Environmental Etiologies Associated with Developmental Disabilities and the Brick Township, NJ Autism Cluster Investigation:

Challenges in identifying environmental etiologies

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Why investigate environmental chemical exposures as possible causes of developmental disabilities?

Why investigate environmental exposures?

- Most developmental disabilities have unknown etiology.
  - etiology is likely to be multi-factorial, involving:
    - genetic factors
    - non-genetic factors

Why investigate environmental exposures?

- A number of chemicals cause neurotoxic effects in human and/or animals studies
  - lead
  - methyl mercury
  - PCBs
  - organophosphate pesticides

Why investigate environmental exposures?

- Chemical exposures have been associated with risk factors for developmental disabilities:
  - IUGR
  - very low birth weight or preterm birth
  - maternal hypothyroidism
  - structural birth defects

Why investigate environmental exposures?

- During the prenatal period, the developing nervous system is most vulnerable to chemical exposures
  - immaturity of blood-brain barrier
  - unidirectional development:
    - damage at one developmental stage can cause cascading damage to later developmental stages
    - inability to replace damaged cells

Why investigate environmental exposures?

- Many, perhaps most, developmental disabilities have a prenatal origin

Why investigate environmental exposures?

- Our knowledge of how environmental exposures modify brain development is extremely limited due to:
  - lack of epidemiologic studies
  - lack of appropriate animal models
  - difficulties assessing exposures during critical periods of vulnerability for the developing nervous system.

Difficulties in determining a causal role for chemical exposures

- Effects will depend on:
  - **timing** of the exposure
  - neuronal processes affected by the exposure
  - dose and duration of exposure

- Exposures at different time periods during gestation can produce different outcomes or no adverse outcome
  - e.g., thalidomide

Age (days) post-fertilization	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**
age (weeks)	3		4							5							6	
Estimates of sensitive periods for eye, ear, thumb, and limb anomalies, and autism due to thalidomide exposure	severe external ear (**severe microtia**)		**microtia** (small ear) / mild inner ear															
		thumb hypoplasia (absent, misplaced, underdeveloped, extra digit)											extra bone in the thumb (**triphalangeal thumb**)					
					upper limbs (absent, rudimentary, abnormally short; hands attached close to the body resembling flippers of a seal)													
								lower limbs (same as upper limbs)										
	incomitant strabismus (misalignment of the eyes), **Duane syndrome**; (gaze of eyes is not parallel due to abnormal innervation of the eye muscles)						**coloboma** (days 24-26) (pupil has keyhole notch) **microphthalmia** (abnormal smallness of one or both eyeballs)											
	facial nerve palsy, Möbius syndrome (e.g., cannot smile)																	
	autism																	

Difficulties in determining a causal role for chemical exposures

- Prenatal “selection”
  - A chemical that causes a developmental disability may also cause early spontaneous abortions at higher doses, distorting dose-response relationships.

- Population exposed may be too small (given the developmental disability of interest) for adequate statistical power

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- Use of surrogates of exposure (e.g., residential proximity) because of "convenience" or lack of data
  - uncertainties concerning who are exposed
- Not all toxic waste sites are the same!
  - different exposure pathways
  - different chemical mixtures
  - different levels of exposure

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- Exposures involve a mixture of chemicals
  - Different mixtures of the same chemicals can produce different effects
  - Which constituent should be measured?
  - Which is the etiologic agent?
    - Is it volatile or non-volatile?

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- Difficulties in disentangling the effects of individual chemicals that generally occur together

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- The need to extrapolate or model sample data over space-time
  - few monitoring stations
  - monitoring stations may not be representative of the study area
  - infrequent samples

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- Differences, or changes, over space-time:
  - sampling methods (locations, frequency)
  - detection limits
  - chemicals analyzed

- Exposure estimates based on unverified assumptions due to limitations of data
  - missing data
  - data uncertainties and inconsistencies

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- Data may be inadequate to identify “hot spots” (i.e., areas where maximum exposures occur)
- Geo-unit (e.g., census tract, zipcode) may poorly fit the exposed population
- Geo-unit may be too large:
  - excessive within-area exposure heterogeneity

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- Inability to take into account:
  - occupational exposures
  - behaviors that might affect total dose or mitigate/enhance the effects of the environmental exposure of interest

Difficulties in determining a causal role for chemical exposures: Exposure Misclassification

- Inadequate maternal recall of behaviors/exposures during pregnancy
- Migration during pregnancy

Difficulties in determining a causal role for chemical exposures: Limitations of environmental databases

- Data linkage problems (e.g., incompatible formats)
- Data entry errors
- Need for supplementary information (e.g., information from water utilities)
- Inaccurate (or inadequate) geo-coding information

Difficulties in determining a causal role for chemical exposures: Limitations of environmental databases

- Federal environmental databases were designed for regulatory/enforcement purposes, **not** epidemiology
  - only violations are reported in the drinking water database, **not** contaminant levels
  - no well production data are available
    - requires assumption that all wells in a system produce the same amount of water
  - many states fail to report data

Difficulties in determining a causal role for chemical exposures: Limitations of environmental databases

- "garbage in ⇒ garbage out"
  - how accurate are point source emissions data (e.g., in TRI database)?

Research Directions

- Use databases to identify study areas for possible epidemiological study
  - supplement database information with:
    - fieldwork data
    - contaminant transport modeling
    - drinking water system distribution modeling

Research Directions

- Exposure biomarker may be feasible **if**:
  - chemical of interest is a persistent organic pollutant (e.g., dioxin, PCBs)
  - biomarker is representative of maternal exposures during appropriate period of gestation

Research Directions

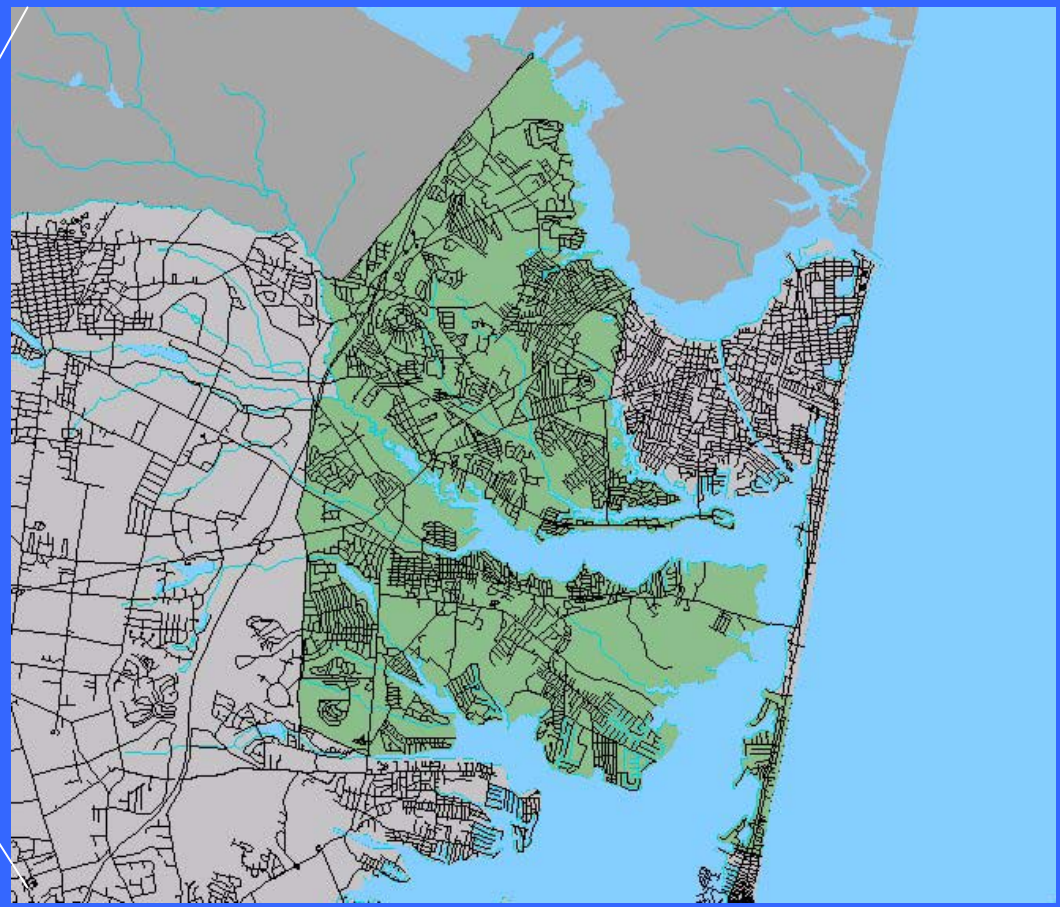
- If environmental database provides adequate information, then perform data linkage study

Examples of successful data linkage studies

- public drinking water monitoring databases and adverse birth outcomes and childhood cancers
- criteria air pollutant monitoring database and adverse birth outcomes, asthma
- CA Pesticide Use Report (agricultural pesticide use) and adverse birth outcomes, childhood cancers

New Jersey

Brick Township



The CDC and ATSDR Public Health Action Plan

- Prepare a literature review
- Determine the prevalence of children with autism spectrum disorders (ASD)
- Investigate environmental pathways for human exposure
- Inform the community

The Prevalence Study

- **The objective of the prevalence study was to determine the prevalence of ASD for children aged 3-10 years who were living in Brick Township in 1998.**

- **The study used 4 sources for case-finding**
  - **special education records**
  - **records from local clinicians**
  - **lists from community parent groups**
  - **media outreach**

Prevalence Study Results

- **The prevalence of autism spectrum disorder (ASD) was 6.7 cases per 1,000 children.**
- **The prevalence for Autistic Disorder was 4 cases per 1,000 children.**

Prevalence Study Conclusions

- **The prevalence of autistic disorder and ASD in Brick Township were:**
  - **high relative to previously conducted studies in this country**
  - **in the upper end of the range for more recent studies conducted in other countries.**
  - **within the range found in a few recent studies of small populations that also used intensive case-finding methods**

The Environmental Investigation

ATSDR assessed possible chemical exposure from:

- **The municipal drinking water supply**
- **The Brick Township Landfill (a superfund site)**

Environmental Investigation Sources of Data

- **Environmental Protection Agency**
  - **information on the NPL site**
- **New Jersey Department of Environmental Protection**
  - **drinking water contaminant level database**
  - **well production information**
- **Brick Township Municipal Utilities Authority**
  - **drinking water distribution map**
  - **additional sample data**
  - **other system characteristics**

Brick Township
Municipal Drinking Water System

Contaminants found in the municipal drinking water supply:

- **Trichloroethylene (TCE)**
- **Tetrachloroethylene (PCE)**
- **Trihalomethanes (THMs)**

Brick Township
Municipal Drinking Water System

- **PCE and TCE found in two small municipal wells**
- **TCE was not detected in tap water samples**
- **PCE was detected in tap water samples between 1987 and 1994 ranging from less than 1 ppb to 6 ppb (MCL=5 ppb)**

Brick Township
Municipal Drinking Water System

- PCE occurrence data were compared with the dates of gestation for the ASD cases.

- Most ASD cases were not exposed to PCE during the gestational period.

Brick Township
Municipal Drinking Water System

- Trihalomethanes (THMs) were found in the municipal drinking water supply.
- Except for a few data outliers, the THM levels in the Brick Twp water system were generally typical of other systems in NJ that relied on a surface water source.

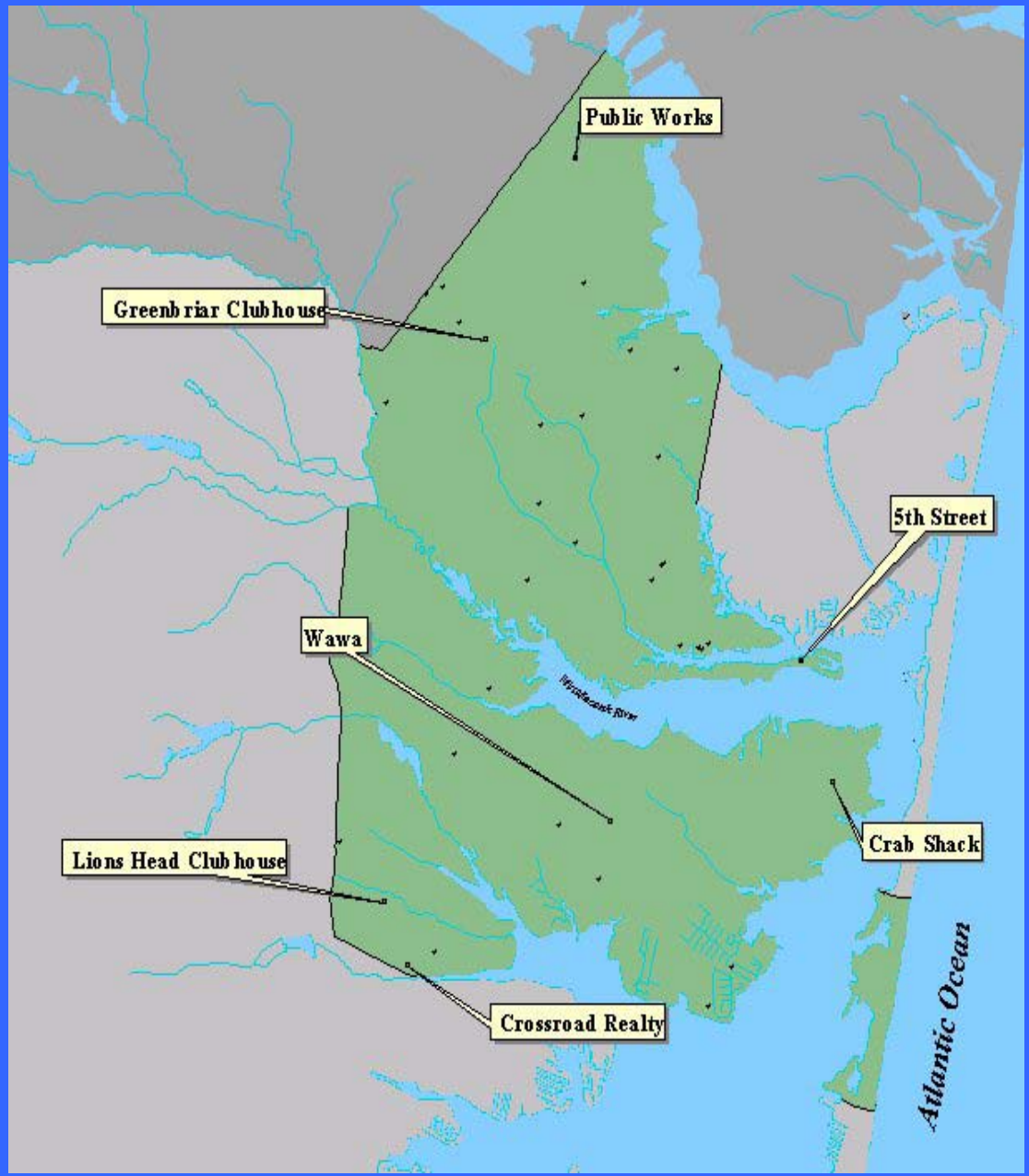
Brick Township
Municipal Drinking Water System

- No study has been conducted to determine if exposure to THMs in drinking water is associated with developmental disabilities
- Exposure to THMs in drinking water has been associated with adverse birth outcomes:
  - –neural tube defects
  - –oral clefts
  - –small for gestational age
  - –fetal death and spontaneous abortion

Brick Township
Municipal Drinking Water System

- Space-time data on THM levels were compared with the time periods and residential locations during gestation for the ASD cases.

- For most ASD cases, the maternal residences during the gestational period were **≥1 mile** from sampling locations with THM levels >60 ppb (current MCL = 80 ppb)



Total Trihalomethane Water Samples with at Least One Sample >80 ppb and maternal residences during the gestational period of the ASD cases

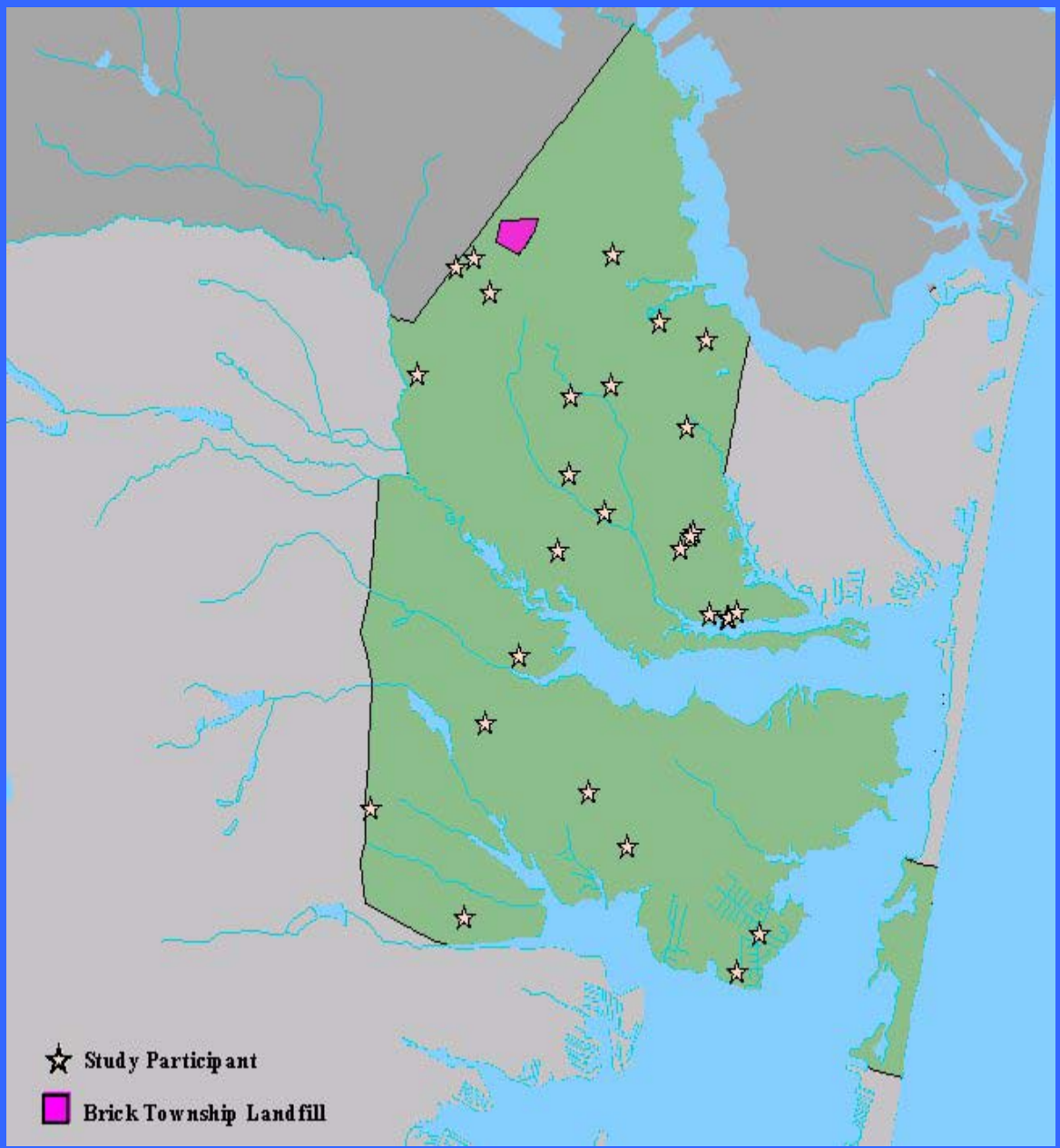
Brick Township
Municipal Drinking Water System

- Maternal residences were not located at distribution system "dead ends"

- ATSDR concluded that no clear pattern existed between the sampling dates and locations where total trihalomethane levels exceeded 60 ppb and the maternal residences during gestation of the ASD cases.

Brick Township Landfill

- **Superfund Site**
- **Ceased operation in 1979**
- **Onsite contamination with Volatile Organic Compounds and Metals**
- **Groundwater contaminant plume is migrating southeast from the site**
  - **a threat to private wells used for irrigation and other outdoor water uses**



Brick Township Landfill and maternal residences during the gestational period of ASD cases

Public Health Conclusions for the Brick Township Landfill

- **The closest maternal residence was about 550 yards southwest of the site.**

- **Maternal residences were not in the path of the groundwater plume from the landfill.**