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National Institute of Environmental Health Sciences

You can't change your genes, But you can change your environment!

How the Environment Affects Your Health

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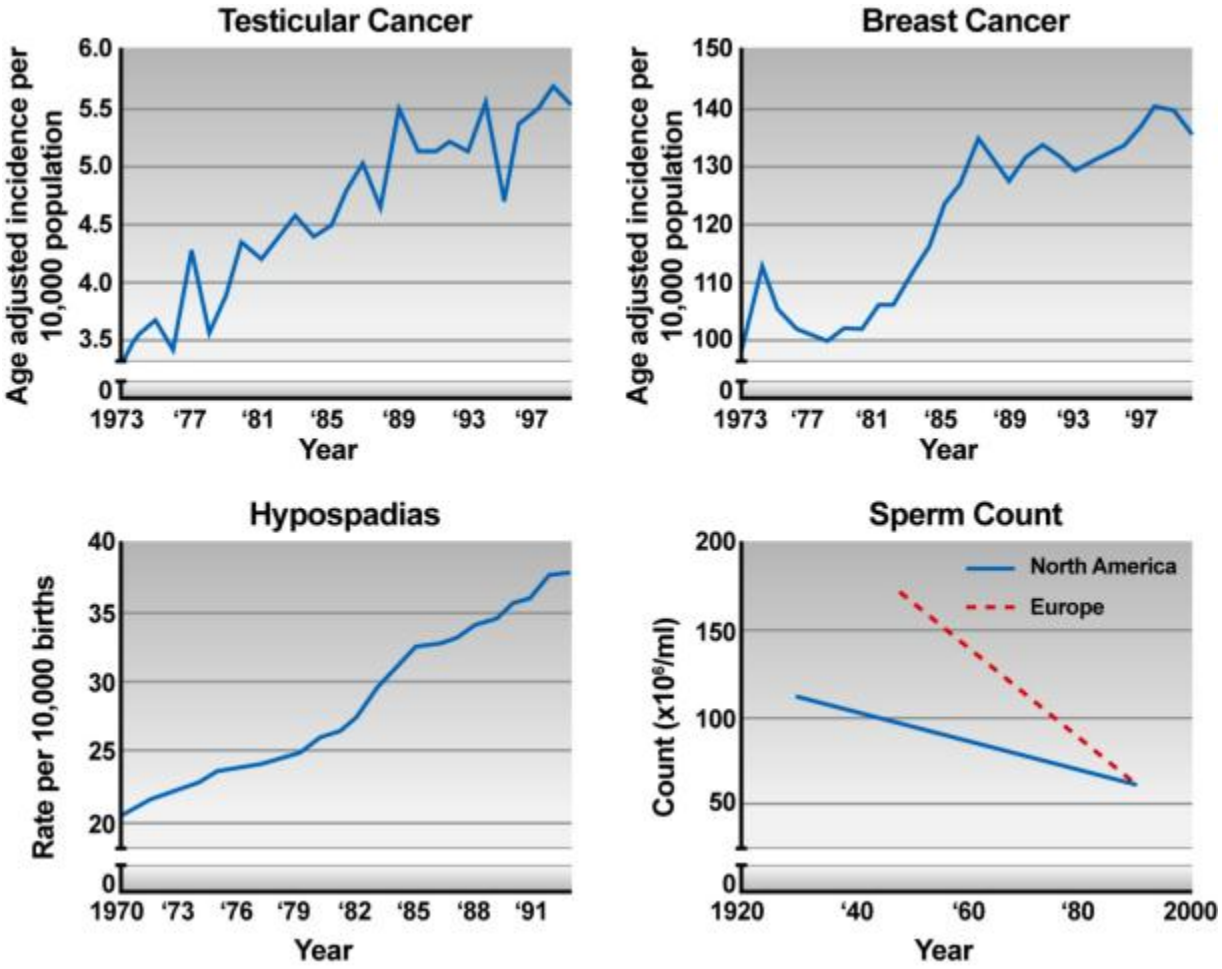
Pesticides & The Chesapeake Bay Watershed Project
Wednesday, October 10, 2012

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

The National Institute of Environmental Health Sciences

- **One of the National Institutes of Health, but located in Research Triangle Park, NC**
- **Wide variety of programs supporting our mission of environmental health:**
  - **-- Intramural laboratories**
  - **-- Extramural funding programs**
  - **-- Disease Prevention**
  - **-- Clinical research program**
  - **-- National Toxicology Program**
  - **-- Public Health Focus**

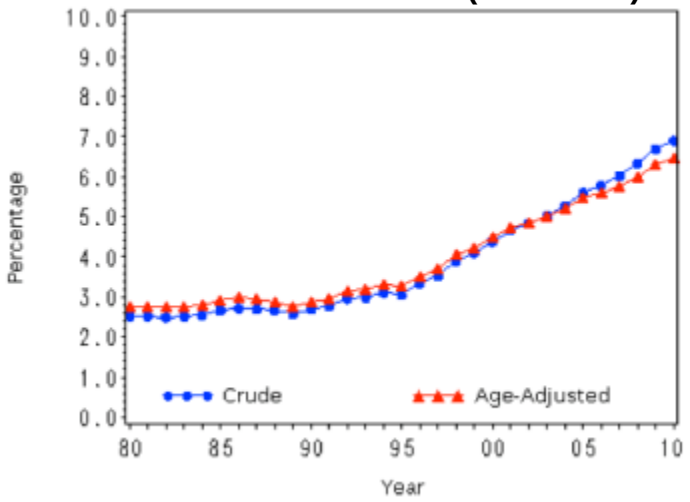
Should We Be Concerned?



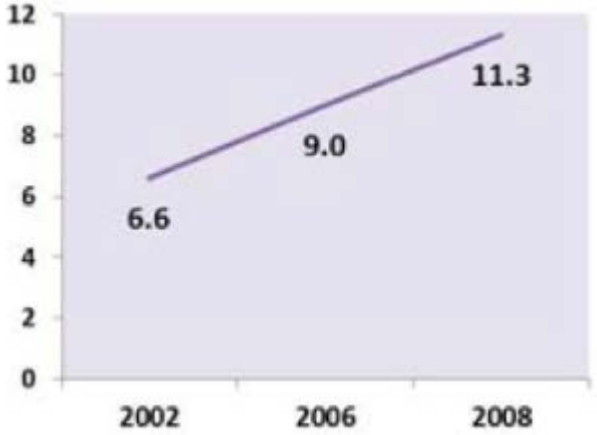
Sharpe and Irvine, 2004

Should We Be Concerned?

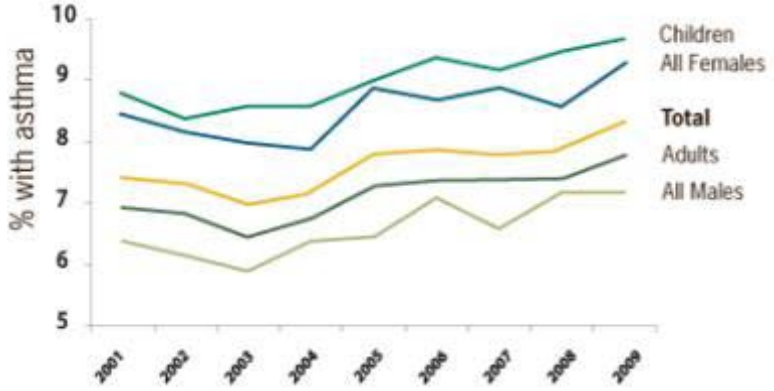
Increase in Diabetes (1980-2010)



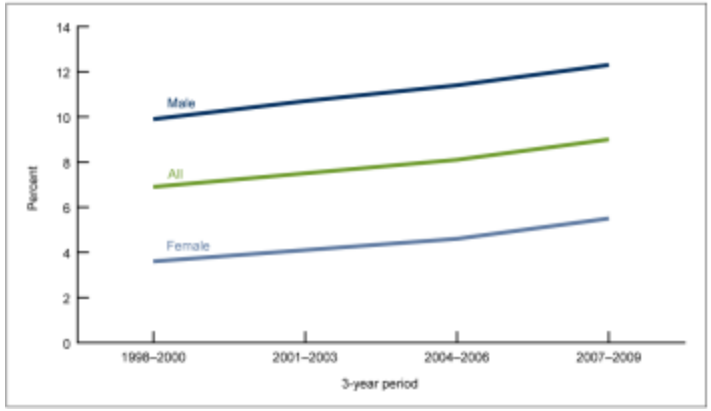
Increase in Autism Prevalence



Increase in Asthma



Increase in ADHD



Data from CDC / National Center for Health Statistics

"ENVIRONMENT" Includes:

- Industrial chemicals
- Agricultural chemicals
- Physical agents (heat, radiation)
- By-products of combustion and industrial processes (dioxin)
- Foods and nutrients
- Prescription drugs
- Lifestyle choices and substance abuse
- Social and economic factors

Diseases with a Known or Suspected Environmental Component Include:

- Cancers
- Birth defects (cleft palate, cardiac malformations)
- Reproductive dysfunction (infertility)
- Lung dysfunction (asthma, asbestosis)
- Neurodegenerative diseases (Parkinson's)
- Neurodevelopmental disorders (autism)
- Cardiovascular disease (air pollution, dioxins)
- Endocrine disorders (diabetes)

Many Endpoints / Outcomes

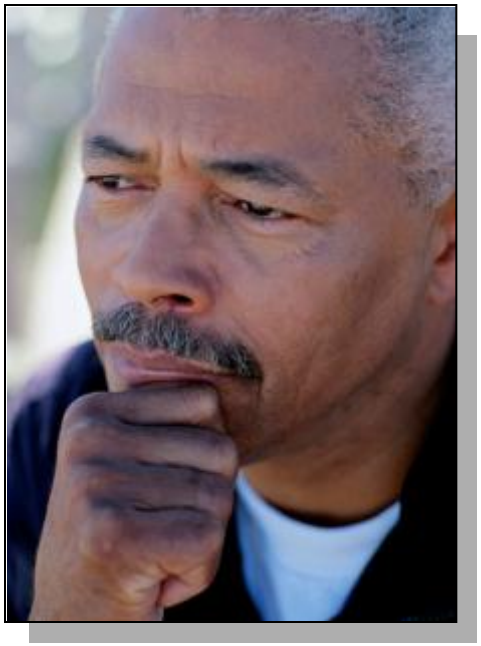
- Cancer and birth defects are not the only endpoints.
- Complex diseases have complex causes.
- Obesity, diabetes, cardiopulmonary disease, cancer, autoimmune disease, neurodevelopmental disorders, schizophrenia, addition, depression are some diseases where the environment acts through epigenetic mechanisms.

Conceptual Shift for Environmental Health Sciences

OLD… chemicals act by overwhelming the body's defenses by brute force at very high doses

NEW… chemicals can act like hormones and drugs to disrupt the control of development and function at very low doses to which the average person is exposed

NEW… susceptibility to disease persists long after exposure (epigenetics)



Priority Areas in Environmental Health Sciences

- Low Dose
- Windows of Exposure
- High-Throughput Screening
- Mixtures
- Routes of Exposures
- Clinical Research
- Emerging Hazards
  - Nanomaterials (including particle/fiber toxicology, e.g. Erionite)
  - Human Health Effects of Climate Change
  - Hydraulic Fracturing (Fracking)

Windows of Susceptibility

- **Development is sensitive time for exposure**
  - Rapid Growth
  - Active and extensive cell differentiation
  - Increased metabolic rate
  - Developing immune system
  - Opportunities for initiation of lesions and promotion of altered cells
  - Development is a highly integrated process
  - Programming (epigenetic marks set)
- **Adolescence also sensitive time for development**

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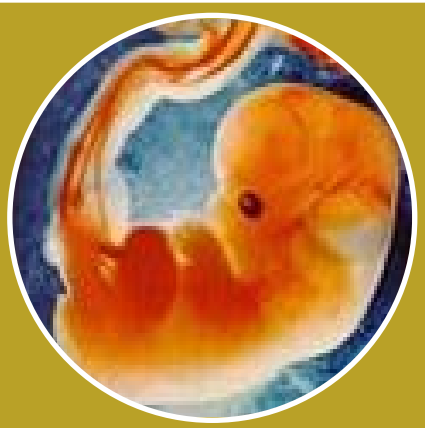
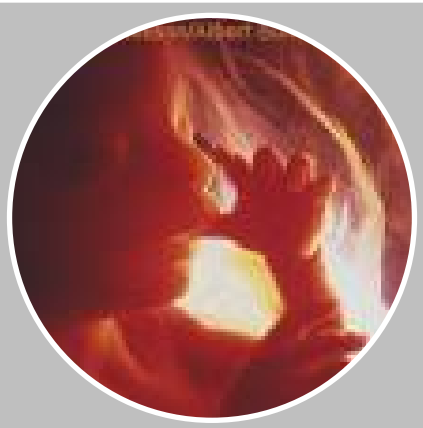




Early Prenatal | Mid-Late Prenatal | Postnatal

Central nervous system (3wks - 20 years)

Ear (4-20 wks)

Kidneys (4-40 wks)

Heart (3-8)

Limbs (4-8wks)

Immune system (8-40 wks; competence & memory birth-10yrs)

Skeleton (1-12 wks)

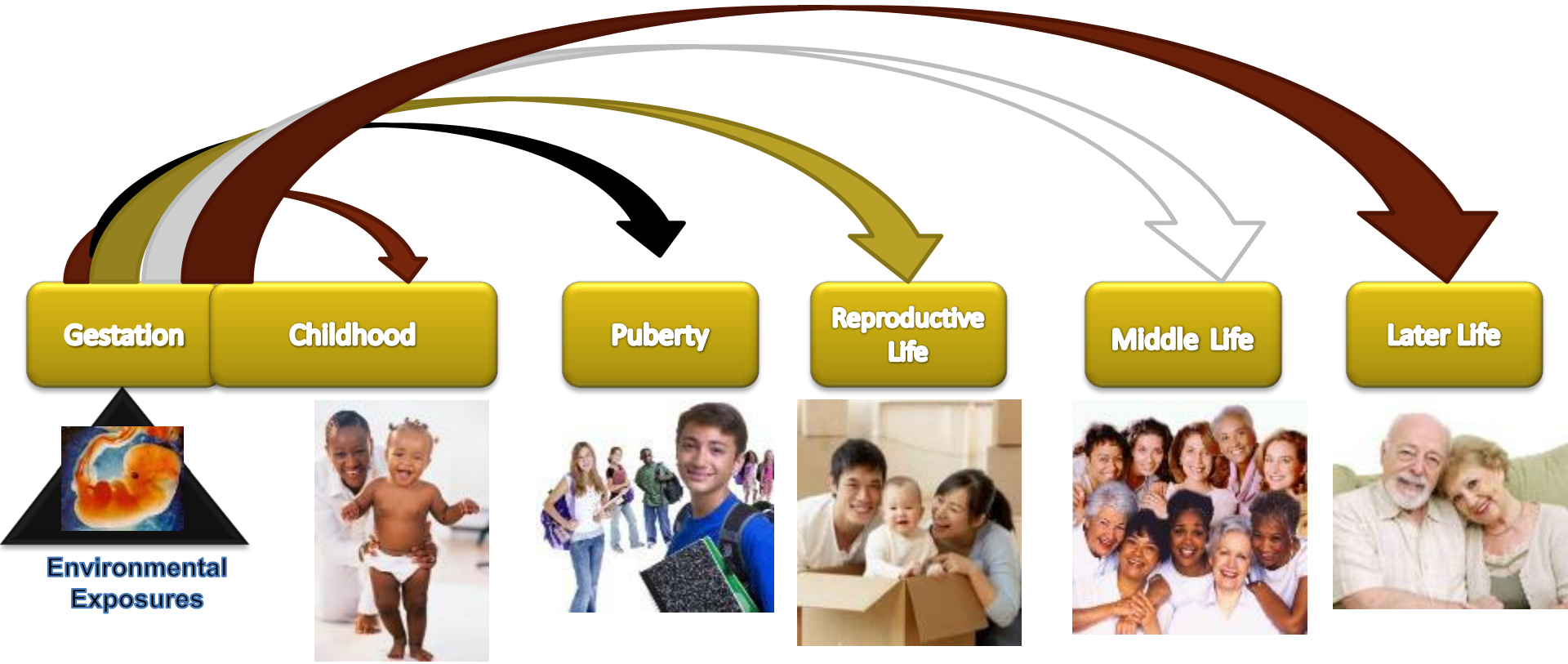
Lungs (3-40 wks; alveoli birth-10yrs)

Reproductive system (7-40wks; maturation in puberty)

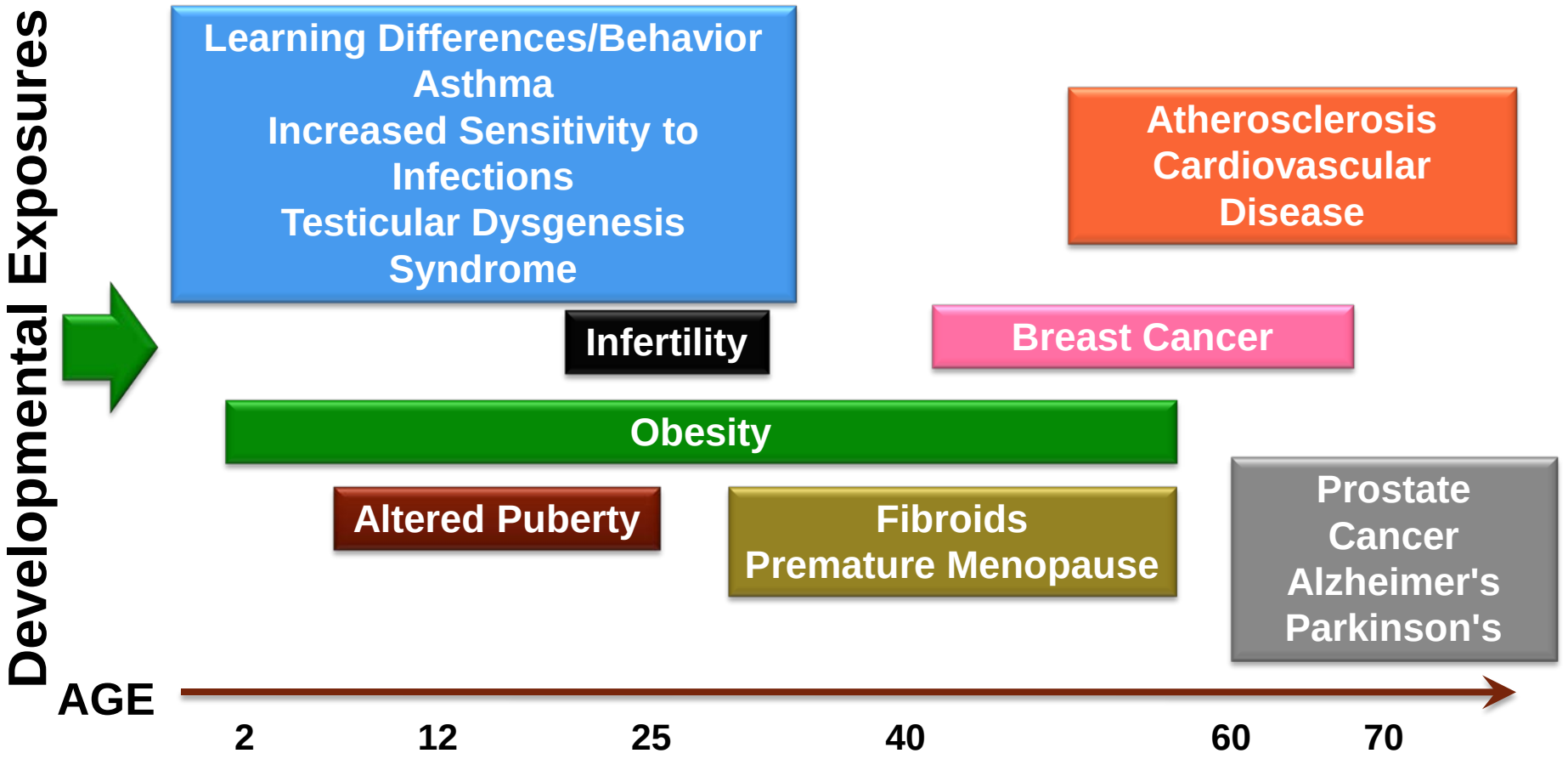
Week 1-16 | Week 17-40 | Birth – 25 years

Source: Altshuler, K; Berg, M et al. *Critical Periods in Development,* OCHP Paper Series on Children's Health and the Environment, February 2003.

Developmental Origins of Disease:
Developmental Stressors Lead to Disease Throughout Life

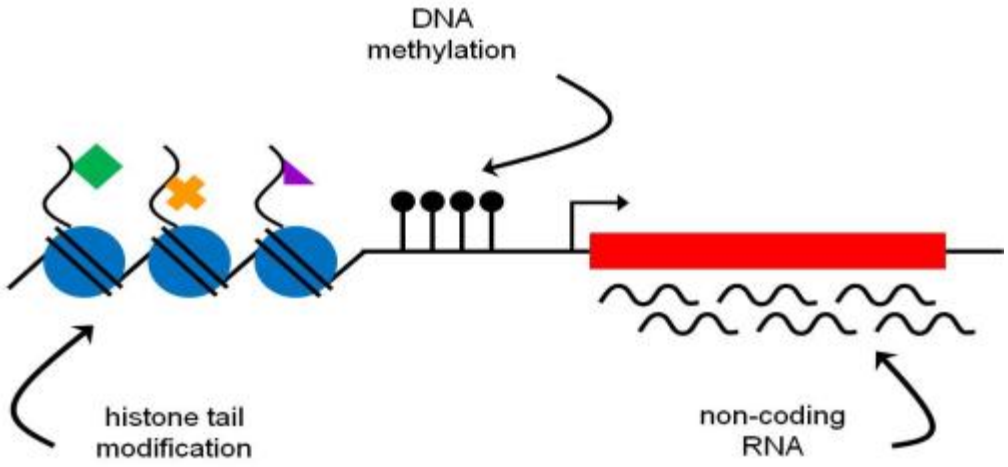


Examples of Developmental Origins of Health and Disease (DOHAD)

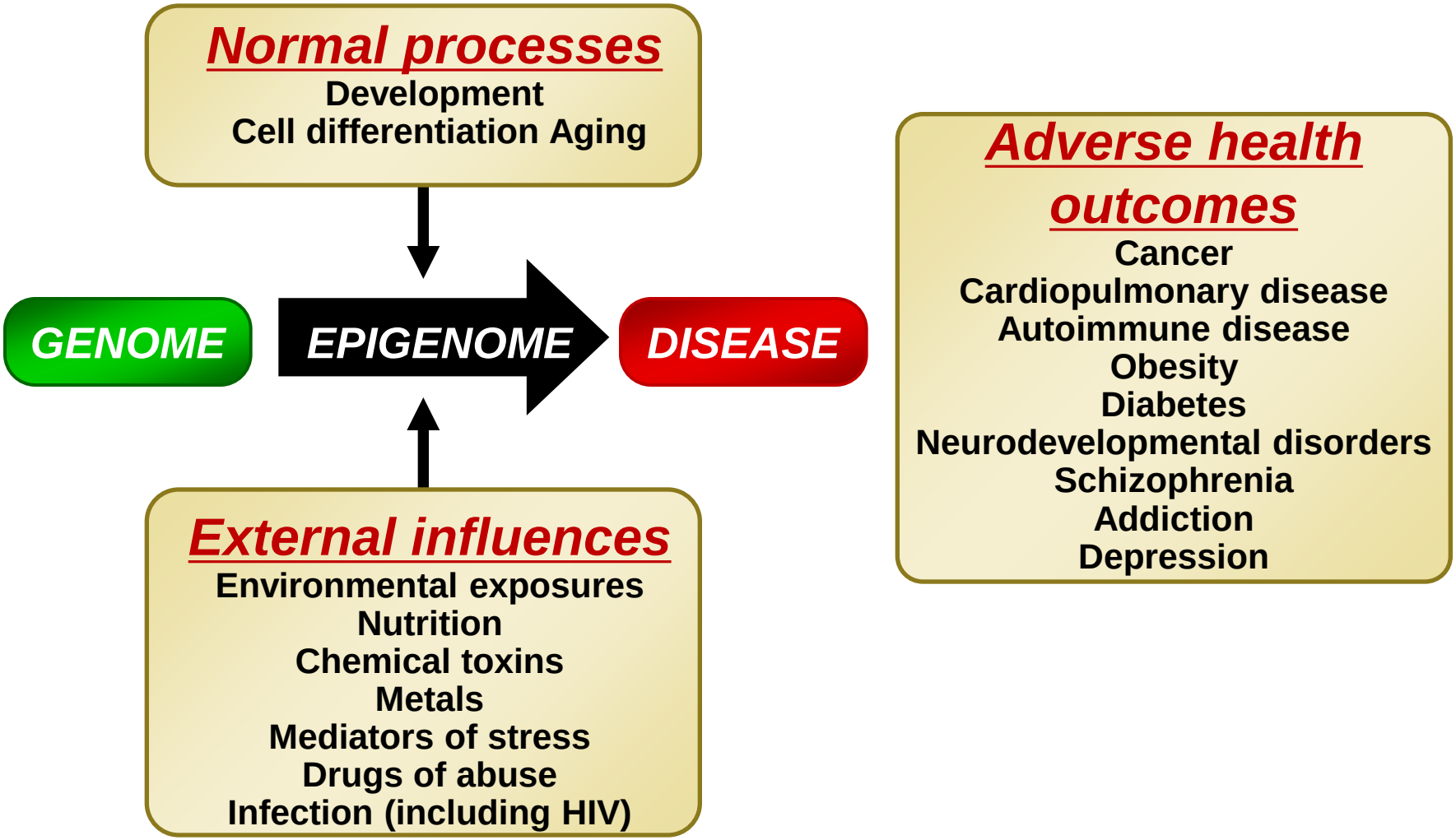


Epigenetics

- The study of changes in DNA expression that are independent of the DNA sequence.
- A person's DNA base sequence doesn't change, but expression of DNA is affected by changes in DNA "packaging."
- Environment is critical factor in DNA expression; we're born with genes, but environment affects epigenetic changes.

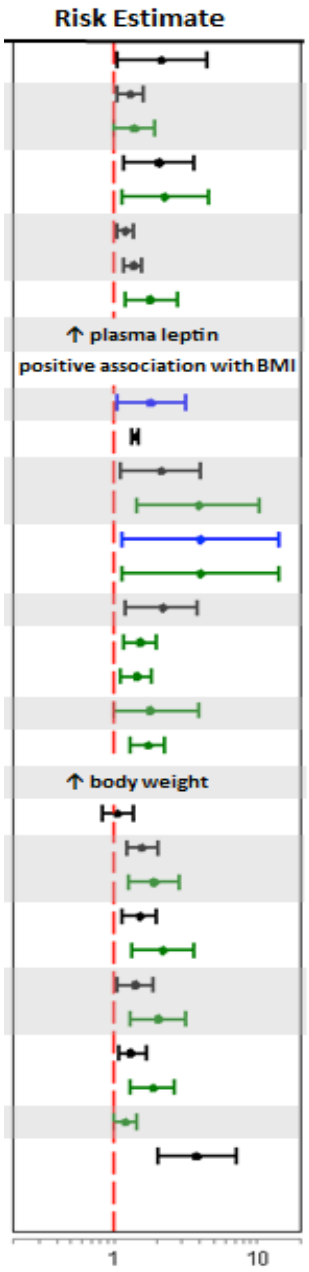


Epigenetic Changes Have Been Implicated in a Wide Variety of Human Diseases



Windows of Susceptibility: Tobacco

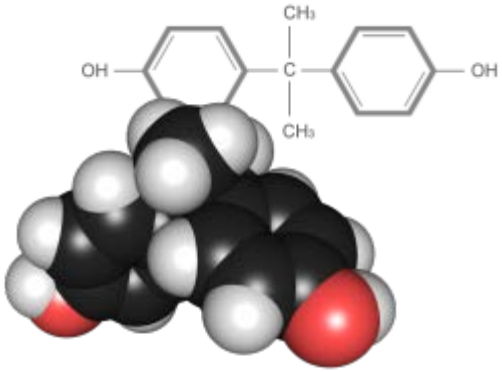
- **Maternal Smoking & Children's Obesity**
  - NTP Review of 23 Studies
  - Studies range from 2001 – 2010
  - Pooled data show:
    - OR=1.5 for obesity (95%CI=1.35-1.65)
    - OR=1.6 for overweight (95%CI=1.42-1.90)



obese overweight or overweight + obese diabetes or risk for metabolic syndrome

Low Dose

- Our endocrine system: ***tiny amounts*** of hormones with profound effects on development and normal health

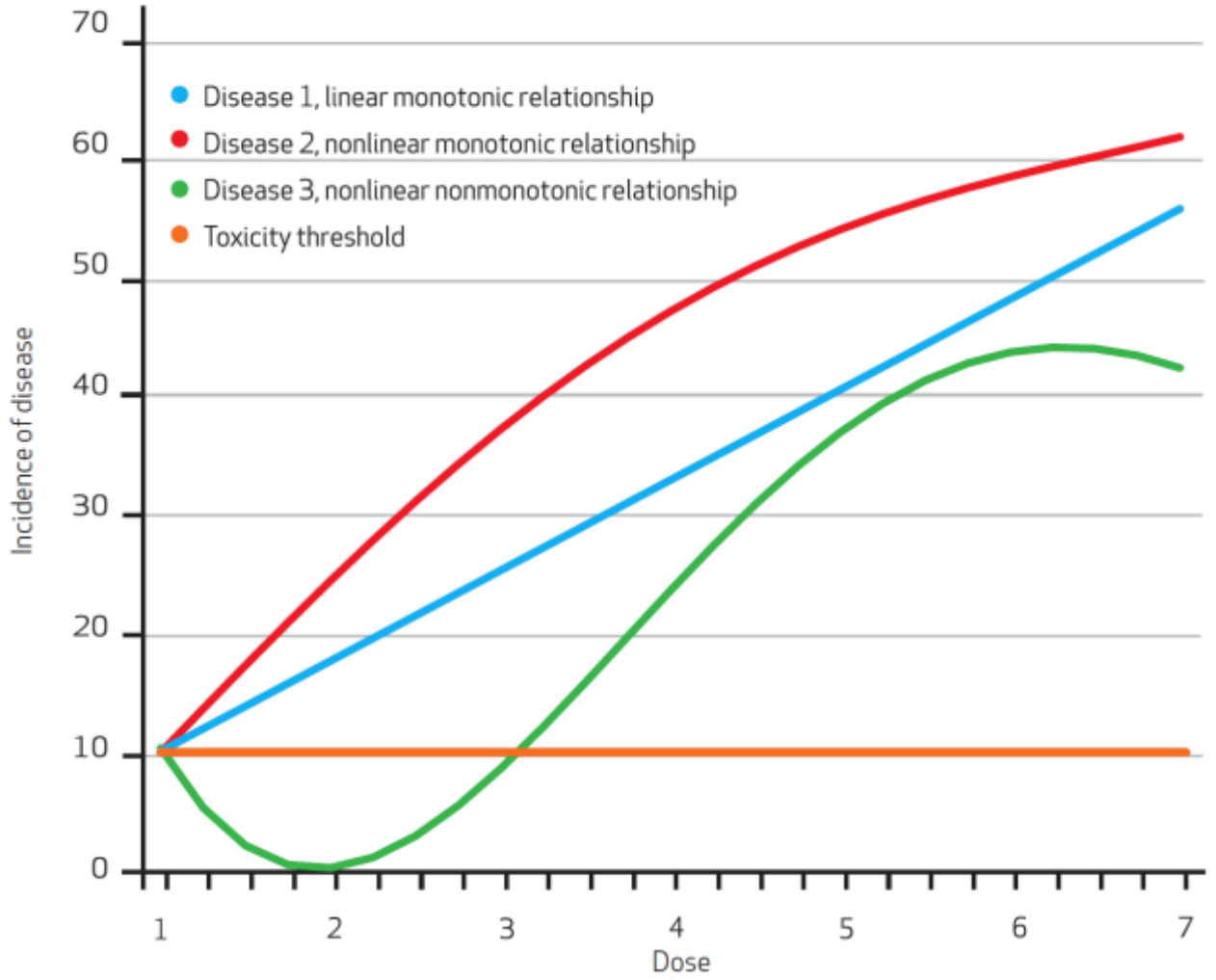


- Chemical exposures, even at low doses, can disrupt delicate endocrine system and create a mechanism for disease
- For some endocrine disruptors, biological changes can be seen at low doses, but not at high doses
- For example, low doses of BPA can change brain structure, function, and behavior in rats and mice exposed during critical periods of development

Non-Monotonic Dose-Response Curves

EXHIBIT 1

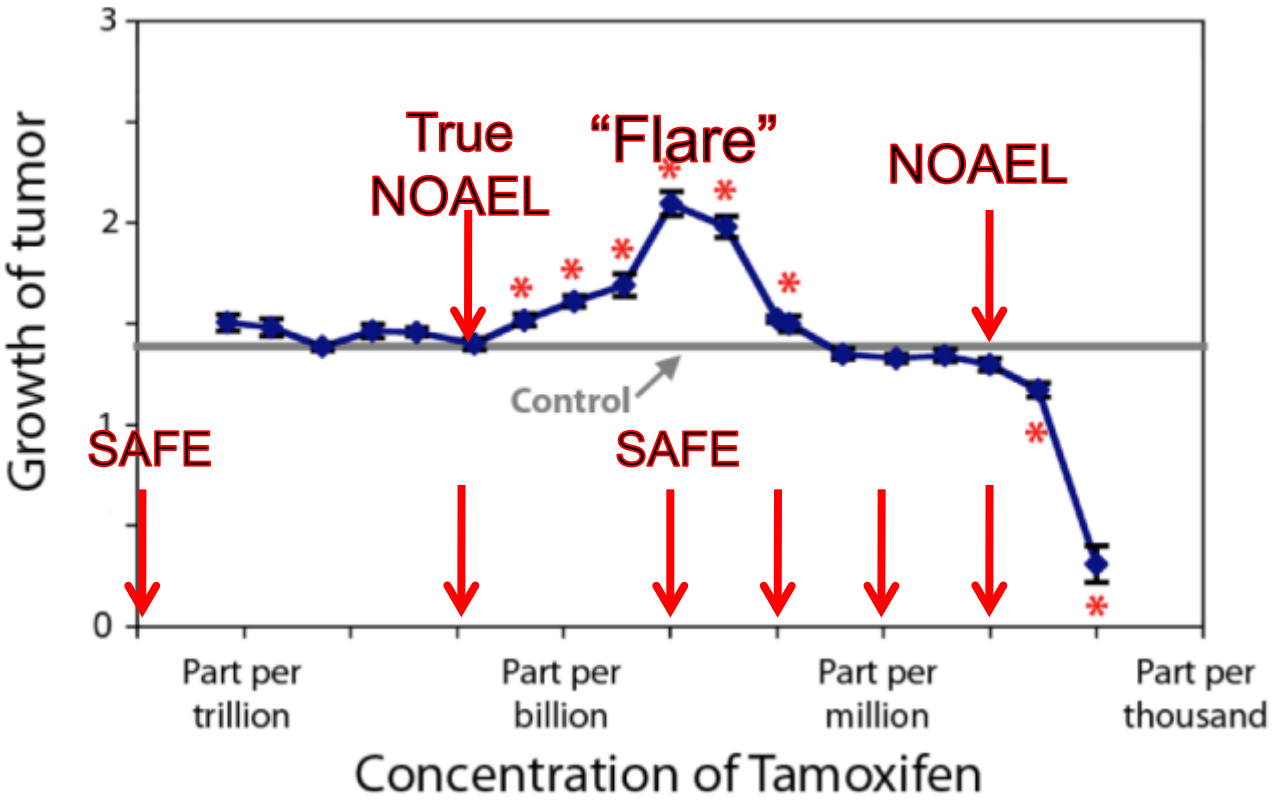
Depiction Of Various Hypothetical Dose-Response Relationships



Non-Monotonic Dose-Response Curves

- NMDRCs in hormones
  - Cortisol
  - Estradiol
  - Progesterone
  - Insulin
  - Growth Hormone
  - Prolactin
  - Testosterone
  - Thyroid Hormone
  - TSH
- NMDRCs in Endocrine Disruptors
  - Atrazine
  - Bisphenol A (BPA)
  - Chlorpyrifos
  - DDT
  - DES
  - Dioxin (TCDD)
  - PBDE-99
  - PCB 180 and PCB Mixtures
  - Perchlorate
  - Sodium fluoride
  - Tributylin oxide
  - Triclosan
  - And others…

A Practical Example: Tamoxifen Flare



Modified from Vandenberg et al, "Hormones and EDCs: Low-Dose Effects and Nonmonotonic Dose Responses," *Endocrine Reviews* 2012.

Obesity Epidemic

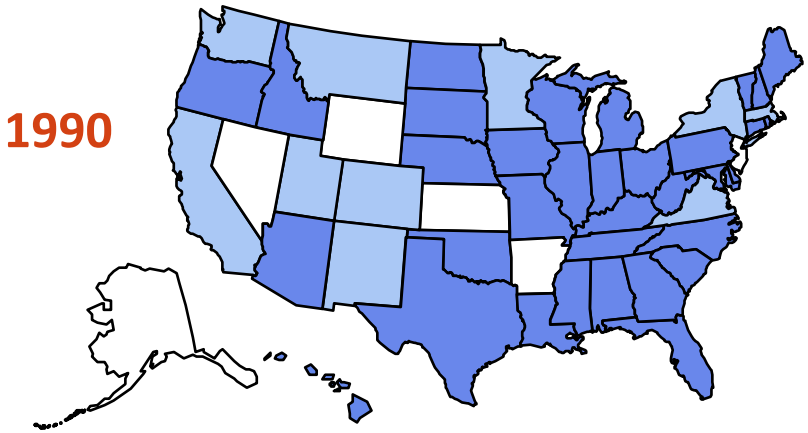
- Prevalence increasing in children, adolescents, adults worldwide
- Risk factors
  - Diet
  - Physical activity
  - Underlying genetics
  - Metabolic programming
- Environmental Exposures?

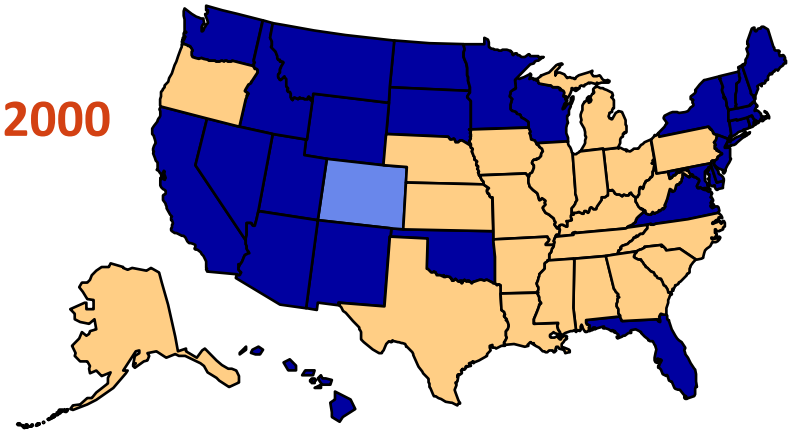
Complex Interrelated Factors Linked to Obesity

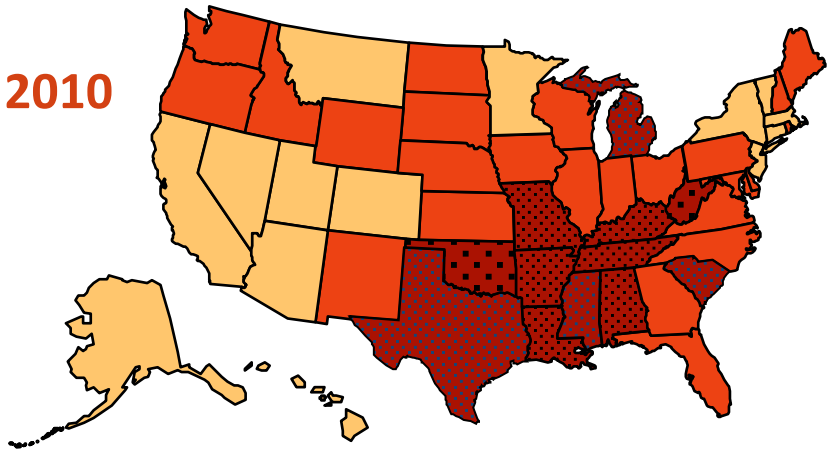
- **Behavior:** Over-nutrition and lack of exercise alone do not explain increased obesity prevalence
- **Genes:** No large-scale population changes
- **Environment:** Chemical exposures, such as POPS, linked to obesity and diabetes

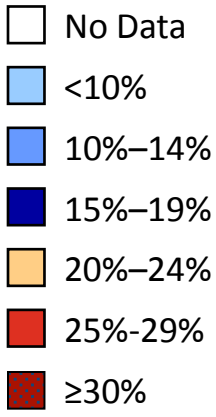
Obesity Trends Among U.S. Adults

Obesity = BMI ≥30, or ~30 lbs. overweight for 5'4" person

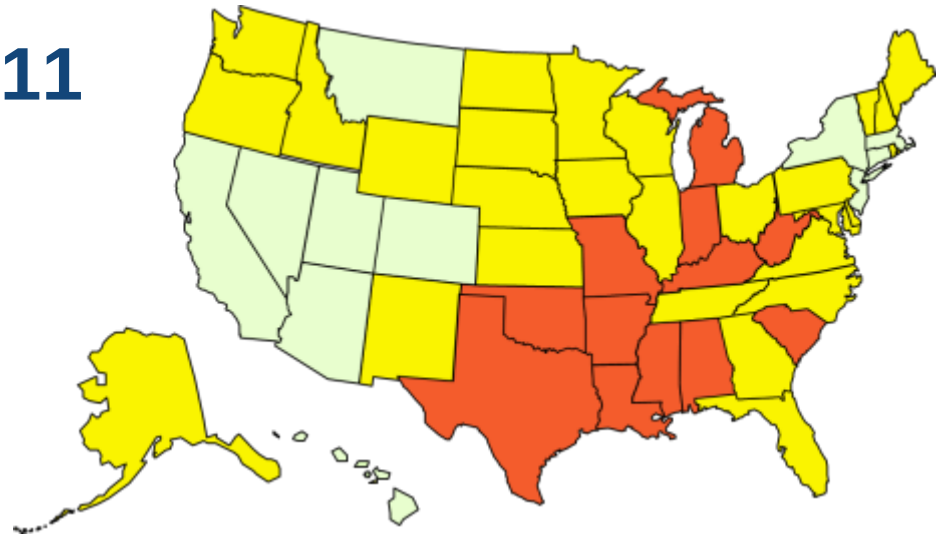








Obesity Prevalence, 2011

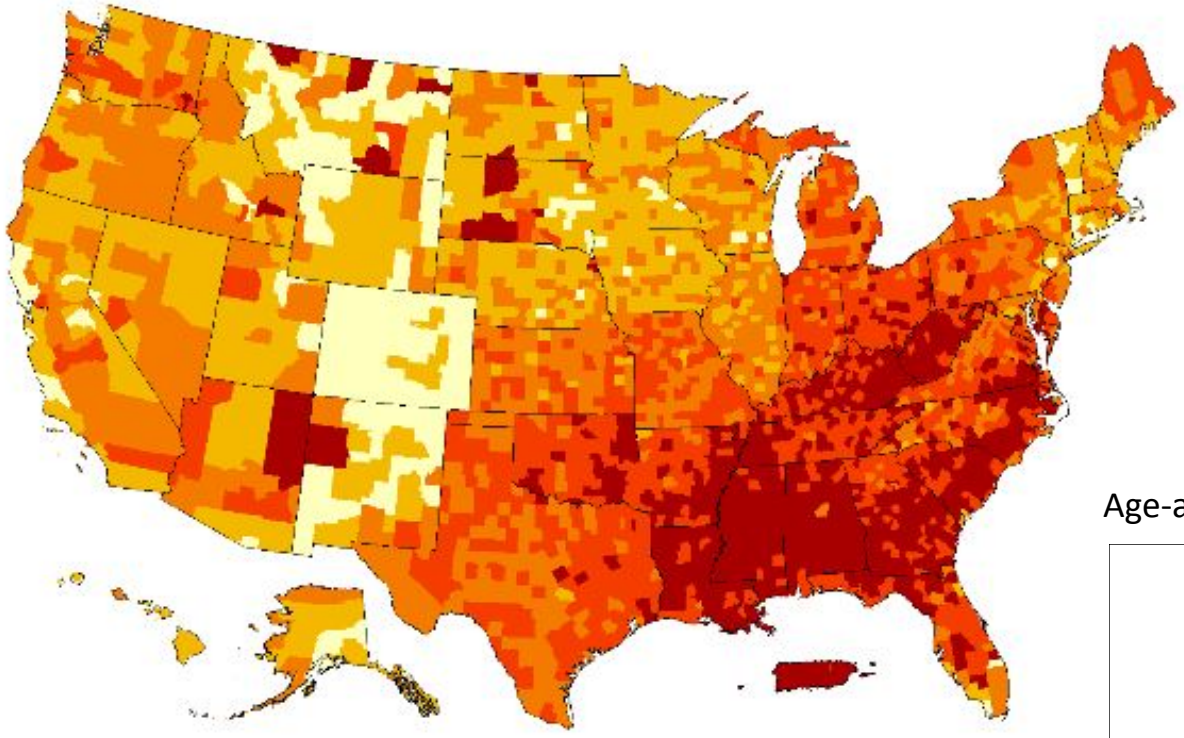


Obesity: BMI of 30 or higher

- No state had a prevalence of obesity less than 20%.
- 11 states and the District of Columbia had a prevalence between 20-30%.
- 12 states (AL, AR, IN, KY, LA, MI, MS, MO, OK, SC, TX, and WV) had a prevalence equal to or greater than 30%.

Diabetes Prevalence

County-level Estimates of Diagnosed Diabetes
Adults aged ≥ 20 years: United States, 2009



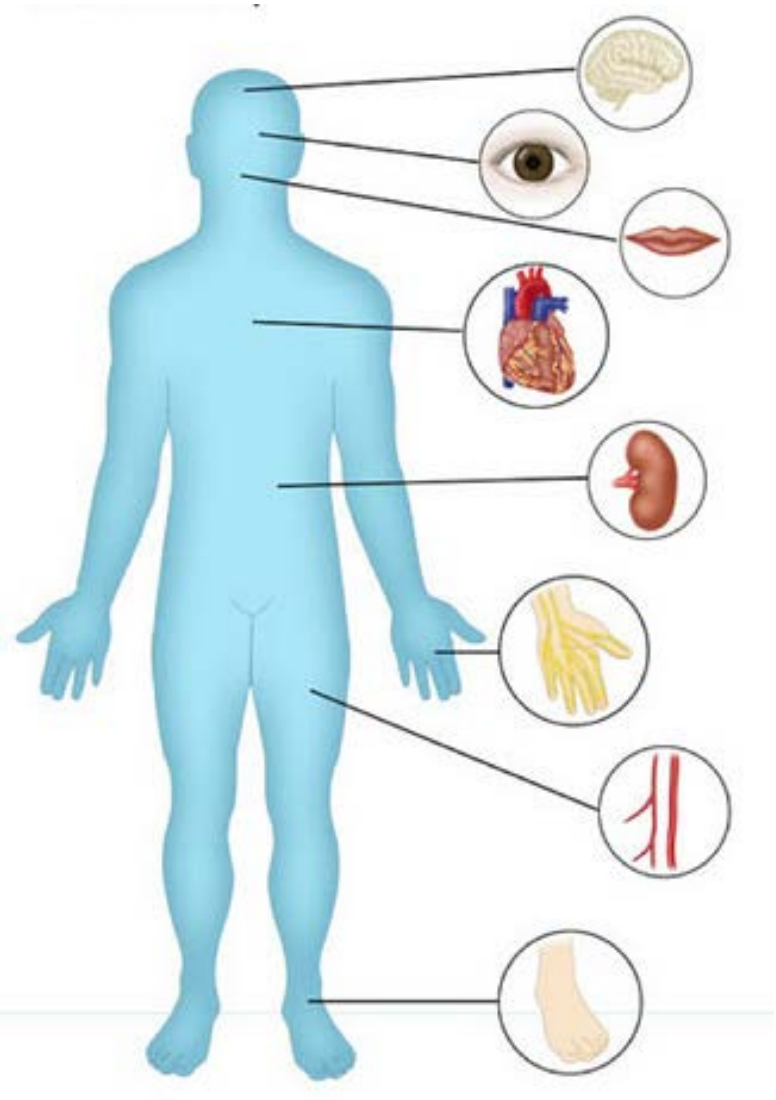
Diabetes affects 25.8 million people, 8.3% of the U.S. population

7th leading U.S. cause of death

Age-adjusted percent

Diabetes Complications

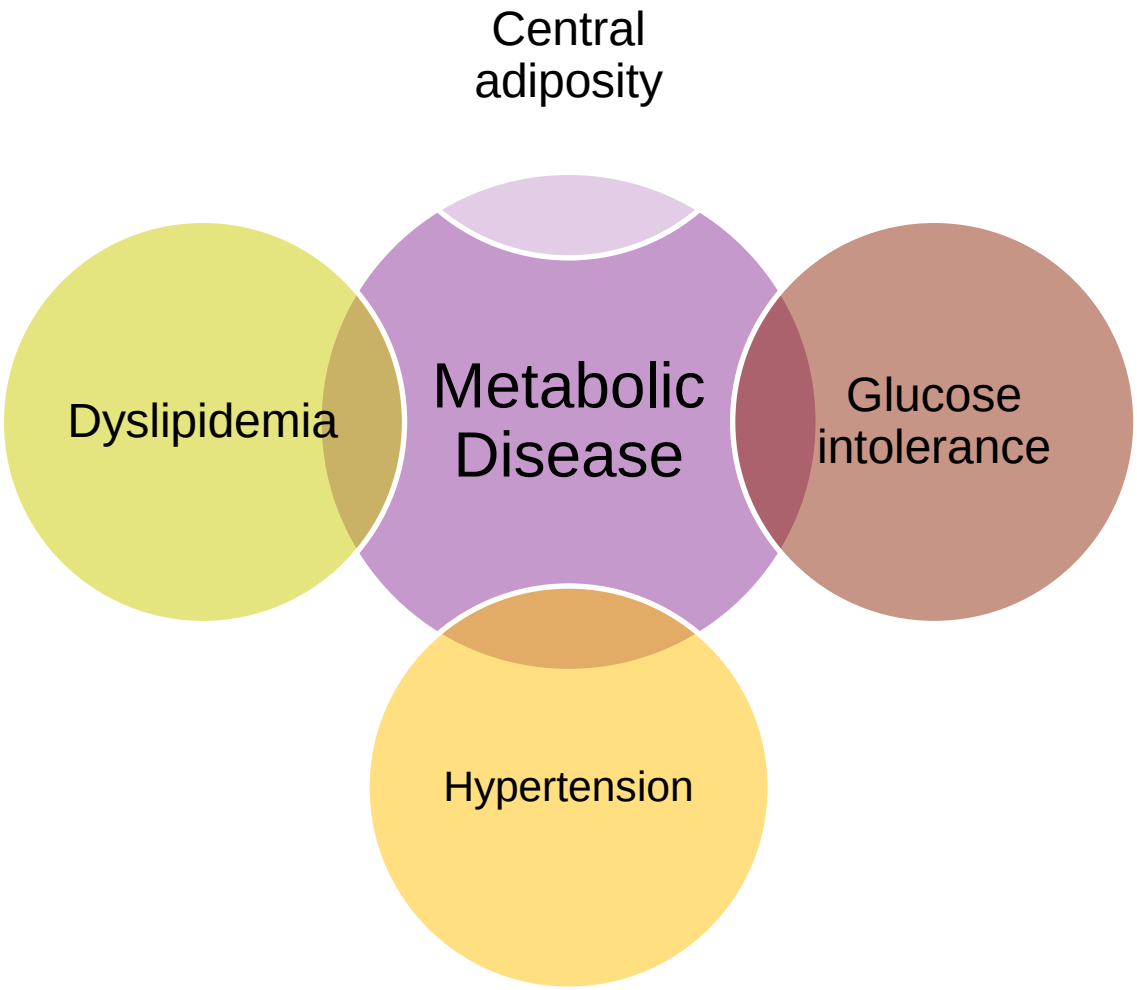
- Nervous system disease
- Blindness/eye problems
- Dental disease
- Heart disease and stroke
- Kidney disease
- Pregnancy problems
- Hypertension
- Amputations



What is Metabolic Syndrome?

A **clustering of phenotypes** thought to be induced by **insulin resistance**.

Affects nearly **50 million** people—almost 1 in 4 American adults.



Causes of Obesity: An Environmental Link?

Even those at the lower end of the BMI curve are gaining weight. Whatever is happening is happening to everyone, suggesting an ***environmental trigger****.*

- Robert H. Lustig, University of California, San Francisco

It makes a lot of sense that chemicals able to reprogram metabolism and favor the development of fat cells could be important contributing factors to obesity. The ***role of obesogens in fat accumulation*** *raises questions about the effectiveness of just diet and exercise in helping people lose pounds and maintain a proper weight.*

- Bruce Blumberg, University of California, Irvine

Evidence from the NTP 2011 Workshop

- Nicotine likely acts as a developmental obesogen in humans
- BPA affects insulin release and cellular signaling in pancreatic β cells
- There is a positive association between diabetes and certain organochlorine POPs
- Exposure to multiple classes of pesticides may affect risk factors for diabetes and obesity, although data gaps remain

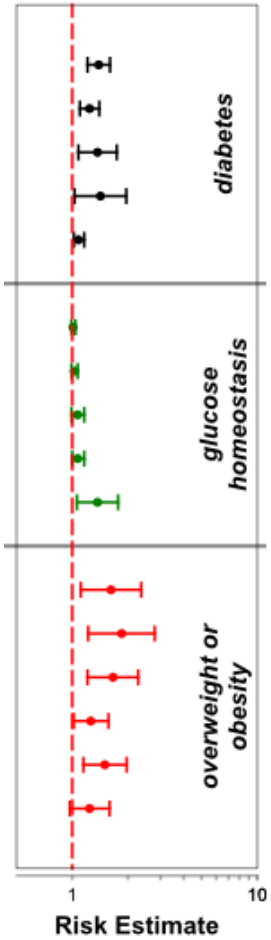
Environmental Chemicals in the Development of Diabetes and Obesity

- Exposure to certain chemicals or chemical classes has been associated with the development of diabetes or obesity in humans

Arsenic	Persistent organic pollutants (POPs)
Bisphenol A (BPA)	Pesticides
Trialkyltins (“Organotins”)	Phthalates
Maternal Smoking	Nicotine

Bisphenol A & Diabetes / Obesity (Human Studies)

- **BPA and Diabetes, Glucose Homeostatis, Obesity**
  - NTP Review of 8 Studies
  - Studies range from 2008 – 2011
  - Risk Estimates show:
    - All Odds Ratios > 1.00 for diabetes
    - All OR > 1.00 for glucose homeostatis
    - All OR > 1.00 for overweight & obesity
    - No pooled OR available yet
  - Recent 2012 Study by Trasande et al adds to the evidence linking BPA and obesity



Major Research Questions at NIEHS-EPA Children's Centers

- Understanding how exposure to environmental toxicants such as air pollutants, pesticides, EDCs, arsenic, heavy metals, PBDEs affect children's health.
- Understanding environmental contribution(s) to deficits in growth and development, asthma, autism, cancer & neurodevelopment.
- How to protect children from harmful exposures and environmental risks and to determine which children are most are susceptible to those risks.

Reducing OP Pesticide Exposure

1999: Animal studies link OP exposure to neurodevelopmental effects

2000: U.S. EPA bans indoor residential use of chlorpyrifos

2004: CCEH researchers show decreases in children's blood levels

2004: Prenatal organophosphate exposure reduces birth weight (Whyatt, 2004)

2005: CCEH investigators' testimony helps pass landmark NYC laws

2011: Human prenatal exposure linked to cognitive deficits (Bouchard, Engel, Raugh, 2011)

Center for the Health Assessment of Mothers And Children Of Salinas (CHAMACOS)

- To assess effects of pesticides in pregnant women and children on childhood growth, neurodevelopment, and respiratory disease.
- The CHAMACOS cohort of pregnant women have organophosphate (OP) pesticide levels 30-40% higher than US.
- 15% of pregnant women in CHAMACOS may have increased risk of adverse health effects resulting from excess OP pesticide exposure.

- Increased OP levels in utero and post-natal are adversely associated with attention levels in children.
- Latino children living in California have much higher flame retardant chemicals (PBDE) levels in their blood compared to Mexican children.

Pesticide Exposure Effects

- 404 multiethnic children and their mothers
- Prenatal total dialkylphosphate metabolite level associated with decrement in mental development at 12 months among blacks & Hispanics
- Associations enhanced among children of mothers who carried the PON1 Q192R QR/RR genotype
  (Engel et al, EHP, 2011)

Prenatal exposure to organophosphate (OP) pesticides can lower a child's IQ

Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year Old Children

Maryse F. Bouchard, Jonathan Chevrier, Kim G. Harley, Katherine Kogut, Michelle Vedar, Norma Calderon, Celina Trujillo, Caroline Johnson, Asa Bradman, Dana Boyd Barr, Brenda Eskenazi

ehp ENVIRONMENTAL HEALTH PERSPECTIVES
ehponline.org
Online 21 April 2011

7-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide

Virginia Rauh, Srikesh Arunajadai, Megan Horton, Frederica Perera, Lori Hoepner, Dana B. Barr, Robin Whyatt

Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood

Stephanie M. Engel, James Wetmur, Jia Chen, Chenbo Zhu, Dana Boyd Barr, Richard L. Canfield, and Mary S. Wolff

Recent NIEHS Studies on Pesticide Effects

- High Pesticide Exposure Events (HPEE) & Cognitive Decline
  - One or more HPEE may contribute to adverse CNS outcomes independent of diagnosed pesticide poisoning.
  - Findings part of Agricultural Health Study.

- Two Pesticides Associated with Parkinson's Disease
  - People who used either rotenone or paraquat developed Parkinson's disease approximately 2.5 times more often than non-users.

Linking Environment to Effects

Exposure Assessment	Biomarkers of Effect Exposure / Susceptibility	Outcome
• Air Pollutants • PAHs Pmy Endotoxin • ETS, Manganese • Allergens • Metals • Pesticides • Phthalate diesters • EDCs, BPA, PBDEs, PDBs, Arsenic • Nutritional deficits • Social stressors	• Exhaled NO • PAH-DNA Adducts • Cotinine • Immune changes • Lead, Mercury • Pesticides • Phthalates • Metabolites • Vitamins A, C, E • Built Environment	• Asthma • Fetal Growth • Child Neurodevelopment • Asthma • Obesity • Autism • Childhood Leukemia • Developmental Delay • Genetic Polymorphisms • Epigenetic marks

Need for Chemical Testing

- Over 80,000 chemicals in commerce today
- Majority of chemicals in commerce are untested
- About 12 chemicals (alcohol, lead, mercury, etc.) have been closely associated with human cognitive impairment
- About 100 chemicals have been shown to impair brain development in animal models

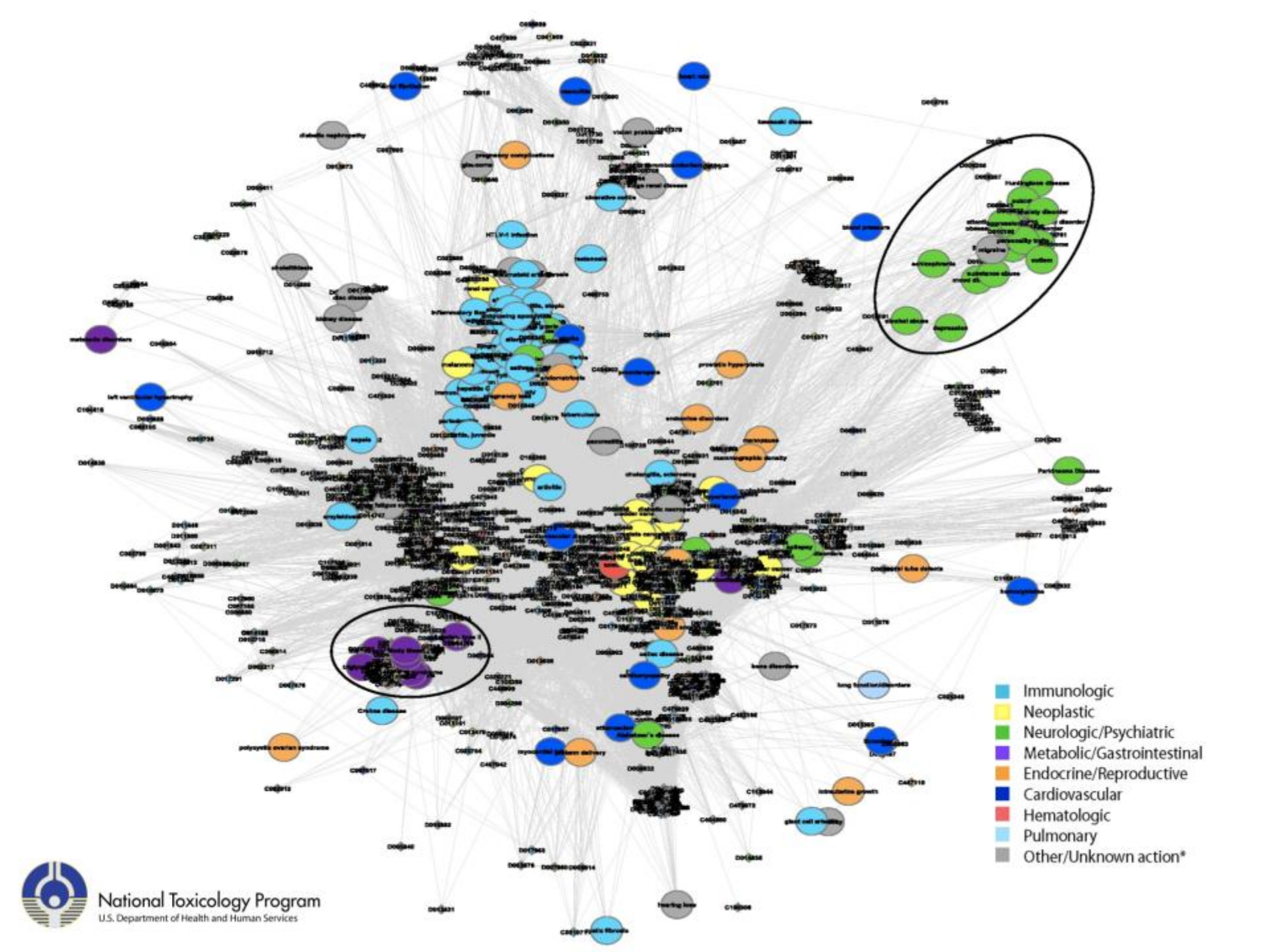



National Toxicology Program Efforts

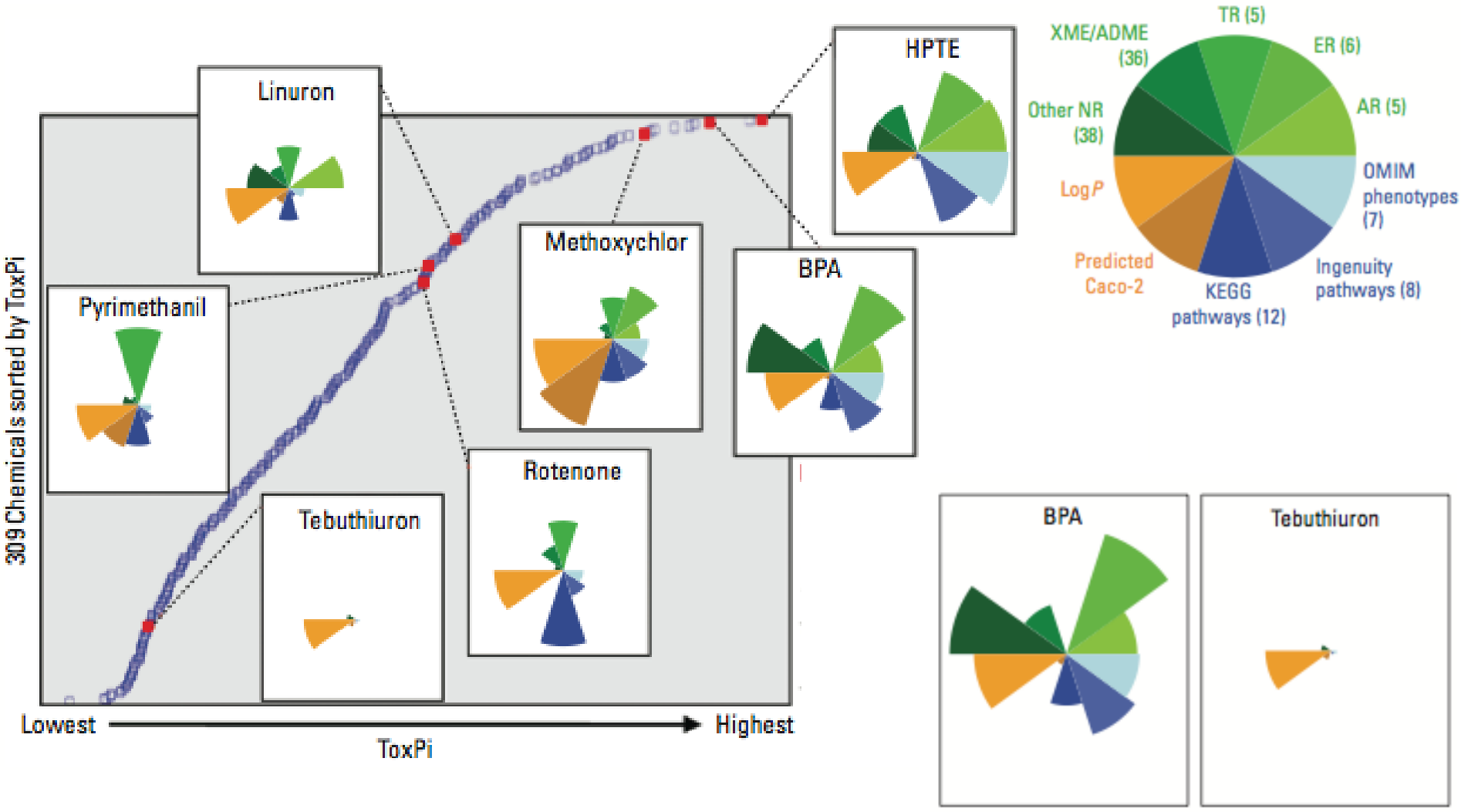
- Better coordination of testing across the Federal government
- Increase understanding of exposure-response relationships
- Develop new methods for efficient, thorough toxicological assessments
- Integrate results from new “data rich” techniques (i.e. genomics, high through-put screening) with traditional toxicology data to provide public health context
- Toxicity for the 21st Century or “Tox21”
  - MOU between NTP, NCATS, EPA and FDA
  - High throughput, robotic testing of toxic compounds in cell and molecular assays
  - Using knowledge of biological response to identify toxicity pathways
  - Prioritization for further testing

Genetics, Genomics and Bioinformatics for Pathways Research

- Use knowledge about genes associated with disease
- Find the pathways linked to the genes and link them to disease
- Evaluate pathways most likely to be relevant targets
  - "Disease Pathways"
- Use toxicogenomics/proteomics databases on chemicals already studied to link chemicals to diseases through pathways
  - "Toxicity Pathways"
- Analyze the "Toxicity Pathways" to find best points for screening
  - Critical proteins/genes
  - Connection points between pathways
- Use "omics" and other molecular tools to validate choices

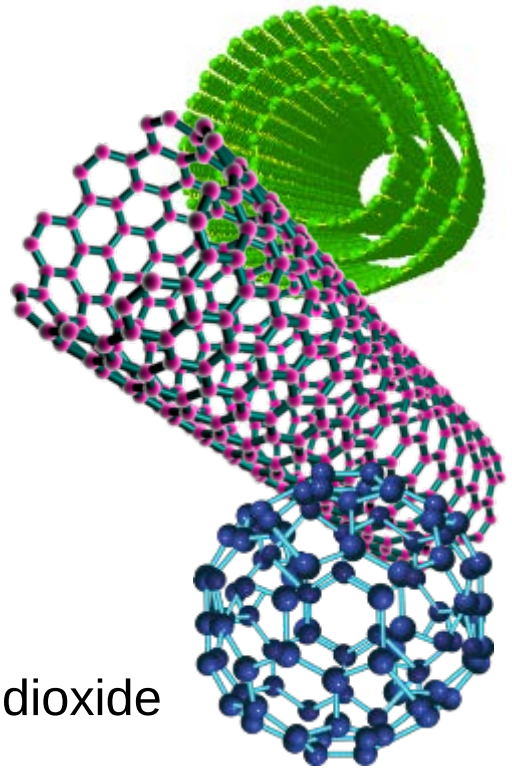

Immunologic
Neoplastic
Neurologic/Psychiatric
Metabolic/Gastrointestinal
Endocrine/Reproductive
Cardiovascular
Hematologic
Pulmonary
Other/Unknown action*
National Toxicology Program
U.S. Department of Health and Human Services

High-Throughput Screening: Bisphenol A



Evaluating the Safety of Engineered Nanomaterials: The NIEHS NanoHealth & Safety Initiative

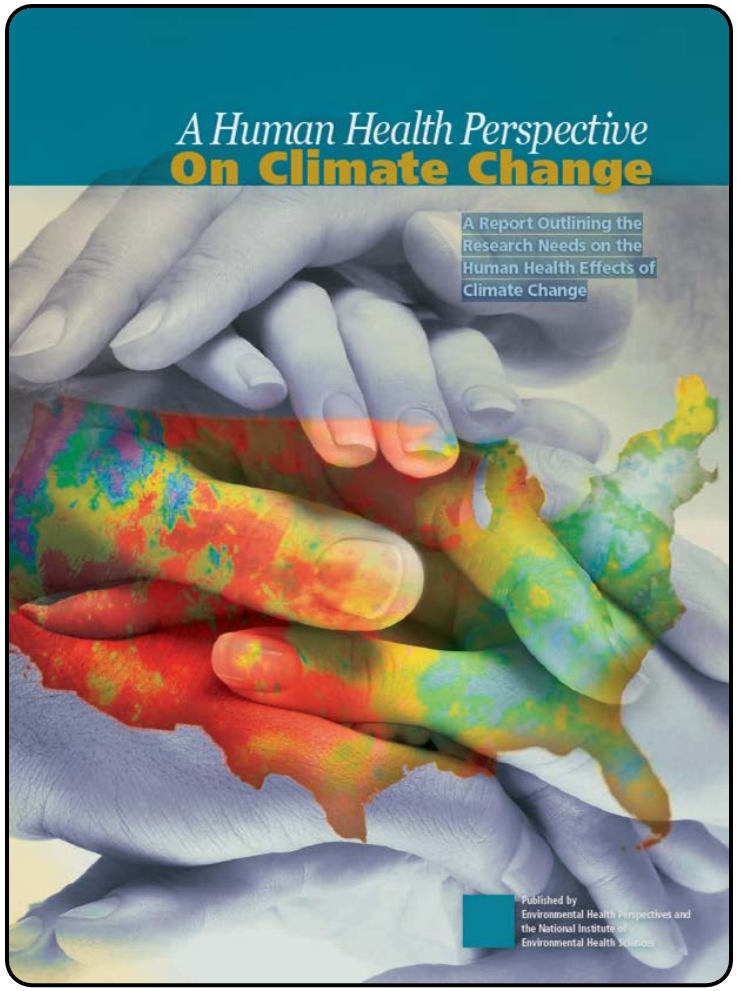
- To expand the base of knowledge on nanomaterials safety and how structural aspects affect biological activity
- Extramural research: Biological interactions
  - Methods for exposure measurement
  - Linking physical/chemical properties to response
  - Capture results in database for meta-analysis
- Intramural research: Impact on chronic disease
  - Carbon nanotubes and asthma
- NTP: Nanotechnology toxicity research
  - Dermal penetration studies of nanoscale titanium dioxide
  - Pharmacokinetics of quantum dots
  - Toxicity studies of carbon fullerenes



Climate Change and Human Health

Consequences of climate change:

- Asthma, Respiratory Allergies, and Airway Diseases
- Cancer
- Cardiovascular Disease and Stroke
- Foodborne Diseases and Nutrition
- Heat-Related Morbidity and Mortality
- Human Developmental Effects
- Mental Health and Stress-Related Disorders
- Neurological Diseases and Disorders
- Vectorborne and Zoonotic Diseases
- Waterborne Diseases
- Weather-Related Morbidity and Mortality



Hydraulic Fracturing (Fracking)

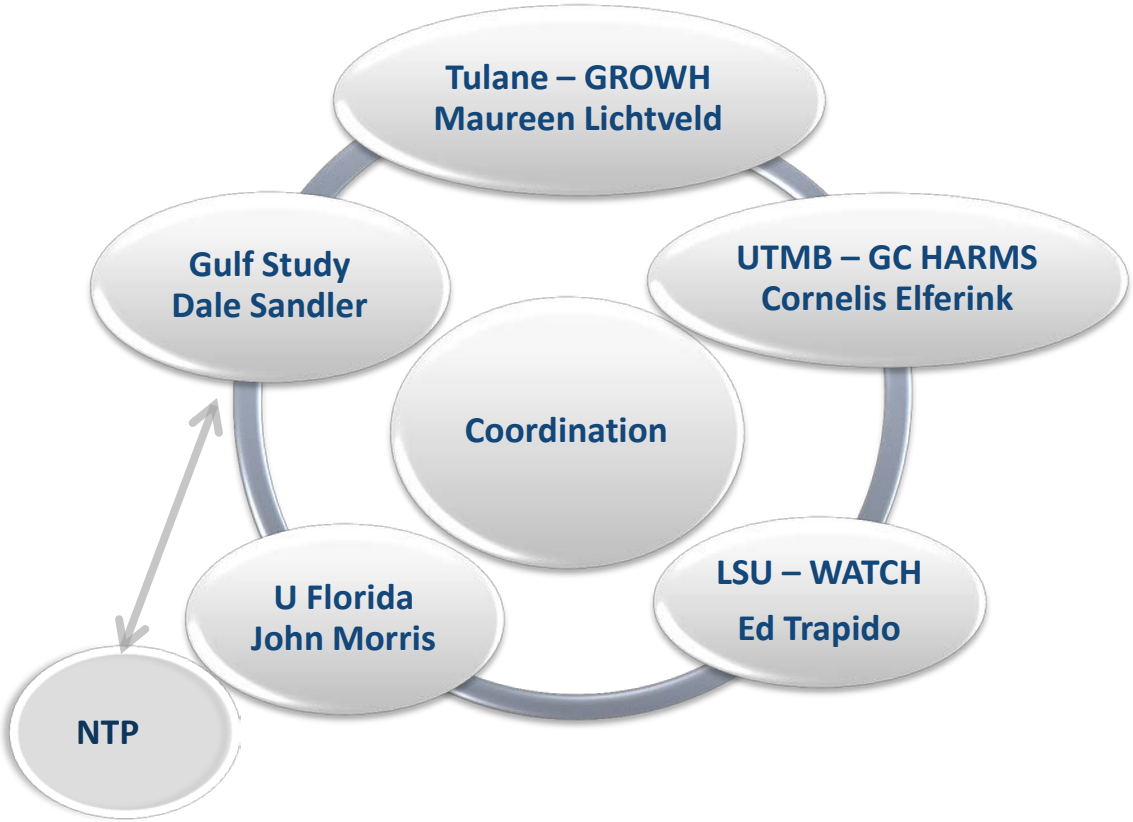
- Drilling for natural gas using large amounts of water under high pressure to fracture rocks and release gas
- Chemicals used with water during drilling
- Chemicals may contaminate drinking water sources
- Large fluid ponds for storage of chemical waste
- Large truck traffic
- Other potential health effects of Fracking
  - Air & noise pollution
  - Earthquakes & explosions
  - Both occupational and residential hazards

NIEHS Fracking Activities

- Research grants related to Fracking
  - time-sensitive funding opportunity (PAR-10-83 & 84)
  - R1: Assessing and Addressing Community Exposures to Environmental Contaminants (PA-12-153)
- Community Outreach & Education Core Centers, fracking webinar, October 2011
- Supported IOM Roundtable on Fracking, April 2012
- Convening NIH Institutes with Fracking activities / interests
- Interagency Steering Cmte. on Unconventional Oil and Gas Research
- Environmental Health Collaborative Summit, October 2012
- NTP data monitoring and Hydrofracking Seminar, November 2011

Gulf Academic-Community Consortium Network

- NIH Cooperative Agreement – allows substantial Federal scientific or programmatic involvement to coordinate and/or guide activities



Steering Committee:

- PI from each consortium
- Community member from each consortium
- PI of GuLF study
- NIH staff

GuLF STUDY

A health study for oil spill clean-up workers and volunteers

Objectives:

- Assess health effects associated with oil spill clean-up following Deepwater Horizon disaster
- Investigate biomarkers of adverse biological effects
- Create a resource for future collaborative research

Our Commitment : *Translating Bench Science into Environmental Public Health*

NIEHS
National Institute of Environmental Health Sciences

NIEHS Strategic Plan

Mission

The mission of the National Institute of Environmental Health Sciences is to discover how the environment affects people in order to promote healthier lives.

Strategic Themes for Environmental Health Sciences

Vision

The vision of the National Institute of Environmental Health Sciences is to provide global leadership for innovative research that improves public health by preventing disease and disability.

Strategic Goal #1:

Identify and understand fundamental shared mechanisms or common biological pathways (e.g., inflammation, epigenetic changes, oxidative stress, mutagenesis) underlying a **broad range of complex diseases**, in order to enable the development of broadly applicable prevention and intervention strategies.

Strategic Goal #2:

Understand **individual susceptibility across the life span** to chronic, complex diseases resulting from environmental factors, in basic and population-based studies, to facilitate prevention and decrease public health burden.

Strategic Goal #3:

Transform exposure science by enabling consideration of the totality of human exposures and links to biological pathways and create a blueprint for incorporating exposure science into human health studies.

Strategic Goal #4:

Understand how **combined environmental exposures** affect disease pathogenesis.

Strategic Goal #5:

Identify and respond to **emerging environmental threats** to human health on both a local and global scale.

Strategic Goal #6:

Establish an **environmental health disparities** research agenda to understand the disproportionate risks of disease and to define and support public health and prevention solutions in affected populations.

Strategic Goal #7:

Use **knowledge management** techniques to create a **collaborative environment** for the EHS community to encourage an **interdisciplinary approach** to investigate, analyze, and disseminate findings.

Strategic Goal #8:

Enhance the teaching of EHS at all levels of education and training (K-professional) to **increase scientific literacy** and **generate awareness of the health consequences** of environmental exposures.

Strategic Goal #9:

Inspire a diverse and well-trained cadre of scientists to move our transformative environmental health science forward; **train the next generation of EHS leaders** from a wider range of scientific disciplines and diverse backgrounds.

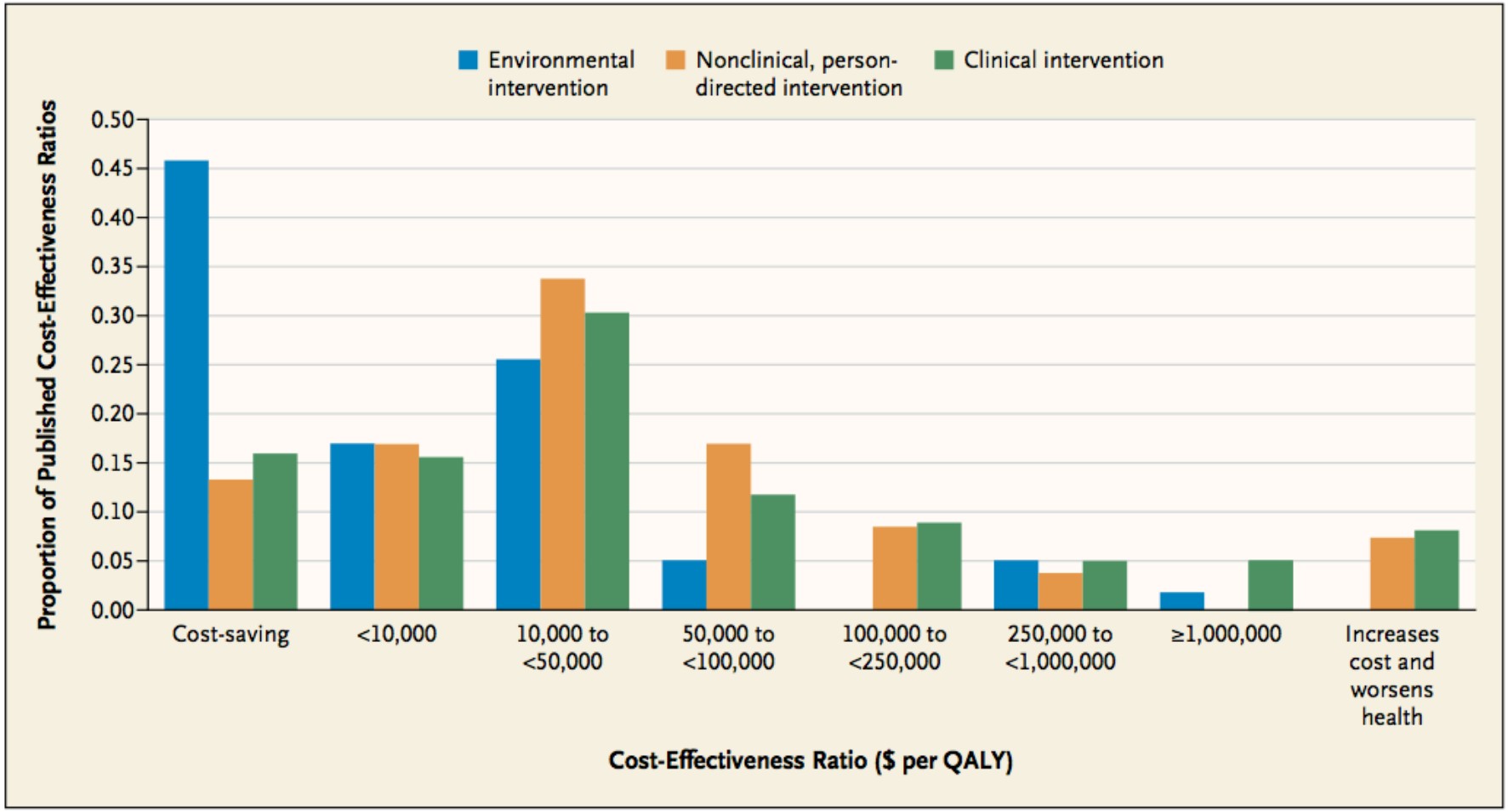
Strategic Goal #10:

Evaluate the **economic impact of policies, practices, and behaviors** that reduce exposure to environmental toxicants through prevention of disease and disabilities; invest in **research programs to test how prevention improves public health and minimizes economic burden**.

Strategic Goal #11:

Promote bidirectional communication and collaboration between researchers and stakeholders (policy makers, clinicians, intervention/prevention practitioners, and the public) in order to advance research translation in the environmental health sciences.

Public Health Implications of Environmental Effects



Cost-Effectiveness of Categories of Preventive Interventions.

Chokshi and Farley, N Engl J Med 2012; 367:295-297.

A New Vision for NIEHS and NTP

- A strong desire to partner with our sister institutes and other federal agencies: EPA, CDC, FDA, DOE….
- Health and Environment is a priority
- New issues and technologies are emerging

- We need the best individual and team science to address complex diseases and complex environmental impacts
- We need to improve integration across research disciplines and with all partners
- We need to improve our translation and communication of basic science findings into human health protection

Thank you!

NIEHS
National Institute of
Environmental Health Sciences

National Toxicology Program
U.S. Department of Health and Human Services

SRP
Superfund
Research Program

NIEHS Strategic Plan Website
http://www.niehs.nih.gov/strategicplan