Welcome to the CLU-IN Internet Seminar

Early-life Exposures - Long-term Health Consequences Part 3: PCE and Phthalates

Sponsored by: NIEHS Superfund Research Program

Delivered: April 2, 2012, 1:00 PM - 3:00 PM, EDT (17:00-19:00 GMT)

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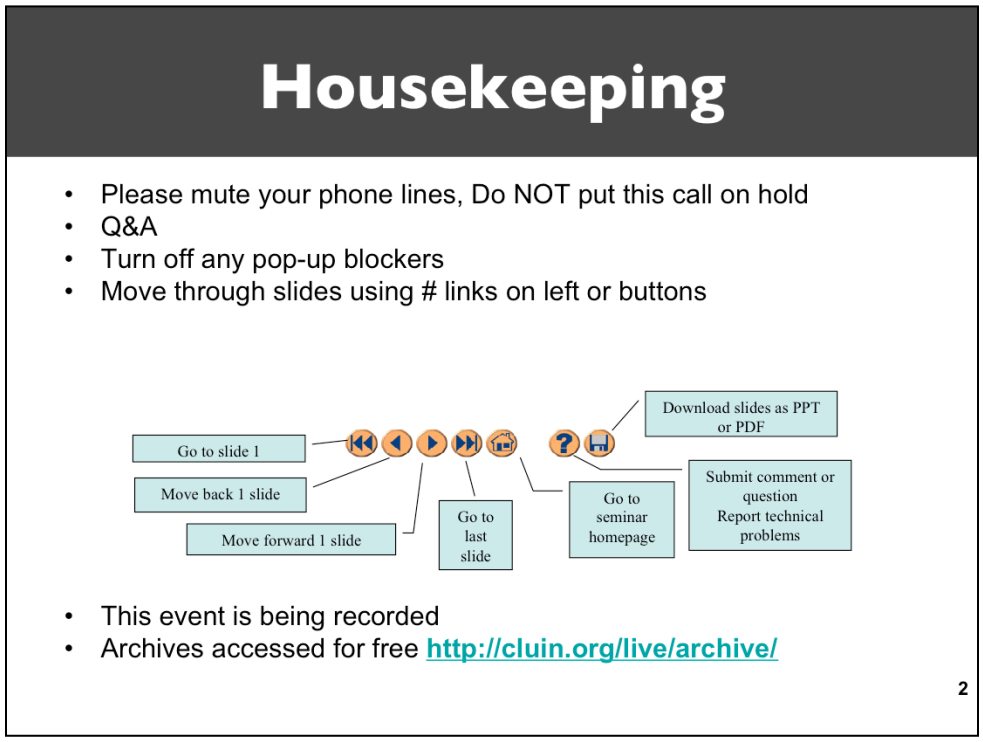

Although I'm sure that some of you have these rules memorized from previous CLU-IN events, let's run through them quickly for our new participants.

Please mute your phone lines during the seminar to minimize disruption and background noise. If you do not have a mute button, press *6 to mute #6 to unmute your lines at anytime. Also, please do NOT put this call on hold as this may bring delightful, but unwanted background music over the lines and interupt the seminar.

You should note that throughout the seminar, we will ask for your feedback. You do not need to wait for Q&A breaks to ask questions or provide comments. To submit comments/questions and report technical problems, please use the ? Icon at the top of your screen. You can move forward/ backward in the slides by using the single arrow buttons (left moves back 1 slide, right moves advances 1 slide). The double arrowed buttons will take you to 1st and last slides respectively. You may also advance to any slide using the numbered links that appear on the left side of your screen. The button with a house icon will take you back to main seminar page which displays our agenda, speaker information, links to the slides and additional resources. Lastly, the button with a computer disc can be used to download and save today's presentation materials.

With that, please move to slide 3.

Neurotoxic Effects of Early Life Exposure to Tetrachloroethyene (PCE)-Contaminated Drinking Water

Ann Aschengrau, ScD
Professor of Epidemiology

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Overview of Presentation

- PCE uses and fate
- How PCE contaminated Cape Cod's drinking water
- Birth cohort study methods and results
  - Risky behaviors (smoking, alcoholic beverage consumption, illicit drug use)
  - Mental illness (depression, bipolar disorder, PTSD, and schizophrenia)

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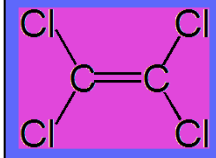

PCE Uses and Fate

- PCE stands for tetrachloroethylene
- Commercially important solvent
  used for dry cleaning, textile processing, and metal degreasing
- About 650,000 persons in US are exposed through their work
- Used in small, geographically dispersed, and poorly controlled facilities –-dry cleaners, garages, machine shops
- Common drinking water contaminant (8-38%)

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PCE in Cape Cod Waters

- In 1980 Massachusetts Department of Environmental Protection discovered that PCE was leaching into drinking water from vinyl lining in water distribution pipes
- Vinyl liner introduced in 1968 in response to complaints about taste and odor of water
- Slurry sprayed onto inner pipe surface
- Slurry = 30% vinyl toluene resin and 70% PCE
- Assumed that PCE would disappear in curing process but substantial quantities remained and leached into drinking water

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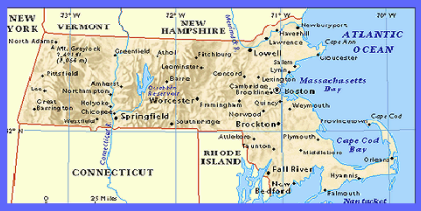
Extent of Problem



- 660 miles of vinyl-lined asbestos cement pipe (VL/AC) pipe had been installed in 91 Massachusetts communities over 12-year period
- 24% installed on Cape Cod: Barnstable (16 mi), Bourne (22), Falmouth (50), Mashpee (1), Sandwich (50), Brewster (6), Chatham (7.5), Harwich (0.2), Provincetown (6)
- Typical levels varied from 1,600-7,750 ug/l at low flow locations and 1.5-80 ug/l at medium/high flow locations

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Original Maps of Vinyl-Lined Water Pipes

Publicity

- In April 1980 Boston Globe broke story to public
- Headline: "Pipes pollute some New England water"
- "Environmental officials disclosed that water flowing into thousands of New England homes was contaminated with a chemical suspected of being a cancer-causing agent."

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Official Response in 1980

- EPA issued an action level of 40 ug/l
- Recommended actions: boil water, purchase bottled water, install AC filters, remove and replace pipe, reline pipes with cement mortar, install bleeder taps to flush the lines
- Water samples taken to determine extent of contamination and monitor success of remediation efforts

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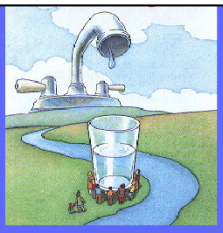
Population Exposure



- Thousands of Massachusetts residents were exposed to PCE-contaminated water for various periods from late 1960s thru 1980s
- We estimate that 15% of the Cape Cod population had some exposure
- Levels before 1980 may have been quite high
- Levels in 1980s may have been as high as 40 ug/l - eight times the current MCL of 5 ug/l

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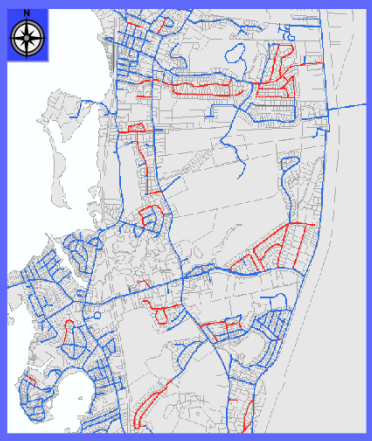
PCE Exposure on Cape Cod

- Unique exposure scenario
  - Irregular pattern of contamination with no point source
  - Wide-range of PCE exposure levels
  - Little confounding by other water contaminants
- Challenging exposure assessment
  - No sampling data prior to 1980
  - Remediation upon discovery



= Vinyl-lined pipe
= Other pipe

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Our Research

Our team at BU has used this natural experiment to learn about the health effects of PCE in drinking water among individuals exposed as adults and in early life

- Carcinogenicity
- Reproductive and developmental effects
- Neurotoxic Effects

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Neurotoxicity of PCE

- Animal and human evidence supports wide range of effects on neurologic function for both acute and chronic exposure
- Acute exposure leads to headache, dizziness, confusion, nausea, and eye irritation. Very high exposure may lead to unconsciousness, and even death from respiratory depression.
- Chronic exposure associated with impairments in memory, cognition, attention, mood changes including anxiety and depression, and vision problems
- Most human research has been conducted on occupationally exposed adults; very little information on early life exposure

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Cape Cod Health Study

- Retrospective cohort study to examine long-term neurotoxic effects of early life exposure
- Source population: Children born from 1969-1983 to women who lived in Cape Cod towns with VL/AC pipes
- Subjects identified by cross-matching maternal addresses from birth records with information from water companies on location and installation year of VL/AC pipes

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Cape Cod Health Study

- Initial exposure assessment based on visual inspection of maps depicting pipe distribution network in immediate vicinity of birth address
- Exposed subjects had birth residence adjacent to VL/AC pipes, N=1,910
- Unexposed subjects randomly selected from remaining resident births and frequency matched on date of birth to exposed subjects, N=1,928

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Cape Cod Health Study

- Older siblings also selected if born in Massachusetts during 1969-1983, N=1,202
- Older sibs initially considered unexposed because they were born before the family moved to an affected Cape Cod residence
- Initial exposure assessment considered provisional until more extensive assessments were completed

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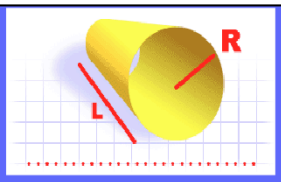
Assessing PCE Exposure



- Used leaching and transport model to estimate mass of PCE delivered to each residence from prenatal period through age of 5 years
- Model estimates quantity of PCE entering drinking water using information on initial quantity of PCE in liner (based on pipe length and diameter), age of pipe, leaching rate of PCE from liner into water.
- Model used to estimate relative delivered dose (RDD), an ordinal estimate of exposure

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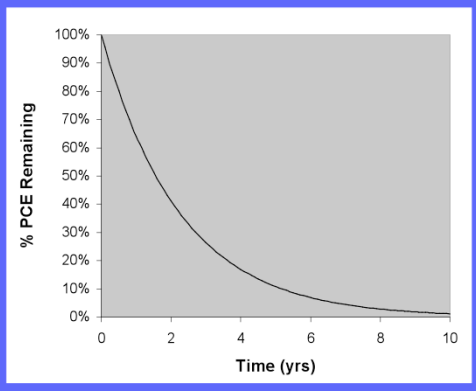
PCE Leaching Rate



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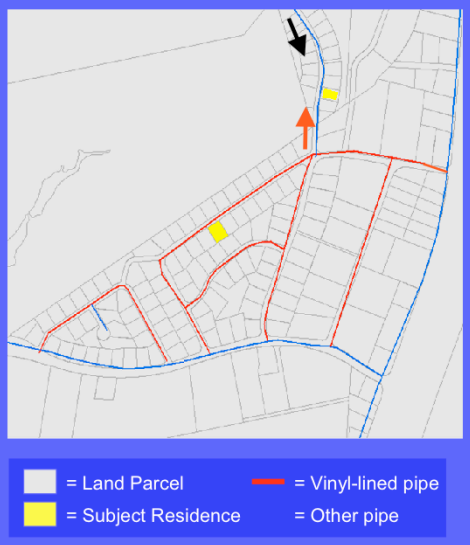
Water Flow



- Very important determinant of exposure
- Flow direction determines exposure status
- Flow magnitude determines exposure amount

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EPANET 2.0 Software

- Model algorithm was incorporated into EPANET software used to estimate water flow and direction
- Developed by the US EPA
- Publicly available, free software & open source code
- Applied in other epidemiological studies

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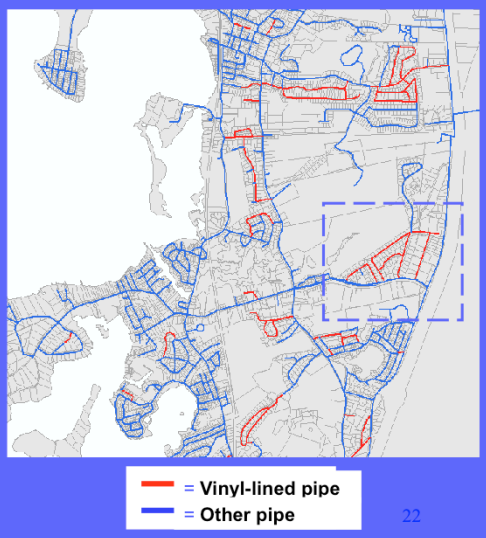
EPANET Water Flow Model

- Greatly improved the assessments; our early studies took into account only small area
- Used entire water distribution system
- Could take into account complex geometries



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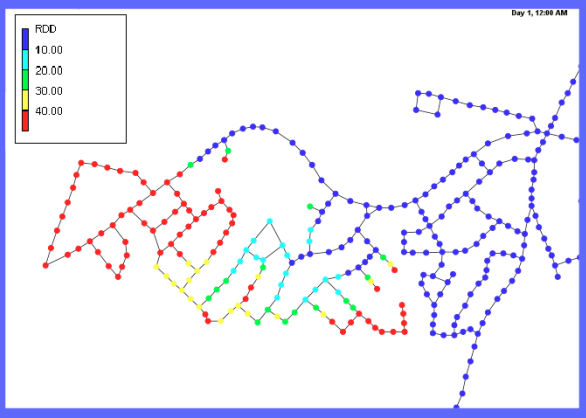
Calculating PCE Exposure



- Calculated PCE exposure by year at every point
- GIS used to create database to match residences to points

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Cape Cod Health Study

	Initial Exposure Status			
Final Exposure Status	Exposed Subject	Unexposed Subject	Unexposed Older Sibling	Total
Both prenatal and early childhood exposure	561	160	110	831
Only early childhood exposure	7	42	85	134
Unexposed	17	360	170	547
Total	585	562	365	1512

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Characteristics of Study Population

Characteristic	Prenatal and Early Childhood Exposure N=831	Unexposed Subject N=547
Current age, mean (sd)	29.2 (3.6)	29.6 (3.8)
% Male	39.8	39.5
% White	98.4	98.5
% College graduate	61.4	61.2
% Mother received prenatal care	95.5	95.1
% Mother smoked cigarettes during gestation	21.9	20.7
% Mother consumed alcoholic beverages during gestation	36.3	36.8
% Mother smoked marijuana during gestation	3.0	3.3
% Subject ever had job with solvent exposure	14.8	13.0

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Risky Behaviors

- Ever became a regular smoker, age at initiation of smoking, smoking frequency
- Ever consumed alcoholic beverages, age at initiation of drinking, drinking frequency as a teen and adult
- Ever use of marijuana, inhalants, cocaine, psychedelics, club drugs as teen and as adult

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Results: Smoking

	Exposure Percentile	% Yes	GEE Risk Ratio (95% CI)
Ever Smoked	>67th	45.0	1.2 (1.0-1.5)
	33rd-<67th	29.1	0.8 (0.7-1.0)
	>0-<33rd	36.8	1.0 (0.9-1.3)
	None	35.2	Referent
Smoked 20+ cigarettes/ day	>67th	15.8	1.3 (0.9-2.0)
	33rd-<67th	12.1	1.0 (0.7-1.6)
	>0-<33rd	10.4	0.9 (0.5-1.4)
	None	12.0	Referent

Many confounders assessed but none changed crude RR by at least 10%

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Results: Alcohol Consumption

	Exposure Percentile	% Yes	GEE Risk Ratio (95% CI)
First drank <=13 years	>67th	21.9	1.2 (0.9-1.6)
	33rd-<67th	18.4	1.0 (0.7-1.4)
	>0-<33rd	18.5	1.0 (0.7-1.4)
	None	18.6	Referent
Drank >8 days/month as teen	>67th	38.8	1.6 (1.1-2.3)
	33rd-<67th	19.8	0.8 (0.5-1.3)
	>0-<33rd	20.2	0.8 (0.5-1.4)
	None	23.7	Referent

Many confounders assessed but none changed crude RR by at least 10%

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Results: Drug Use

	Exposure Percentile	% Yes	GEE Risk Ratio (95% CI)
2+ Major drugs as a teen	>67th	43.3	1.6 (1.2-2.2)
	33rd-<67th	30.8	1.2 (0.8-1.6)
	>0-<33rd	34.5	1.3 (0.9-1.8)
	None	26.5	Referent
2+ Major drugs as an adult	>67th	53.9	1.5 (1.2-1.9)
	33rd-<67th	37.1	1.1 (0.8-1.4)
	>0-<33rd	43.5	1.2 (1.0-1.6)
	None	34.7	Referent

Many confounders assessed but none changed crude RR by at least 10%

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Results: Drug Use

- Specific drugs for which increased risks were observed……

	GEE Risk Ratio	95% CI
Crack/cocaine as a teen	2.1	1.4-3.0
Psychdelics/hallucinogens as a teen	1.4	1.1-1.8
Club/designer drugs as adult	1.5	1.2-1.9
Ritalin w/o a prescription as adult	1.9	1.3-2.8

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Results: Drug Use

Among Subjects Without History of Prenatal Exposure to Cigarette Smoke, Marijuana, Alcohol

	Exposure Percentile	% Yes	GEE Risk Ratio (95% CI)
2+ Major drugs as a teen	>67th	44.1	2.3 (1.3-4.1)
	33rd-<67th	21.6	1.1 (0.6-2.2)
	>0-<33rd	15.8	0.9 (0.4-2.0)
	None	18.9	Referent
2+ Major drugs as an adult	>67th	48.6	2.1 (1.3-3.5)
	33rd-<67th	35.5	1.5 (0.9-2.5)
	>0-<33rd	28.9	1.3 (0.7-2.3
	None	22.2	Referent

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Results: Risky Behaviors

- Results suggest that the occurrence of risky behaviors, particularly drug use, is increased among adults with high PCE exposure levels during gestation and early childhood .

- Findings published in *Environmental Health* in December, 2011

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Mental Illness

- "Has a doctor or health care provider ever said that you had…..
  - Depression?"
  - Schizophrenia?"
  - Bipolar or manic depressive disorder?"
  - Post-traumatic stress disorder?"

  If yes, obtained year of diagnosis

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Results: Mental Illness

	Exposure Percentile	% Yes	GEE Risk Ratio (95% CI)
Depression	>67th	19.0	1.1 (0.8-1.5)
	33rd-<67th	20.8	1.2 (0.9-1.6)
	>0-<33rd	19.5	1.1 (0.8-1.5)
	None	17.8	Referent
Bipolar disorder	>67th	8.2	2.7 (1.3-5.6)
	33rd-<67th	3.2	1.1 (0.4-2.7)
	>0-<33rd	5.1	1.6 (0.7-3.7)
	None	3.2	Referent

Many confounders assessed but none changed crude RR by at least 10%

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Results: Mental Illness

	Exposure Percentile	% Yes	GEE Risk Ratio (95% CI)
Post -Traumatic Stress Disorder	>67th	8.2	1.7 (0.9-3.2)
	33rd-<67th	6.7	1.4 (0.7-2.7)
	>0-<33rd	6.4	1.4 (0.7-2.6)
	None	4.7	Referent
Schizophrenia	>67th	0.5 (n=1)	-----
	33rd-<67th	0.9 (n=2)	-----
	>0-<33rd	0.0 (n=0)	-----
	None	0.2 (n=1)	Referent

Many confounders assessed but none changed crude RR by at least 10%

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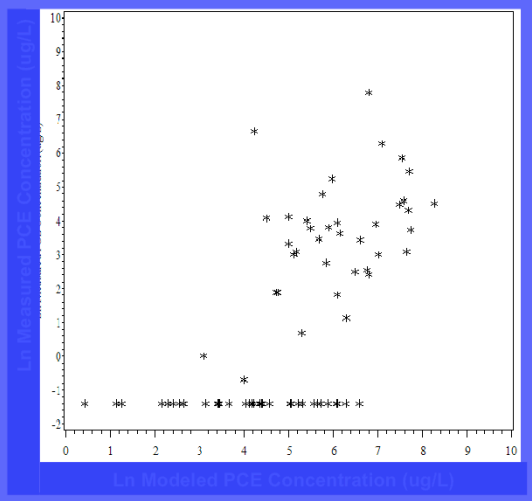
Results: Mental Illness

- Results suggest that:
  - The risks of bipolar disorder and post-traumatic stress disorder are increased among adults with high PCE exposure levels during gestation and early childhood
  - Depression is not related to early life PCE exposure
- Results published in *Environmental Health* in January 2012.

Study Limitations

- Self-reported data on risky behaviors and mental illnesses
- Low response rate
- Residual confounding by unmeasured variables (e.g., poor parental supervision, social supports)
- Exposure misclassification

Validation of PCE Exposure Assessment: Measured vs. Model-Estimated Concentrations



ρ=0.65

p<0.0001

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Context of Findings

- No prior studies on risky behaviors
- Prior studies of neurotoxic effects among individuals with early life exposure to solvents have produced mixed results.
- These studies mainly examined learning, attention, and behavior among young children
- Only one prior study examined risk of schizophrenia among offspring of men and women who worked in dry cleaning operations

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Conclusions

- Provocative findings need to be corroborated.
- Difficult to find other suitable populations for long-term studies.
- PCE remains a commercially ubiquitous solvent and common contaminant of drinking water, so it is important to determine its impact on health of vulnerable populations.

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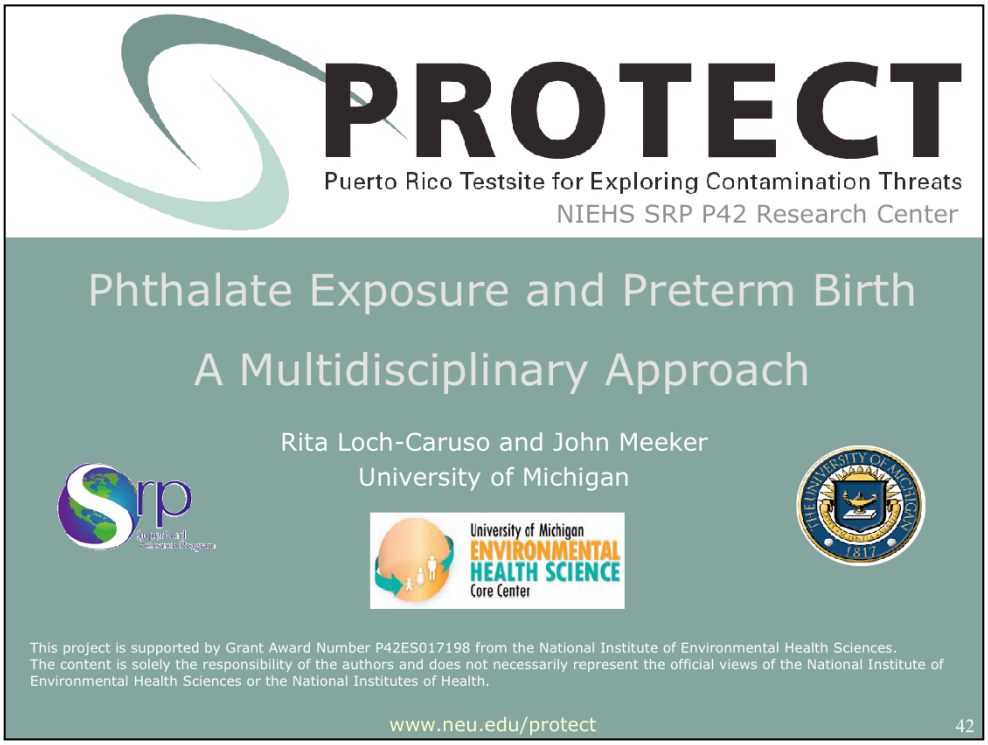
Thanks to my collaborators….








PROTECT
Puerto Rico Testsite for Exploring Contamination Threats
NIEHS SRP P42 Research Center
Phthalate Exposure and Preterm Birth
A Multidisciplinary Approach
Rita Loch-Caruso and John Meeker
University of Michigan
University of Michigan
ENVIRONMENTAL
HEALTH SCIENCE
Core Center
This project is supported by Grant Award Number P42ES017198 from the National Institute of Environmental Health Sciences.
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Fetal Growth & Birth Outcomes

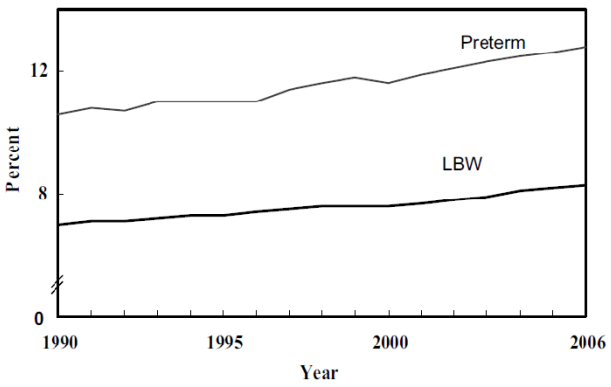


FIGURE 3
Percent preterm and percent LBW: United States, 1990–2006 (preliminary). LBW is <2500 g, and preterm is <37 completed weeks of gestation.

Martin et al. 2008, Pediatrics

Preterm Birth Consequences

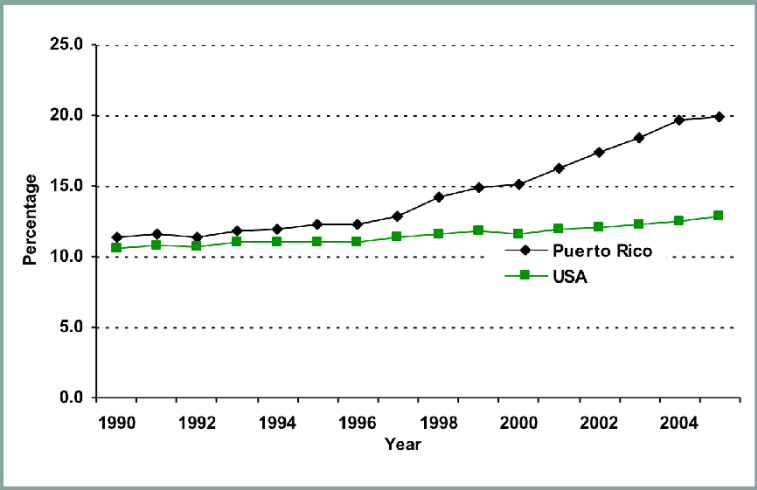
- Economic costs (2003 data)
  - Hospital costs for a preterm or low birth weight infant averaged $77,000 compared with $1,700 for term infants
  - Premature infants accounted for half of the hospital charges for all infants
  - Annual USA medical cost of $26 billion
- Psychological costs
  - Parents suffer increased symptoms of depression, stress & posttraumatic stress disorder

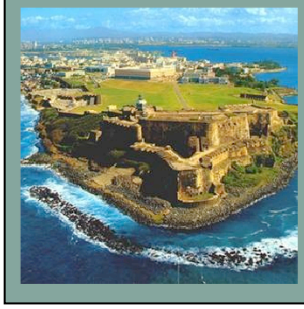
Photo by Tina Stallard. 2005 Visions of Science winner.

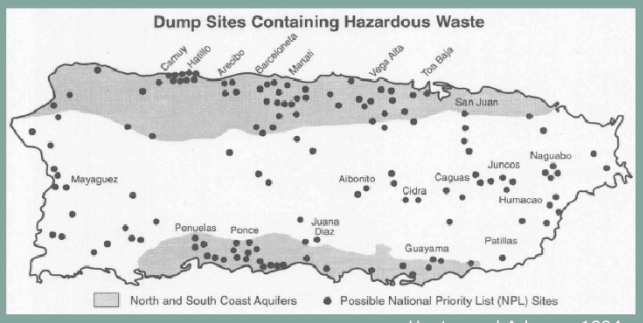
Preterm Birth Medical Consequences for Infant

- Leading cause of infant death
  - 19.7% of infant deaths
- Medical complications
  - Respiratory distress syndrome
  - Bleeding in the brain (intraventricular hemorrhage)
  - Nearly half of all congenital neurological defects (e.g., cerebral palsy)
  - Chronic lung disease (bronchopulmonary dysplasia)
  - Apnea
  - Retinopathy of prematurity (can lead to blindness)
  - Anemia
  - Infections

Preterm Birth Rates in US & Puerto Rico, 1990 - 2005







www.neu.edu/protect

Hunter and Arbonna 1994

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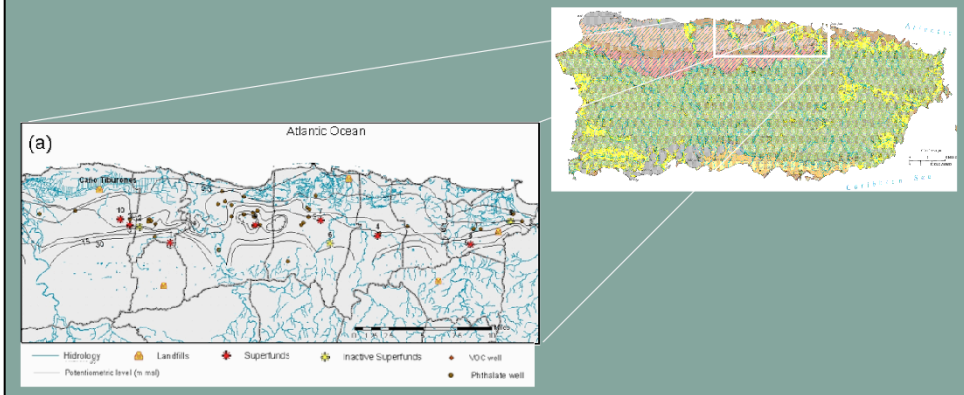
Phthalate Contamination in Puerto Rico



Phthalates and Fetal Growth, Birth Outcomes

- Latini et al. 2003, *EHP* (n = 84)
  - MEHP in cord blood inversely and significantly associated with decreased gestation length
- Whyatt et al. 2009, *Pediatrics* (n = 311)
  - Urinary DEHP metabolites inversely associated with gestation length
  - Highest MEHP quartile delivered 5 days earlier than lowest quartile
- Zhang et al. 2009, *J Pediatr* (n = 88 cases, 113 controls)
  - DEHP and DBP or metabolites in cord blood/meconium associated with dose-dependent increased odds for low birth weight
- Wolff et al. 2008, *EHP* (n = 404)
  - Urinary MEHP associated with increased gestation length
- Adibi et al. 2009, *Am J Epidemiol* (n = 284)
  - DEHP metabolites associated with increased gestation length

Meeker JD, Ferguson KK. Phthalates: Human Exposure and Related Health Effects. In: Schecter A, Gasiewicz T, eds. Dioxins and Persistent Organic Pollutants: Health and Toxicity, 3rd Edition. John Wiley & Sons, Hoboken, NJ; In press.

Phthalate Metabolites and Preterm Birth

Geometric mean and median 3rd trimester urinary phthalate metabolite concentrations in women with term or preterm births.

Phthalate Metabolite	Geometric Mean		Median (25th, 75th percentile)		p-value
	Term (n=30)	Preterm (n=30)	Term (n=30)	Preterm (n=30)	
MBP	38.1	89.9	33.4 (21.3, 74.0)	97.1 (56.0, 139)	**0.005**
MCPP	1.1	2.4	1.3 (0.5, 2.0)	2.3 (1.1, 4.9)	**0.002**
MBzP	2.3	5.2	2.9 (1.0, 5.2)	5.4 (2.6, 9.5)	**0.01**
MEP	112	204	108 (47.1, 224)	171 (69.4, 437)	0.1
MEHP	2.3	3.7	3.0 (0.6, 4.4)	4.3 (2.2, 7.1)	**0.06**
MEHHP	13.6	24.0	17.1 (6.2, 28.4)	28.7 (18.1, 37.5)	**0.04**
MEOHP	10.4	18.9	13.6 (5.0, 24.5)	20.8 (14.4, 25.5)	**0.04**
MECPP	29.7	51.2	38.2 (14.3, 53.8)	55.2 (39.2, 73.3)	**0.02**
Sum DEHP metab.	57.8	99.3	71.5 (26.8, 113)	112 (69.8, 135)	**0.03**

Meeker JD, Hu H, Cantonwine D, Loch-Caruso R, et al. Urinary phthalate metabolites in relation to preterm birth in Mexico City. *Environ Health Perspect*, 2009; 117:1587-2.

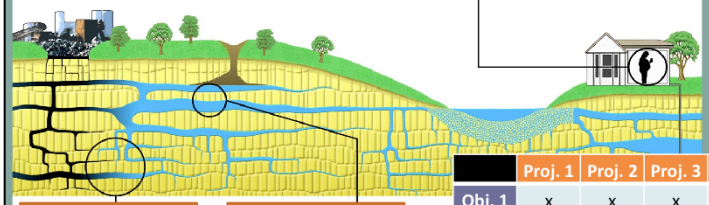
Project 1: Non-targeted Analysis

Project 2: Gestation Membrane Inflammation

Project 3: Epidemiology/ Targeted Analysis

Core D: Data Management and Modeling

Core C: Human Subjects Sampling



Project 4: Fate and Transport

Project 5: Green Remediation

	Proj. 1	Proj. 2	Proj. 3	Proj. 4	Proj. 5	Core C	Core D
Obj. 1	x	x	x		x	x	x
Obj. 2	x	x	x			x	x
Obj. 3	x		x	x		x	x
Obj. 4	x		x	x	x	x	x
Obj. 5	x	x	x	x	x		

OBJECTIVES

1. Examine the evidence that environmental contaminants contribute to preterm birth; identify the causative chemicals; and learn how to remediate these chemicals in karstic aquifers by a green process
2. Build a better understanding of the potential role, mechanisms and relevance of pollution-induced oxidative stress in preterm birth
3. Discover and understand risk factors and their interactions for preterm birth by developing and mining an integrated, centralized, indexed biomedical and environmental data repository for Puerto Rico
4. Determine the effect of episodic transport on patterns of exposure through highly mobile karstic aquifers and develop adaptable remedial actions
5. Improve and apply non-targeted chemical analysis including bioassay-directed chemical analysis to biological samples and environmental samples

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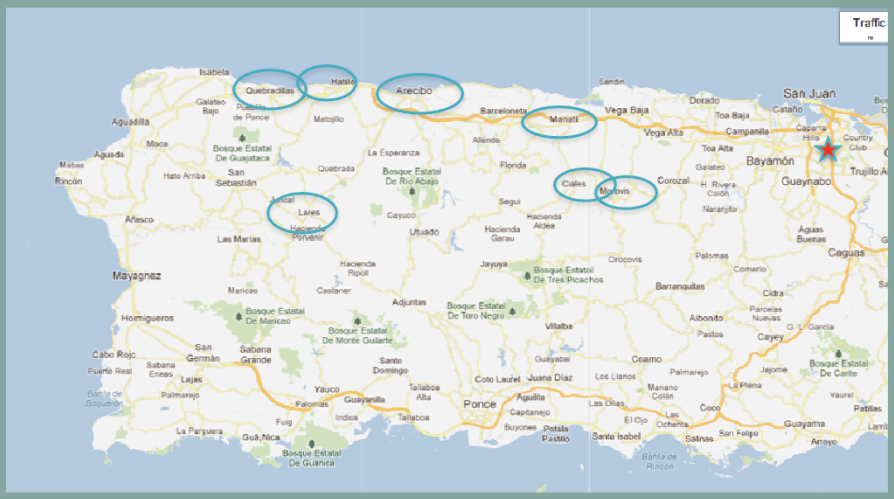
PROTECT Recruitment Sites



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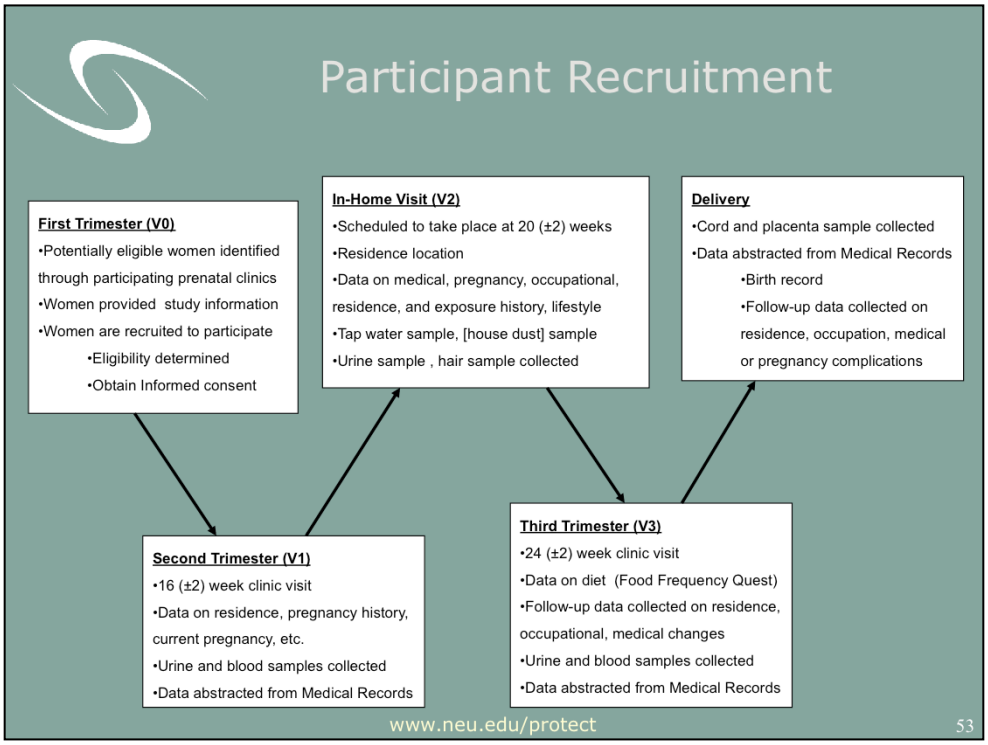
Participant Recruitment
First Trimester (V0)
•Potentially eligible women identified through participating prenatal clinics
•Women provided study information
•Women are recruited to participate
•Eligibility determined
•Obtain Informed consent
In-Home Visit (V2)
•Scheduled to take place at 20 (±2) weeks
•Residence location
•Data on medical, pregnancy, occupational, residence, and exposure history, lifestyle
•Tap water sample, [house dust] sample
•Urine sample , hair sample collected
Delivery
•Cord and placenta sample collected
•Data abstracted from Medical Records
•Birth record
•Follow-up data collected on residence, occupation, medical or pregnancy complications
Second Trimester (V1)
•16 (±2) week clinic visit
•Data on residence, pregnancy history, current pregnancy, etc.
•Urine and blood samples collected
•Data abstracted from Medical Records
Third Trimester (V3)
•24 (±2) week clinic visit
•Data on diet (Food Frequency Quest)
•Follow-up data collected on residence, occupational, medical changes
•Urine and blood samples collected
•Data abstracted from Medical Records
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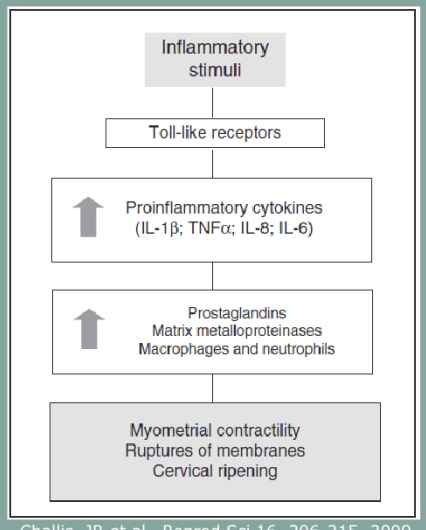
Model of Parturition Activation

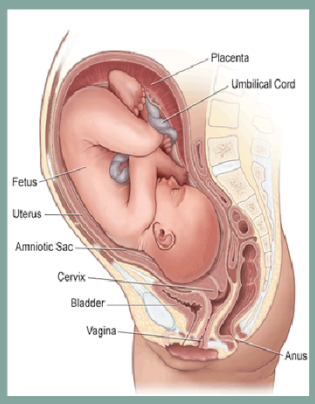


Challis, JR et al., Reprod Sci 16, 206-215, 2009

Toxicant Activation of Parturition

Toxicants

Toxicants



knowabouthealth.com

Bacteria

Oxidative Stress

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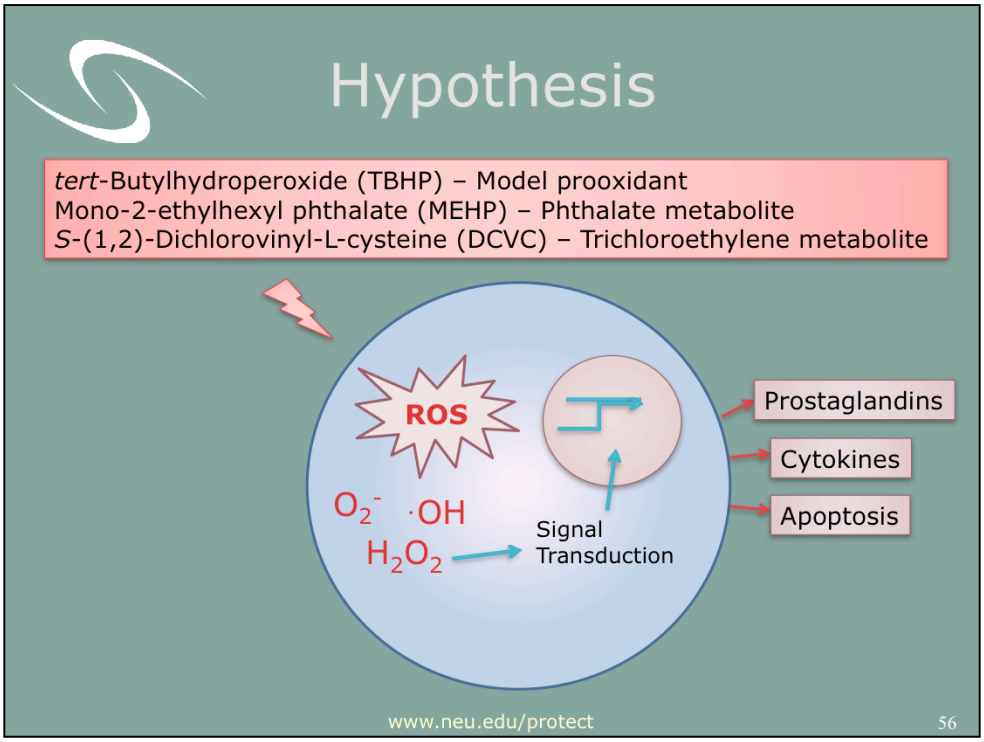
Hypothesis
tert-Butylhydroperoxide (TBHP) – Model prooxidant
Mono-2-ethylhexyl phthalate (MEHP) – Phthalate metabolite
S-(1,2)-Dichlorovinyl-L-cysteine (DCVC) – Trichloroethylene metabolite
ROS
O_2^- ·OH
H_2O_2
Signal Transduction
Prostaglandins
Cytokines
Apoptosis
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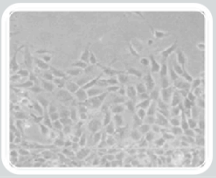
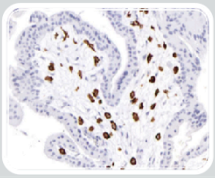
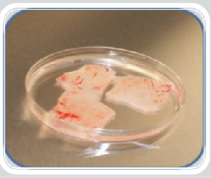
In Vitro Models



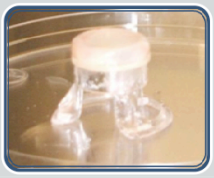
HTR-8/Svneo cells



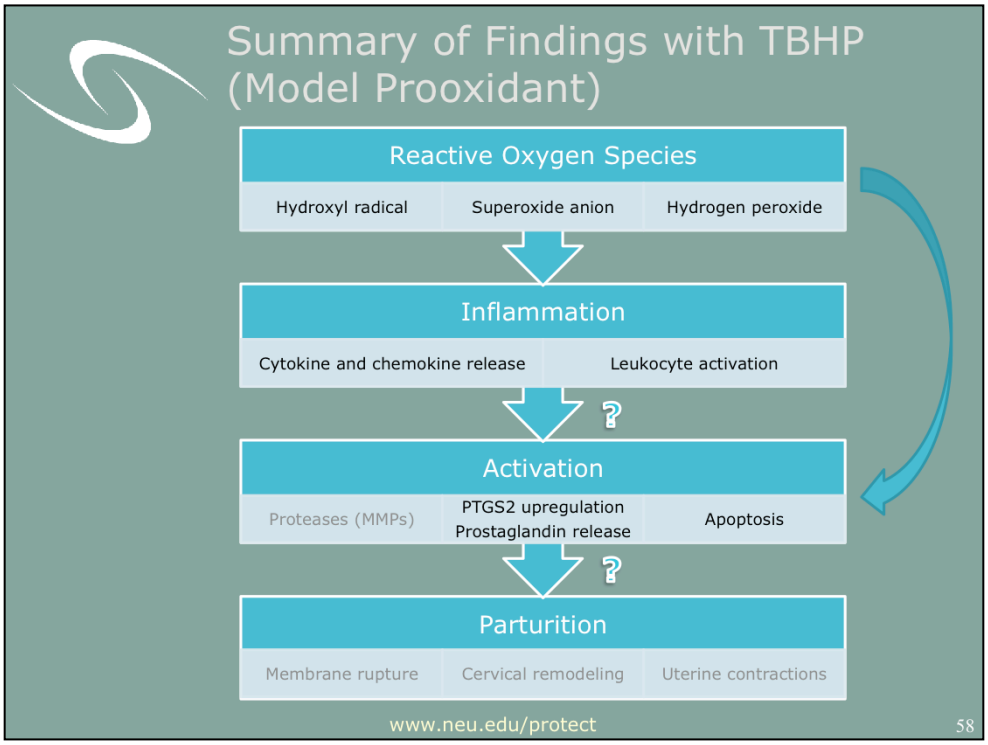
Primary placental macrophages



Gestational membrane tissue explants



Gestational membranes mounted on Transwell inserts


Summary of Findings with TBHP (Model Prooxidant)
Reactive Oxygen Species
Hydroxyl radical
Superoxide anion
Hydrogen peroxide
Inflammation
Cytokine and chemokine release
Leukocyte activation
?
Activation
Proteases (MMPs)
PTGS2 upregulation
Prostaglandin release
Apoptosis
?
Parturition
Membrane rupture
Cervical remodeling
Uterine contractions
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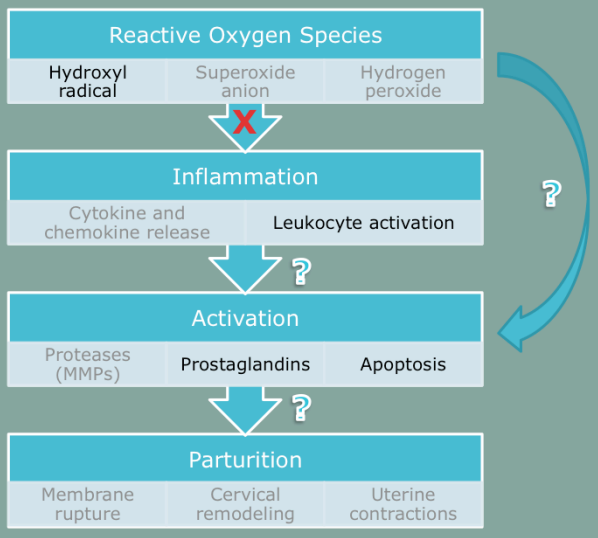
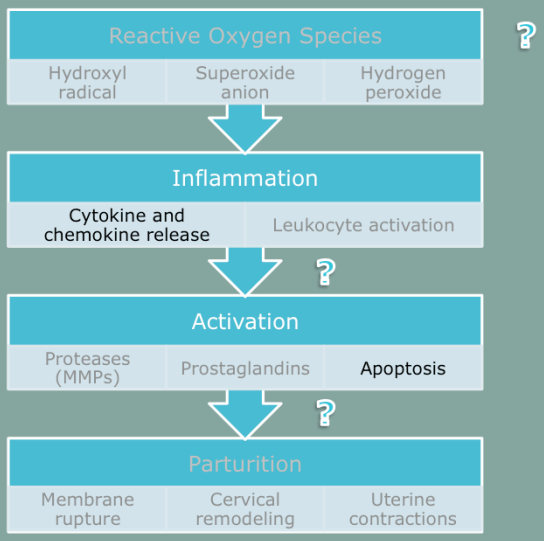
Summary of Findings with MEHP (DEHP Phthalate Metabolite)



Summary of Findings with DCVC (Trichloroethylene Metabolite)



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Oxidative Stress and Inflammation in US Population

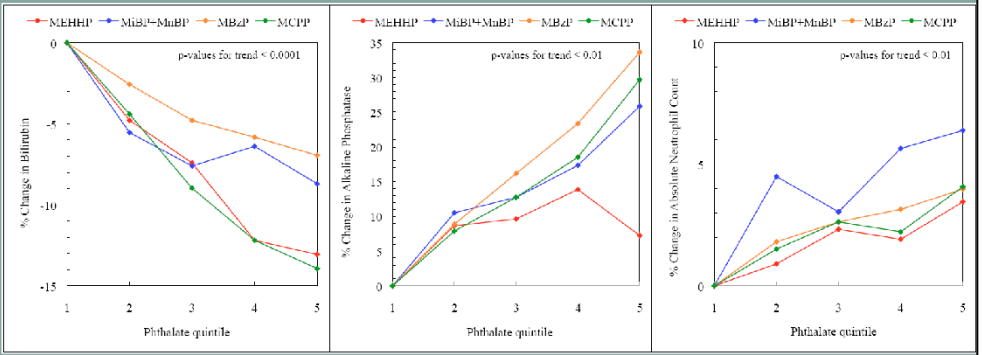
- Used the NHANES databases
  - Publicly available data collected by CDC
  - Exploratory analyses of phthalate metabolite associations with potential response biomarkers
- Putative biomarkers of oxidative stress
  - NHANES 1999-2006 database
  - Bilirubin (a potent antioxidant), inverse association
  - Gamma glutamyltransferase (GGT)

Oxidative Stress and Inflammation

- Putative biomarkers of inflammation (positive associations)
  - NHANES 1999-2006 database
  - C-reactive protein (CRP)
  - Alkaline phosphatase (ALP)
  - Absolute neutrophil count (ANC)
  - Ferritin
  - Fibrinogen

Some phthalate metabolites were associated with markers of increased oxidative stress & inflammation

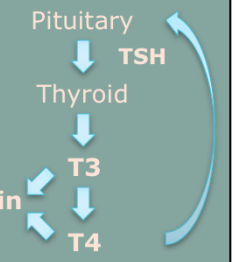
Selected results



Ferguson KK, Loch-Caruso R, Meeker JD. Exploration of oxidative stress and inflammatory markers in relation to phthalate metabolites: NHANES 1999-2006. *Environ Sci Technol* 2012. 46(1):477-85.

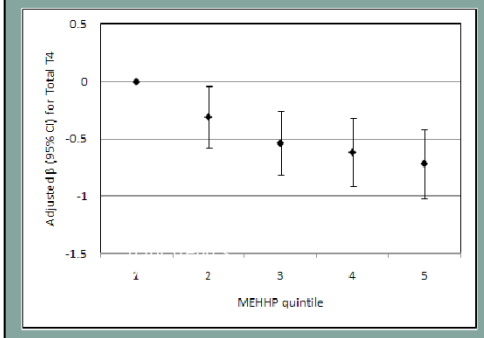
Ferguson KK, Loch-Caruso R, Meeker JD. Urinary phthalate metabolites in relation to biomarkers of inflammation and oxidative stress: NHANES 1999-2006. *Environ Res* 2011. 111(5):718-26.

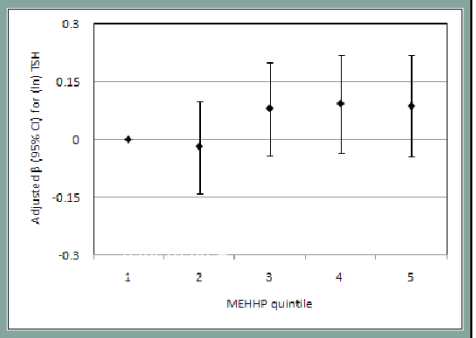
DEHP metabolites were associated with changes in thyroid hormone biomarkers



- NHANES 2007-08
- Decreased T4, T3, & thyroglobulin
- Increased TSH

Selected results:





Meeker JD, Ferguson KK. Relationship between Urinary Phthalate and Bisphenol A Concentrations and Serum Thyroid Measures in U.S. Adults and Adolescents from NHANES 2007-08. Environ Health Perspect, 119(10):1396-402.

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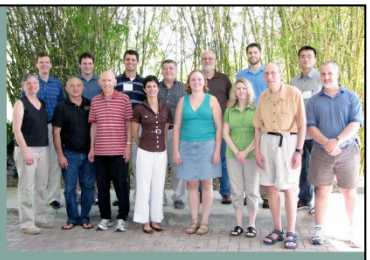
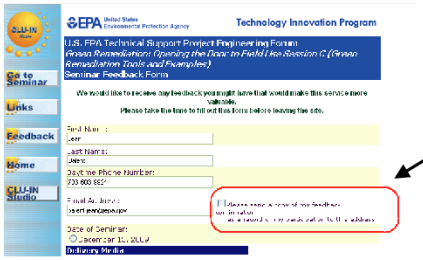
Summary



- Phthalates may have a role in preterm birth
- Experimental and human observational data support potential mechanistic links
  - may have relevance for other environmental contaminants and human health effects
- Multidisciplinarity is needed to address complex environmental health challenges
  - NIEHS Superfund Research Program Centers facilitate these partnerships

Resources & Feedback

- To view a complete list of resources for this seminar, please visit the **Additional Resources**
- Please complete the **Feedback Form** to help ensure events like this are offered in the future



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