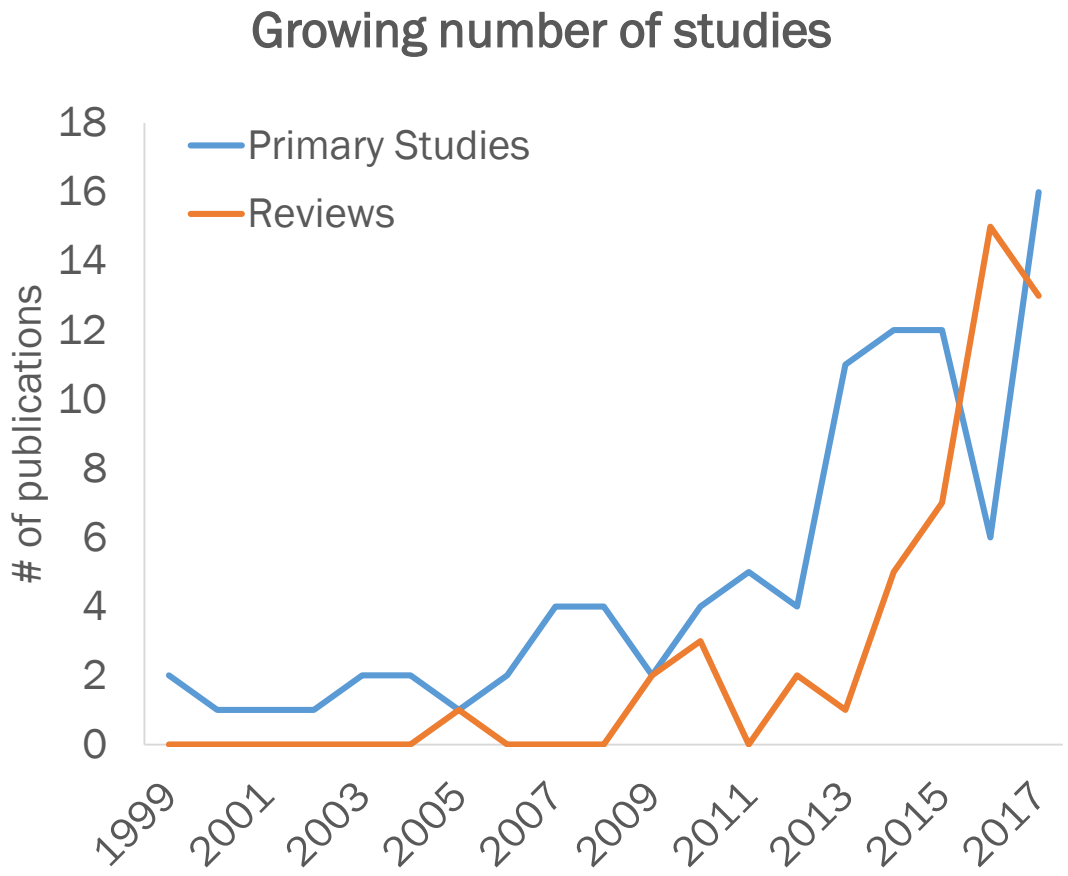
HEAL

The prevalence of autism has been increasing



https://www.cdc.gov/ncbddd/autism/data.html

Maybe its environmental?



- What chemicals have been studied?
- What should be prioritized for future research?
- Scoping reviews do not reach conclusions about hazards or risks

Considering all the evidence

Animal models of autism

Reciprocal social communicative behaviors

- three chambered test
- open field test with social component
- ultrasonic vocalizations

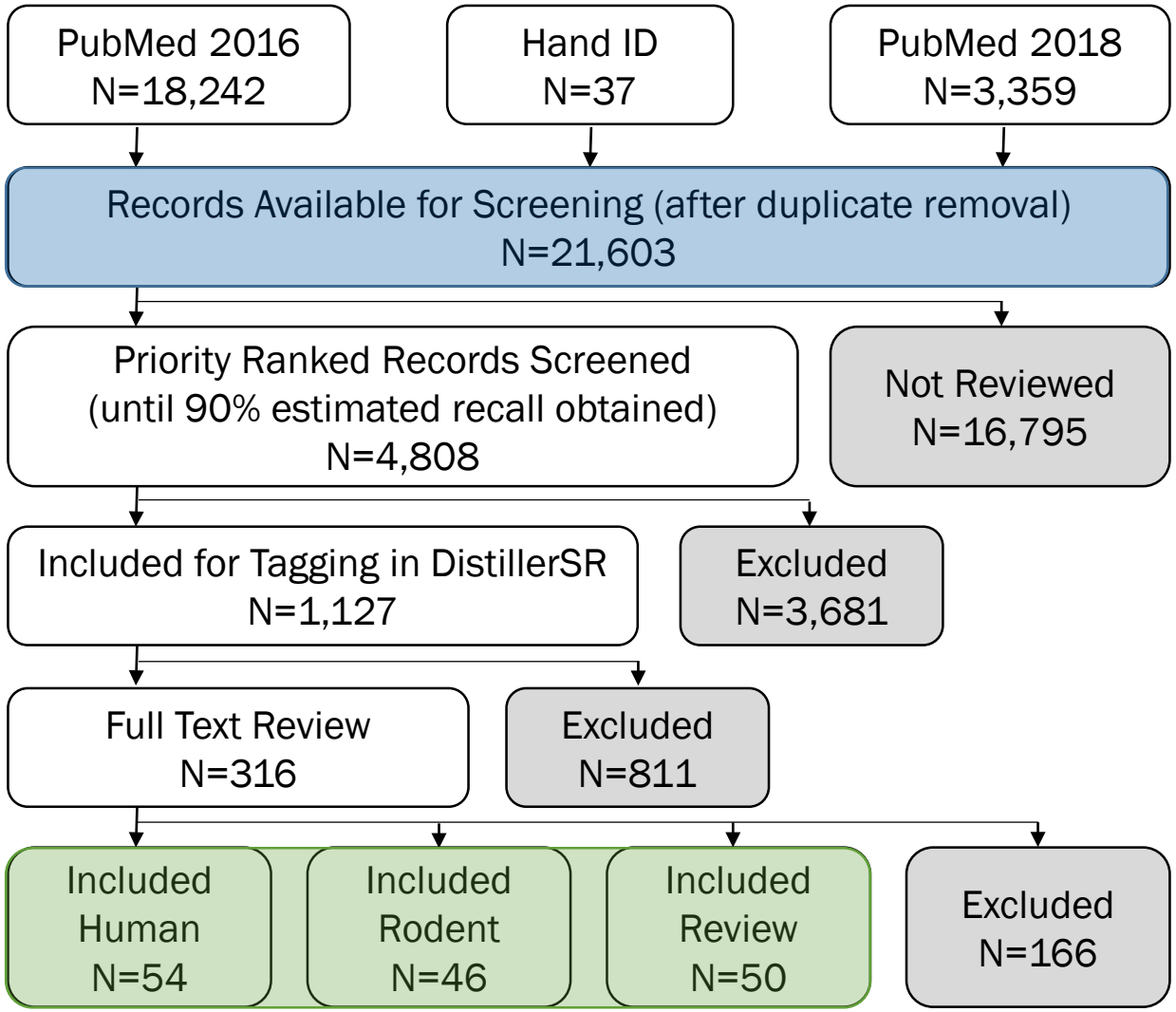
Repetitive and stereotyped behaviors

- Compulsively gnawing, circling, or rearing
- T, Y, or Morris water mazes

Digging in to the studies

- Overview of the scoping review
- Demonstration of interactive database
- Explore the chlorpyrifos studies

Identifying studies for the review



Retrieved
> 21k Papers

150 Included

Data extraction and coding of human studies

- Which chemicals were evaluated
- How autism cases were defined
- Study type
- Number of participants
- Study location
- Cohort name
- Birth years of study participants
- Age of diagnosis
- When was exposure measured
- How exposure was assessed

Human evidence overview

of Studies
1 14

How Cases of Autism Were Defined

	Diagnostic Definition	Diagnostic Tools	Screening Tools	Grand Total
Grand Total	**33**	**23**	**26**	**54**
Air Pollution	14	13	11	**22**
Metals & Semi-metals	14	7	7	**19**
Industrial Chemicals & Byproducts	11	3	6	**16**
Pesticides	6	6	6	**12**
Miscellaneous	4	3	2	**5**
Plastics & Plastic Additives	1		3	**4**

https://public.tableau.com/profile/the.endocrine.disruption.exchange#!/vizhome/Fig3_Enviornmentalchemicalsandautism-epidemiologicaldata/Interactive

THE ENDOCRINE DISRUPTION EXCHANGE

# of Studies
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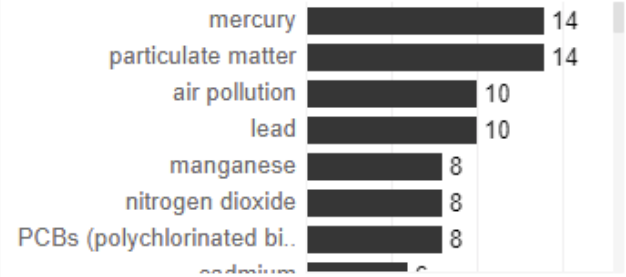
Exposure



Study Details

Abdullah et al. 2012
Adams et al. 2007
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Becerra et al. 2013
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Dickerson et al. 2015
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Geier et al. 2009
Gong et al. 2014
Gong et al. 2017
Goodrich et al. 2018

Study Type

THE ENDOCRINE DISRUPTION EXCHANGE

# of Studies
1 9

		How Cases of Autism Were Defined			
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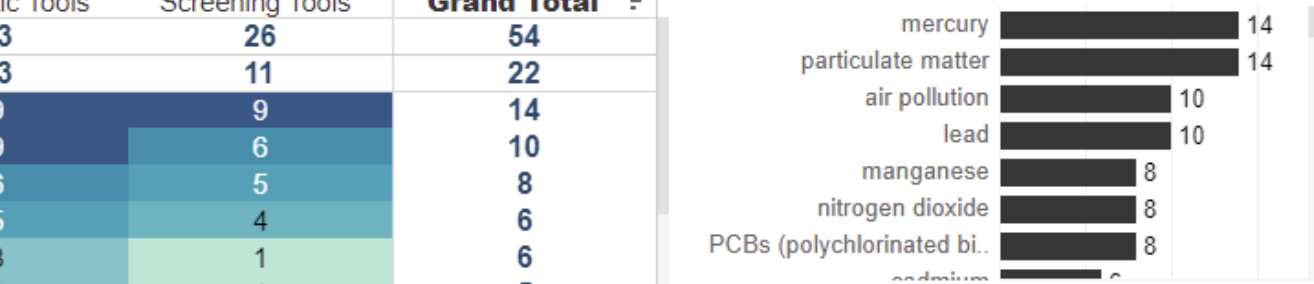
Grand Total		**33**	**23**	**26**	**54**
Air Pollutants	**Total**	**14**	**13**	**11**	**22**
	particulate matter	8	9	9	14
	air pollution	4	9	6	10
	nitrogen dioxide	3	6	5	8
	ozone	2	5	4	6
	lead	6	3	1	6
	manganese	5	3	1	5
	cadmium	5	3	1	5
	nitrogen oxides	1	3	4	5
	trichloroethylene	4	2	1	4
	nickel	4	2	1	4
	methylene chloride	4	2	1	4
	mercury	4	2	1	4
	chromium	4	2	1	4
	arsenic	4	2	1	4
	vinyl chloride	3	2	1	3
	styrene	3	2	1	3
	xylenes	3	1	1	3
	toluene	3	1	1	3
	perchloroethylene	3	1	1	3
	PAHs (polycyclic aromati..	3	1	1	3
	ethylbenzene	3	1	1	3
	benzene	3	1	1	3
	selenium	2	1	1	2
	metals	2	2		2
	hydrazine	2	1	1	2
	hexane	2	1	1	2
	ethylene oxide	2	1	1	2
	methanol	1	1	1	1

Exposure



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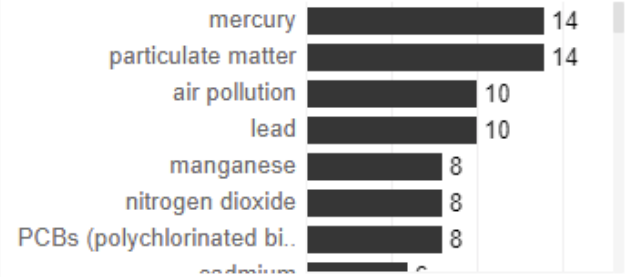

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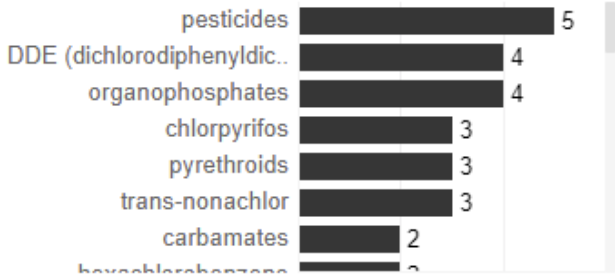


Study Details

Braun et al. 2014
Cheslack-Postava et al. 2013
Keil et al. 2014
Lyall et al. 2017a
McCanlies et al. 2012
Millenson et al. 2017
Roberts et al. 2007
Schmidt et al. 2016
Schmidt et al. 2017
Shelton et al. 2014
Traglia et al. 2017
Windham et al. 2013

Study Type

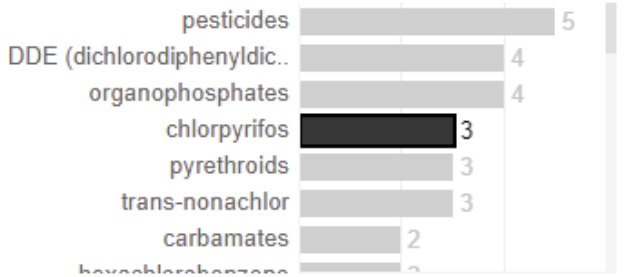
nested case-control
population based case-control
prospective cohort

# of Studies
1 2

How Cases of Autism Were Defined

	Diagnostic Definition	Diagnostic Tools	Screening Tools	Grand Total
Grand Total	1	2	2	3
Pesticides	1	2	2	**3**

Exposure



Study Details

Roberts et al. 2007
Schmidt et al. 2017
Shelton et al. 2014

Study Type

population based case-control

TEDX THE ENDOCRINE DISRUPTION EXCHANGE

# of Studies
1 2

How Cases of Autism Were Defined

Grand Total	Diagnostic Definition	Diagnostic Tools	Screening Tools	Grand Total
Pesticides				

Roberts et al. 2007

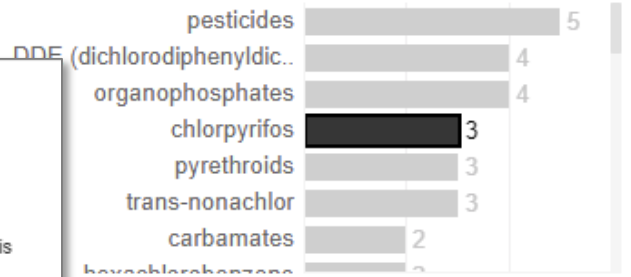
Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley

Ambient levels of pesticides ("pesticides drift") are detectable at residences near agricultural field sites. Our goal was to evaluate the hypothesis that maternal residence near agricultural pesticides applications during key periods of gestation could be associated with the development of autism spectrum disorders (ASD) in children. We identified 465 children with ASD born during 1996-1998 using the California Department of Developmental Services electronic files, and matched them by maternal date of last menstrual period to 6, 975 live-born, normal-birth-weight, term infants as controls. We determined proximity to pesticides applications using California Department of pesticides Regulation records refined using Department of Water Resources land use polygons. A staged analytic design applying a priori criteria to the results of conditional logistic regressions was employed to exclude associations likely due to multiple testing error. Of 249 unique hypotheses, four that described organochlorine pesticides applications--specifically those of dicofol and endosulfan--occurring during the period immediately before and concurrent with central nervous system embryogenesis (clinical weeks 1 through 8) met a priori criteria and were unlikely to be a result of multiple testing. Multivariate a posteriori models comparing children of mothers living within 500 m of field sites with the highest nonzero quartile of organochlorine poundage to those with mothers not living near field sites suggested an odds ratio for ASD of 6.1 (95% confidence interval, 2.4-15.3). ASD risk increased with the poundage of organochlorine applied and decreased with distance from field sites. The association between residential proximity to organochlorine pesticides applications during gestation and ASD among children should be further studied.

Study type:	population based case-control
Study size:	7,440
Location of study:	Central Valley, California
Study name:	no
Birth years of study participants:	1996-1998
Age of diagnosis:	not provided
Method of diagnosis/case definition:	DSMIV/DSMV, Pediatrician or psychiatrist diagnosis- method undescribed
What was exposure:	1,3-dichloropropene, avermectins, bifenthrin, bromacil acid, chloropicrin, chlorpyrifos, cholinesterase inhibitors, copper-containing compounds, copper sulfates, cypermethrin, dazomet, dicofol, diuron, endosulfan, fenarimol, fumigants, glyphosate, halogenated organics, metam-sodium, methyl bromide, molinate, myclobutanil, N-methyl carbamates, norflurazon, organochlorines, organophosphates, oxadiazon, paraquat, pyrethroids, thiocarbamates, trifluralin
Nature of expsoure:	general population
When was exposure measured:	gestation

Link: https://www.ncbi.nlm.nih.gov/pubmed/17938740

Exposure



dy Details

erts et al. 2007
midt et al. 2017
lton et al. 2014

dy Type

population based case-control

Data extraction and coding of animal studies

- Which chemicals were evaluated
- Autism relevant behaviors
  - Reciprocal social communicative behaviors
  - Repetitive and stereotyped behaviors
  - Comorbid behaviors
  - Mechanistic outcomes

- Species & strain
- Exposure timing
- Route of exposure
- Outcome timing

Animal evidence overview

of Studies
1 10

	Reciprocal Social Communicative Behaviors	Repetitive & Stereotyped Behaviors	Comorbid Behaviors	Mechanistic Outcomes	Grand Total
Grand Total	19	23	22	12	36
Pesticides	5	10	9	2	14
Metals	3	6	5	4	8
Industrial Chemicals & Byproducts	4	1	2	3	5
Air Pollutants	4	3	4	1	4
Plastics & Plastic Additives	1	3	2	2	3
Preservatives	2				2

https://public.tableau.com/profile/the.endocrine.disruption.exchange#!/vizhome/SupplementalFigure2_Environmentalchemicalsandautism-rodentdata/Interactive

Summary of results

- 100 primary studies + 50 reviews identified
- 142 exposures in epi studies, 25 exposures in rodent studies

- Most studied chemicals
  - Epi studies: mercury (n=14), particulate matter (n=14), lead (n=10)
  - Rodent studies: chlorpyrifos (n=9),mercury (n=6), lead (n=4)

Summary of our main conclusions

- Human epidemiological studies
  - Improved reporting
  - More prospective studies
  - More diversity in study location
- Experimental animal studies
  - Harmonization with epi studies in chemicals evaluated
  - Improved model characterization
- Reviews
  - Evaluation of both epi and animal model data
  - Systematic reviews of chlorpyrifos, lead, PCBs

Chlorpyrifos

- Organophosphate insecticide
- Termites, mosquitoes, roundworms
- Use in agriculture
  - Food crops – corn, soy beans, row crops
  - Cattle ear tags
- Non ag uses – golf courses

https://www.epa.gov/ingredients-used-pesticide-products/chlorpyrifos

Why did we call out chlorpyrifos?

- Both human and animal studies were identified
- Animal studies included both types of behaviors in same study
- Increased concern due to existing exposures and health concerns

Human autism studies

Study	# Participants	Study Name	# of Exposures Assessed	Exposure assessment	Result
Roberts et al. 2007	7,440	-	10 functional categories + 19 specific chemicals	Residence addresses at time of birth	NS
Shelton et al. 2014	802	CHARGE	5	Residence addresses at 3 months prior to conception to time of birth	aOR = 1.14 95% CI: 1.0, 1.32
Schmidt et al. 2017	516	CHARGE	6	Residence addresses at 3 months prior to conception to time of birth	OR=2.3 95% CI: 0.98, 5.3

Rodent autism studies

De Felice et al. 2015	Mouse	S C S S R
Lan et al. 2017	Mouse	S S S R
Laviola et al. 2006	Mouse	S M C R
Maurissen et al. 2000	Rat	R R
Mullen et al. 2013	Mouse	S M S S C M R
Riceerri et al. 2003	Mouse	S S M S C C
Venerosi et al. 2006	Mouse	S S S
Venerosi et al. 2008	Mouse	S S C
Venerosi et al. 2009	Mouse	S C

S=social communication behavior
R=repetitive behavior
C=comorbid behavior
M=mechanistic outcome

Rodent autism studies

De Felice et al. 2015	Mouse	S C S S R	Not associated with autism phenotype
Lan et al. 2017	Mouse	S S S R	**Reduced sociability**
Laviola et al. 2006	Mouse	S M C R	Gene x exposure effects
Maurissen et al. 2000	Rat	R R	Not associated with autism phenotype
Mullen et al. 2013	Mouse	S M S S C M R	Gene x exposure effects
Riceerri et al. 2003	Mouse	S S M S C C	Not associated with autism phenotype
Venerosi et al. 2006	Mouse	S S S	Increased USV and socialability
Venerosi et al. 2008	Mouse	S S C	No effect on social preference
Venerosi et al. 2009	Mouse	S C	**Reduced USV**

S=social communication behavior
R=repetitive behavior
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M=mechanistic outcome

Why a systematic review

- Reaches a hazard conclusion
- Assess confidence in body of evidence
- Excludes potentially biased studies
- Can include meta-analysis

www.tedx.org

Carol Kwiatkowski
Executive Director

Christina Ribbens
Business Manager

Kim Schultz
Oil & Gas Program Coordinator

Ashley Bolden

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Our paper is available open access at:
https://ehp.niehs.nih.gov/doi/10.1289/EHP4386