South Texas Autism Research (STAR)

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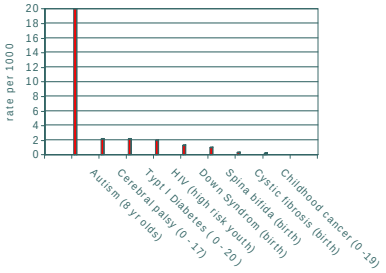
Contextual Overview of Autism

- The Autism Epidemic
- Environmental Research examples
- Biology and Environment Interaction
- Current Research Work leading to Prevention
- Questions

The Problem

- Every 5 minutes, someone is being diagnosed with debilitating deficits in:
  - communication & language use
  - social interaction and behavior
  - stereotypic or repetitive movements
- No established biological markers – behaviorally diagnosed
- Acquired while in-utero or up to 18 months old.
- A common disease of unknown cause, few treatment options, and too few community/educational/medical resources

Autism more prevalent than other top childhood diseases

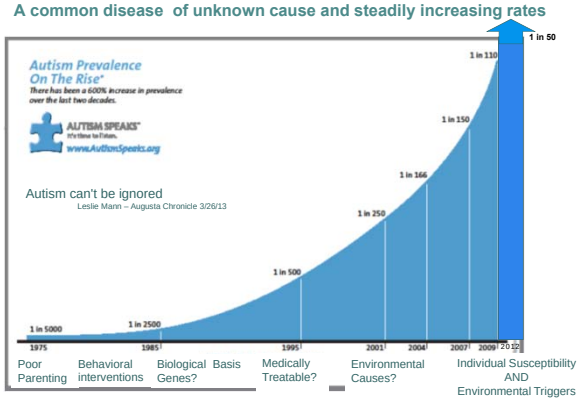


Estimates are derived from NIH and CDC sources

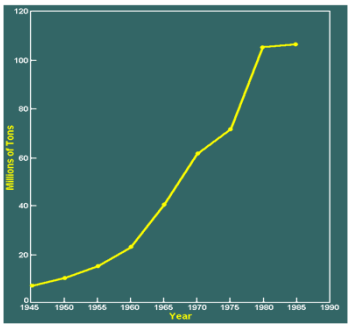
A great social cost

- Lifetime cost of caring for a child with autism ranges from $3.5 to $5 million.
- United States is facing approximately $137 billion annually in costs for autism.
- $200-300 billion dollars in 10 years

A common disease of unknown cause and steadily increasing rates



Synthetic organic chemical production, United States, 1945 - 1985



Source: U.S. Intern. Trade Commission

Chemical Intolerance

- About 5-15% of people report multiple chemical intolerances
- "Do you consider yourself sensitive to everyday chemicals like those in household cleaning supplies, paints, perfumes, soaps, garden sprays, or things like that?" (15%)
- Frequently, intolerances also include foods, medications, alcoholic beverages, and caffeine.

Toxicant-induced Loss of Tolerance (TILT) involves:

- Initiating toxic exposure(s)
- Fundamental breakdown in innate tolerance
- Adverse and amplified responses to *previously tolerated* and structurally diverse exposures including common chemicals, foods, drugs, alcoholic beverages, caffeine, and tobacco smoke

Evidence for Toxicant-induced Loss of Tolerance

"Our results suggest that serious and multiple dysfunctions of *chemical defensive system* found in these patients may mainly not depend on genetic defects, but instead may rely on non-genetic modifications of metabolizing/antioxidant enzyme expression and/or activity…."

(De Luca et al. 2010)

e.g., epigenetic changes

How are chemical intolerances and autism alike?

Symptoms/Intolerances	CI	Autism
Multisystem symptoms, especially neurocognitive, mood, GI	X	X
Can be initiated by pesticides and other toxicants	X	X
Food intolerances	X	X
Food cravings	X	X
Chemical intolerances	X	X
Drug allergies/adverse drug reactions	X	X

Chemical Intolerance and Autism Study

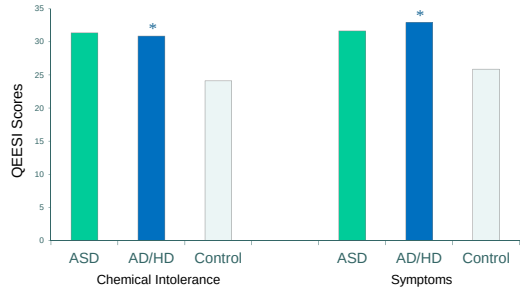
Are mothers of children with autism and/or AD/HD more chemically intolerant than mothers of neurotypical children?

National online survey >600 mothers

AD/HD: professional diagnosis, DSM criteria

Autism: parental report of professional diagnosis

Mothers of children with Autism (n=282), ADHD (n=258) and Controls (n=93)



* Statistical Significance

Chemical Intolerance vs. Autism

- Exposures in chemically susceptible adults may lead to Toxicant-induced Loss of Tolerance (TILT)
- Exposures *in utero* or in children affect their developing nervous, immune, and endocrine systems causing permanent changes.

Specific effects may depend on:

1. Nature of chemicals
2. Timing of exposure
3. Dose
4. Susceptibility of the individual

Chemicals Associated with Autism

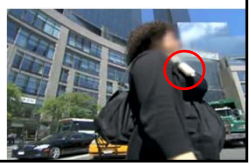
Top 10

- Lead
- Methylmercury
- PCBs
- Organophosphate pesticides
- Organochlorine pesticides
- Endocrine disruptors
- Automotive exhaust
- Polycyclic aromatic hydrocarbons
- Brominated flame retardants
- Perfluorinated compounds

A Comparative Study of Pesticide Use in Homes of Pregnant Women Living at the Texas-Mexico Border and in New York City

Beatriz Tapia, Patsy G. Bortoni, Enrique Escobedo, David Camann, Lynne P. Heilbrun, Robin M. Whyatt, Claudia S. Miller

Used air monitoring equipment to measure:
- Organophosphates
- Synthetic Pyrethroids
- Organochlorines
- Carbamates
- Fungicides
- Herbicides



Pesticide comparison: New York City vs. South Texas

Pesticide Exposure in South Texas

Study Population:

25 Pregnant Hispanic Women 18-35 y/o, 30-34 weeks gestation, recruited from maternity clinics in Hidalgo County

Inclusion criteria:

- Stable residency within drivable distance
- Non smoker/no illicit drugs/moderate drinker
- No major health problems (DM, AHT, HIV, NS)
- Homemakers who spend majority day in home

Pesticide Exposure in South Texas

Methods:

- Questionnaire covering demographics, home characteristics, residential history, and lifestyle
- Installation of PUF sampler in home
- two weeks later - f/u questionnaire,
- all samples (air and dust) sent for analysis

Pesticides analyzed in home air and dust (~45 total)

Organophosphates
- Azinophos-methyl
- **Chlorpyrifos**
- **Diazinon**
- Ethyl Parathion
- **Malathion**
- Methyl parathion
- Propetamophos

Carbamates
- Bendiocarb
- Carbaryl
- Carbofuran
- Fenoxycarb (also IGR)
- **Propoxur**

Synergists
- **MGK 264**
- **Piperonyl butoxide**

Fungicides
- Captan

Synthetic Pyrethroids
- Bioallethrin
- **Bifenthrin**
- **Cis-permethrin**
- Cyfluthrin
- **Cypermethrin**
- Deltamethrin/tralomethrin
- Fenvalerate
- Lamda-cyhalothrin
- Prallethrin
- Sumithrin
- Tetramethrin
- **Trans-permethrin**

Pesticides analyzed (continued)

Insect Growth Retardant (IGR)
- Fenoxycarb (also carbamate)
- Hydroprene
- Methoprene

Organochlorines
- 4,4'-DDD
- 4,4,'-DDE
- 4,4'-DDT
- **Alpha-chlordane**
- Dieldrin
- **Gamma-chlordane**
- Heptachlor
- Lindane

Herbicides
- Atrazine
- Metolachlor
- Pendimethalin
- Simazinc
- **Trifluralin**

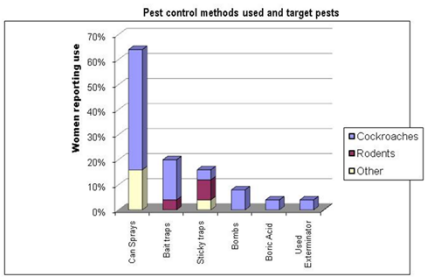
Others
- Fipronil
- **Ortho-phenylphenol**
- Sulfluramid

Pesticide Exposure in South Texas

Results:

- 68% of these households reported pesticide use vs. 85% of previously studied NYC households
- 35% used two or more pest control methods
- 14 pesticides detected including several organophosphates: ortho-phenylphenol in 92% of home air samples, followed by chlorpyrifos in 80%, propoxur in 76%, diazinon in 72%, and trifluralin in 60%

Pest control methods used and target pests for Texas women who reported pest control measures used in their homes during pregnancy. N=17



Conclusions

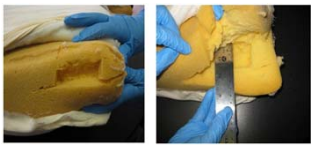
Result cont.

- Household pesticide exposures during pregnancy in South Texas were similar to those in NYC
- In both Hidalgo County and NYC, the principal reason for organophosphate pesticide use were roaches
- Offspring of mothers exposed in NYC showed significant neurodevelopmental problems
- Neurodevelopmental studies among South Texas children exposed to pesticides are lacking

Case Study

- 36 year old woman with no prior problems
- Exposed to Dursban (Chlorpyrifos) in 2000
- TILT
- Multiple system symptoms
- Child with AD/HD
- Child with PDD/NOS
- History of extermination services > 10 years

Pesticide Sampling



- Tested foam cushions in homes treated with pesticides
- Dust samples from window sills, over under refrigerator, door thresholds, 24 hour air samples

(Camann et. al, 2011)

Persistence of Pesticides in Homes

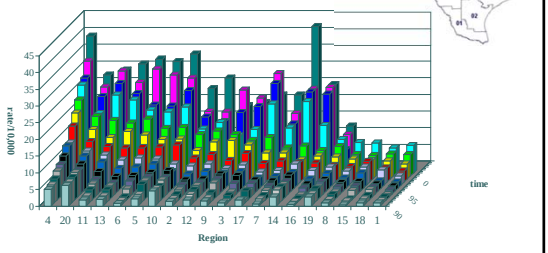
Indoor Air ng/m³		Chair Cushion (µg/g)			
2004	2010	2006		2010	
		Outer	Inner	Outer	Inner
6.8	2.78	0.20	<0.002	0.05	<0.02

Pesticide levels in dust and air were highly correlated in the 2 homes

Half-life Chlorpyrifos: 4.5 – 6 years

Persistence of Pesticides in Residential Indoor Air and Chair Seat Foam Camann DE, Yau A, Heilbrun LP, Walker T, Miller CS (Indoor Air 2011 Conference)

Autism rates over 12 years by Texas Educational Agency (TEA) Regions



Mercury in Texas related to autism rates

ELSEVIER

Health & Place 12 (2006) 203–209

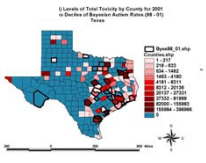
HEALTH & PLACE

www.elsevier.com/locate/healthplace

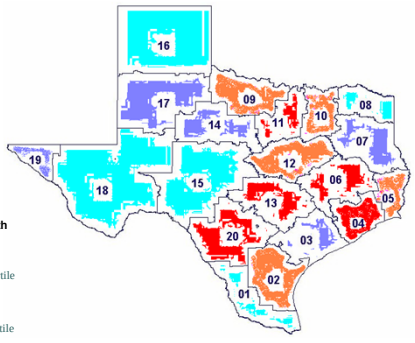
Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas

Raymond F. Palmer[a,*], Steven Blanchard[b], Zachary Stein[a], David Mandell[c], Claudia Miller[a]

Results: For every 100 pounds of Hg Release There is a 2% increase in autism rates



Where has it changed over time?



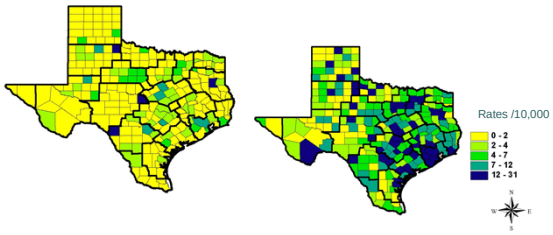
Rates of Autism Growth by TEA Regions:

Highest Growth Quartile

Lowest Growth Quartile

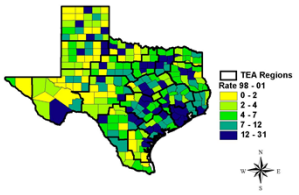
1990-93 Autism rates

1998-2000 Autism rates

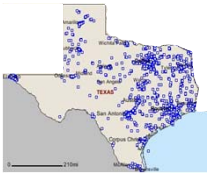


Autism rates and point sources of environmental pollution in Texas counties.

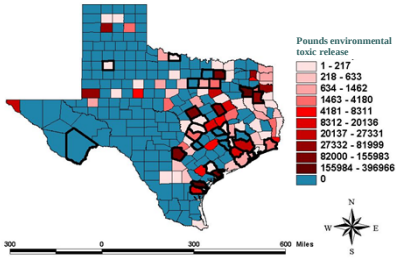
Autism rates 1998 - 2001 by counties in Texas. Aggregated from administrative data from the Texas Educational Agency (TEA)

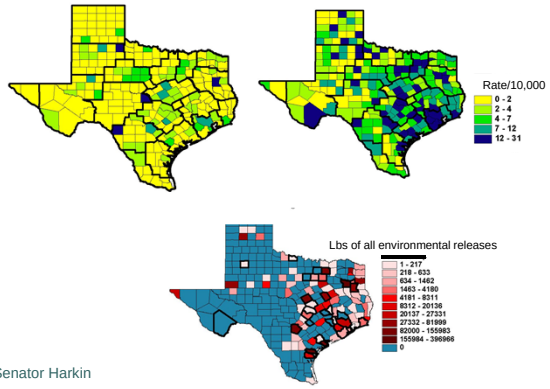


All Reporting Facilities, All Chemicals
TRI-(1987-2002) – Map shows 3,683 of 48,205 facilities reporting nationwide

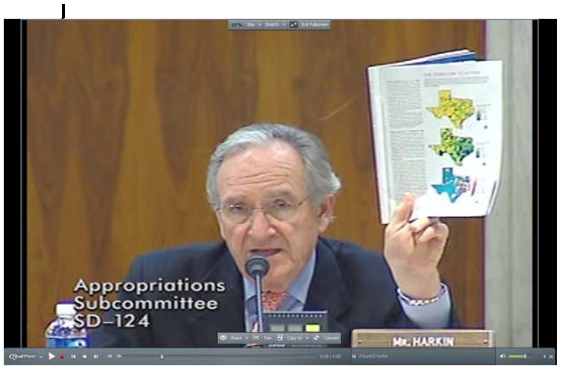


Total levels of toxic release by Texas county for 2001. Darkly shaded counties represent the top 20% in 10 year increases in autism

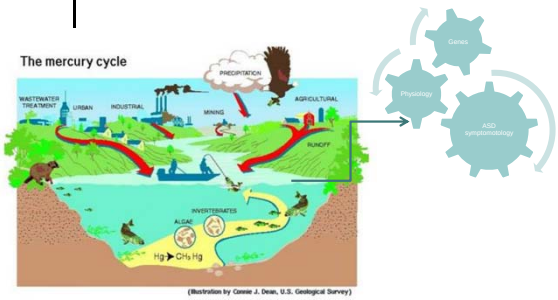




Senator Harkin



Mercury: a ubiquitous neurotoxin in food, air, water, and medicine



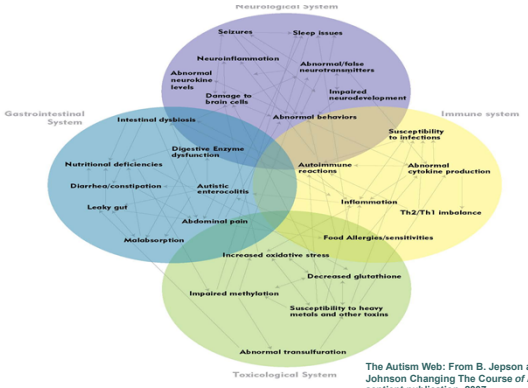
Rev Environ Health 2011;26(2):111–118 © 2011 by Walter de Gruyter • Berlin • Bokston. DOI 10.1515/REVEH.2011.015

The value of ecologic studies: mercury concentration in ambient air and the risk of autism

K. Stephen Blanchard[1,*], Raymond F. Palmer[2] and Zachary Stein[3]

[1] Department of Sociology, Our Lady of the Lake University, San Antonio, TX, USA
[2] San Antonio Department of Family and Community Medicine, University of Texas Health Science Center, San Antonio, TX, USA
[3] Department of Biophysics, University of Michigan, Ann Arbor, MI, USA

What we know about BIOLOGY: Involves impairment in multiple systems.



The Autism Web: From B. Jepson and J. Johnson Changing The Course of Autism, sentient publication, 2007

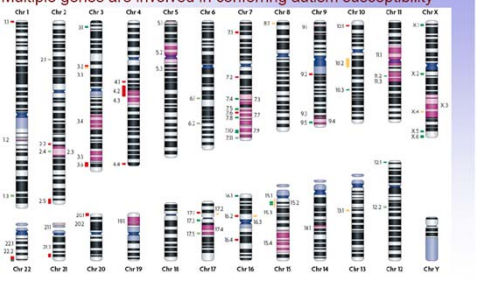
Genes AND Environment

Various environmental triggers interact with various susceptible genotypes.

Genes: Individual susceptibility, one size doesn't fit all.

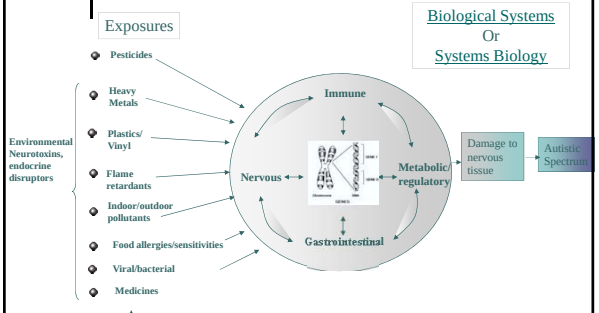
Autism is a Complex *Set* of Disorders

Multiple genes are involved in conferring autism susceptibility



Abrahams and Geschwind (2008) Nature Reviews Genetics 9, 341-355

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. (2011) Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry* 68:1095–1102.

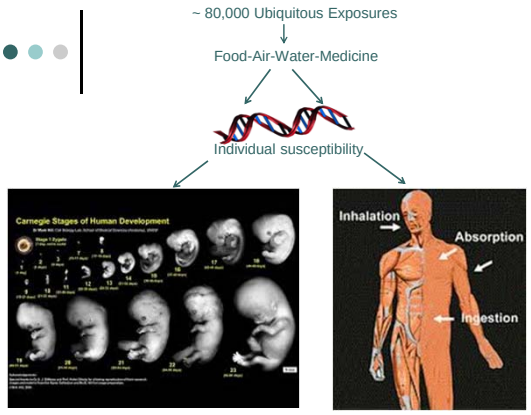


Prevention efforts through understanding G x E

Environment: 80,000 untested chemicals in use

Broad literature on the adverse consequences of environmental pollutants effecting childhood development

- Exposure of the U.S. population to toxic environmental chemicals has increased over the last 20 years.
- Human exposure to ubiquitous neurotoxins affects women of child bearing age and their infants.
- The developing fetus is exquisitely vulnerable to pharmaceutical products and other environmental chemical exposures that come from food, air, water, and medicine.
- Ubiquitous Environment Exposures (neurotoxins and/or endocrine and immune disruptors) associated with ASD:
  - Air Pollution
  - Pesticides
  - Heavy metals
  - Various Medicines
  - Plastics, Vinyl, Flame retardants
  - Where you live makes a difference



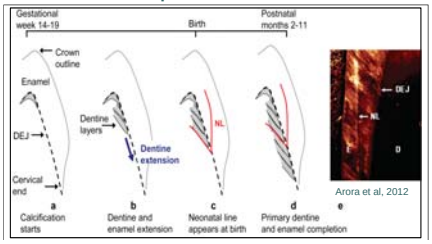
How do you measure Environmental exposure?

- **Comprehensive Survey?**
  - Recall bias or not knowing
- **Blood, hair, urine, nails?**
  - Can only reveal relatively recent exposure
- **Home air samples?**
- **Foam biopsies from furniture cushions, teddy bears, mattress from the house of conception**

Submitted to state-of-the-art Mass Spectrometry methods

None of these samples can reliably capture exposure during critical windows of neurodevelopment in the womb or shortly after birth.

Tooth development



Do organic chemicals circulating in the bloodstream during development absorb into forming dental tissues?

Do they remain in the tooth and can we detect them?

Can prenatal timing of chemical exposure be estimated?

Autism Tooth Fairy Study:

Environmental Exposures Measured in Baby Teeth as Biomarkers of In-utero Exposure

- **Study recruitment and tooth collection through parent donation, existing autism studies, community resources, pediatric dentists.**
- **Over 900 deciduous teeth from around the nation including Mexico**
- **Continue to recruit – please help**
- **Completed various pilot studies and analysis**

Results

- Acetaminophen, pesticides, plastics, and essential fatty acids in deciduous molars: potential biomarkers of perinatal exposure.
  Camann DE, Schultz ST, Yau AY, Heilbrun LP, Zuniga MM, Palmer RF, Miller CS. 2013. *J Expo Sci. Environ Epidemiol*. 23:190-196. (22 NT teeth)

  Autism Speaks 2013 Trail Blazer award: 71 ASD teeth analyzed
- Exploring other chemicals stored in baby teeth.
- Significance:
  - None of the chemicals we detected have previously been detected in human teeth.
  - Preponderance of organic chemicals measured in teeth appear to represent perinatal uptake during crown formation, but some small fraction likely reflects later childhood uptake after crown formation.

	No. Teeth	Detections	
		No.	Percent
Acetaminophen: active ingredient of widely used analgesic for children	71	31	44%
DEET	71	53	75%
TCPy: 3,5,6-trichloro-2-pyridinol (specific metabolite of chlorpyrifos), in Dursban insecticides. Residential use was discontinued in 2001.	71	9	13%
IMPy (diazinon) 2-isopropyl-6-methyl-4-pyrimidinol (the specific metabolite of diazinon), in Spectracide products. Residential use discontinued in 2001	71	9	13%
MEP monoethyl phthalate (MEP): metabolite of diethyl phthalate, in perfumes, fragrances. (Diethyl phthalate is commonly used to make plastics more flexible. Diethyl phthalate is found in products such as toothbrushes, automobile parts, tools, toys, and food packaging. Diethyl phthalate is also used in cosmetics, insecticides, and aspirin.)	31	31	100%
MnBP (DnBP,BzBP)mono-n-butyl phthalate: metabolite of di-n-butyl phthalate, in nail polish. (Di-n-butyl phthalate is used to make plastics more flexible and is also in carpet backings, paints, glue, insect repellents, hair spray, nail polish, and rocket fuel.)	71	61	86%
MiBP (DiBP)monoisobutyl phthalate : metabolite of diisobutyl phthalate. (DIBP is an odorless plasticizer and has excellent heat and light stability. It is the lowest cost plasticizer for cellulose nitrate. It has similar properties as dibutyl phthalate and can be used as a substitute for it. Used in nitro cellulose plastic, nail polish, lacquer manufacturing.	71	50	70%
MEHP:metabolite of diethylhexyl phthalate, in polyvinyl chloride (PVC) products, most toxic phthalate. (Due to its suitable properties and low cost, is widely used as a plasticizer in manufacturing of articles made of PVC)	66	30	45%

	No. Teeth	Detections	
		No.	Percent
Polyunsaturated fatty acids			
LA, C18:2 n6, linoleic acid (LA): source of all omega 6 fatty acids; major dietary sources are cereals, eggs, poultry, most vegetable oils, whole-grain breads.	71	71	100%
ALA, C18:3 n3, alpha-linolenic acid (ALA): source of all omega 3 fatty acids; in chlorophyll; major dietary sources are canola and flaxseed oils, leafy green vegetables, walnuts.	71	15	21%
ARA, C20:4 n6, arachidonic acid (ARA): omega 6; major dietary sources are human breast milk, red meat, egg yolks. (Individuals with an arachidonic acid deficiency may not be able to grow correctly, or may have difficulty fighting off infections. However, too much arachidonic acid can also lead to some specific health risks including cardiovascular issues.)	71	60	85%
DHA, C22:6 n3, docosahexaenoic acid (DHA): omega 3; main dietary source is cold-water marine fish. (DHA is the most abundant long-chain polyunsaturated fatty acid in the brain. DHA is essential for the growth and functional development of the brain in infants. DHA is also required for maintenance of normal brain function in adults. The inclusion of plentiful DHA in the diet improves learning ability, whereas deficiencies of DHA are associated with deficits in learning)	71	14	20%

U.S Hispanic Research Center (HARC)- A Pilot Study

Research Question:

Is autism among the Hispanic population insufficiently understood?

To investigate environmental and genetic factors

U.S Hispanic Research Center (HARC)- A Pilot Study

Initially a replication and expansion of the Childhood Autism Risks from Genetics and Environment (CHARGE) Study

UC Davis

Biorepository

Maintain biosamples for future investigations as new advances take place

U.S Hispanic Research Center (HARC) A Pilot Study

- Study population
  - 20 cases and their biological mother
  - 20 controls
  - Mexican-American ethnicity, child between the ages of 2—21 (recent change), living with biological mother, English speaking,
- Residing in the study catchment areas
  - Hidalgo and Cameron counties
  - Or no more than a 2-hour drive assessment sites

U.S Hispanic Research Center (HARC)- A Pilot Study

Methods

- Pre-screening – phone interview
- Three clinic visits:
  - Obtain consent, master questionnaire, diagnostician evaluations, and biosamples collection
  - Travel stipend and completion of study compensation

Biosamples to be Collected

- Blood Samples (Mother and Child)
  - Testing for:
    - Immunology
    - Genetics
- Hair (Child Only)
  - Heavy metals
- Saliva (Mother and Child)
  - Genetics
- Deciduous Teeth (Child Only)
  - Heavy metals
  - Medication, pesticides and other chemicals
- Urine (Child Only)
  - Pesticides

Expected Outcomes and Implications

- Demonstrate feasibility of U.S Hispanic Autism Research Center (HARC) in South Texas
- Shed light into significant differences in autism in Hispanic children and possible lack of diagnosis
- Identify specific challenges faced by families that have children with autism in the Lower Rio Grande Valley (LRGV)
- Become a resource of LRGV

South Texas Autism Research (STAR): Autism Tooth Fairy Study

Mission: To investigate gene/environment interactions as risk factors for the prevention of Autism Spectrum Disorders

Currently seeking funding

Phase 1: to compare chemical concentrations between typically developing children and those with Developmental Disabilities.

Phase 2: understand what kind of individual genetic susceptibilities to specific chemical exposures lead to Developmental Disabilities.

South Texas Autism Research (STAR)

- Mission: To investigate gene/environment interactions as risk factors for the prevention of Autism Spectrum Disorders
- Through our research, we will eventually understand the environmental causes and individual susceptibility mechanisms underlying autism and other developmental disabilities.
- *Identify key areas for the prevention of ASD under the context of GxE as per PKU example*
- *Precautionary principal*
- *Just one*

It takes a village

Ray Palmer, PhD (PI, UTHSCSA-STAR/HARC – Department of Family and Community Medicine)
Claudia Miller, MD (Co-PI, UTHSCSA-STAR/HARC Department Family and Community Medicine)
Lynne Heilbrun MPH (UTHSCSA- STAR project coordinator)
Viola Elisco, BS (UTHSCSA-FCM-STAR project associate)
Beatriz Tapia, MD, MPH (UTHSCSA RAHC: HARC Project coordinator)
Noe Garza, DDS (UTHSCSA RAHC: Dentist, ADRI Diagnostician. HARC project associate)
Juan Reyna, RN (UTHSCSA RAHC: Director Clinical Research Unit: Bio-repository)
Georgiana Gould, PhD (UTHSCSA: Neurobiologist: ASD Mouse models)
Steve Schultz, DDS, PhD (US Air Force: Dentist-Epidemiologist)
David Camann, MS (Southwest Research Institute: analytic chemistry)
JoAnne Curran, Ph.D. (Texas Biomedical Research Institute: genetics/tissue processing)
Doug Williamson, Ph.D. (UTHSCSA-psychiatry-epidemiologist-epigenetics)
Carlos Jean, M.D. Ph.D. (UTHSCSA-Chair FCM)