The National Institute of Environmental Health Sciences and the Future of Environmental Health

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What is the NIH?

- The National Institutes of Health is the primary Federal agency for conducting and supporting medical research for the Nation.
- More than $30 billion invested annually in medical research
- 50,000 competitive grants awarded to more than 200,000 researchers at over 2,800 universities, medical schools, and other research institutions in every state -- and around the world
The National Institute of Environmental Health Sciences

- One of the 27 National Institutes of Health, but located in RTP, 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
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.

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.
NIEHS Strategic Plan Goals

Goal 1
- Identify and understand fundamental shared mechanisms or common biological pathways underlying a broad range of complex diseases

Goal 2
- Individual susceptibility across the life span

Goal 3
- Transform exposure science

Goal 4
- Combined environmental exposures

Goal 5
- Emerging environmental threats

Goal 6
- Environmental health disparities
NIEHS Strategic Plan

Goal 7
- Knowledge management, collaborative environment, interdisciplinary approach

Goal 8
- Enhance the teaching of EHS, increase scientific literacy
- Generate awareness of health consequences

Goal 9
- Inspire a diverse, well-trained cadre of scientists
- Train the next generation of EHS leaders

Goal 10
- Economic impact of policies, practices and behaviors
- Research programs to test how prevention improves public health and minimizes economic burden

Goal 11
- Promote bidirectional communication and collaboration between researchers and stakeholders
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
Trends in human health

- **Testicular cancer**
  - Age adjusted incidence per 10,000 population
  - Year: 1973 to 1997

- **Breast cancer**
  - Age adjusted incidence per 10,000 population
  - Year: 1973 to 1997

- **Hypospadias**
  - Rate per 10,000 births
  - Year: 1970 to 1991

- **Sperm counts**
  - Count (x10^6/ml)
  - Year: 1920 to 2000
  - North America: 
  - Europe: 

*Sharpe et al. 2004*
Why environmental health matters

• 13 million deaths could be *prevented* per year by improving our environment

• Environmental factors influence 85 out of the 102 non-communicable diseases in WHO report

• Environmental factors account for at least 2/3 of cancer cases in the United States

• You can’t change your genes, but you **CAN** change your environment

NIEHS research is focused on understanding the interaction of our genetic susceptibilities and our environmental exposures.
“ENVIRONMENT” includes:

- Industrial and agricultural chemicals
- Physical agents \((heat, radiation)\)
- By-products of combustion and industrial processes \((air\ pollution, dioxin)\)
- Infectious agents
- Microbiome \((gut\ flora)\)
- Prescription drugs
- Foods and nutrients
- Lifestyle choices and substance abuse
- Social and economic factors
- Climate and weather
Non-communicable diseases with a known or suspected environmental component

- Cancers
- Cardiovascular disease (*air pollution, dioxins*)
- Endocrine disorders (*diabetes*)
- Birth defects (*cleft palate, cardiac malformations*)
- Reproductive dysfunction (*infertility*)
- Lung dysfunction (*asthma, asbestosis*)
- Neurodegenerative diseases (*Parkinson’s*)
- Neurodevelopmental disorders (*autism*)
- Obesity, cardiopulmonary disease, autoimmune disease, schizophrenia, addiction, Alzheimer’s Disease, and depression…
Exposure is ubiquitous

- Chemicals are widely dispersed in our environment
- Chemicals are often dispersed at biologically effective levels, exposure to humans is common
- Exposures do not occur singly
- One exposure can alter body’s response to other exposures
- Combinations must be studied
- “Exposome” is the totality of exposures for a person
Air pollution exposure contributes to:

- Obesity
- Asthma
- COPD
- Cancer
- Decreased IQ
- Developmental Disabilities
- Autism
- Behavioral Effects
- Autoimmunity
- Pulmonary Disease
- Pneumonia
- Lower Respiratory Infections
- Cardiovascular Disease
The air we breathe...indoors

- 3 billion people exposed
- Over 4 million people die prematurely from cooking with solid fuels
- More than 50% of premature deaths among children under 5 are due to pneumonia caused by particulate matter (soot) inhaled from indoor air pollution
- 3.8 million premature deaths annually from non-communicable diseases

Indoor air quality associated with multiple adverse health outcomes

- Decreased *neurodevelopmental* performance associated with woodsmoke exposure (Dix-Cooper *et al.* 2012)
- Indoor biomass fuel exposure is associated with increased risk of *LBW* (49%), *respiratory illness* (39%) and *infant mortality* (21%) (Tielsch *et al.* 2009)
- **Asthma** associated with open-fire cooking in Venezuela (Kraai *et al.* 2013)
- Household air pollution is a major avoidable risk factor for *cardiorespiratory disease* (Mortimer *et al.* 2012)
- **Decreased lung function** associated with carbon monoxide exposure in household air pollution (Pope *et al.* 2014)
Exposure to arsenic in drinking water

• Levels higher in rural US communities (SW, MW, NE)

• In approximately 7% of US wells levels thought to exceed EPA standards

• Health effects are broad:
  – Cancer (lung, larynx, liver, kidney, bladder, skin)
  – Respiratory (bronchiectasis, COPD, emphysema, chronic lung infections)
  – Vascular and cardiovascular disease
  – Reproductive and developmental problems
  – Neurological problems (reduced cognitive function in children)
  – Type 2 diabetes
  – Endocrine disruptor
Exposure to endocrine disrupting chemicals (EDC) may contribute to obesity

- ≥30% of women and men 18+ are obese in the US
- Differences in obesity prevalence between sexes in some regions

- Prevalence higher in women (ex. Mexico, Chile, S. Africa)
- Prevalence higher in men (ex. Sweden, Finland, Germany)

WHO, 2015
EDC exposures and metabolic disease

• 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
BPA – cause for concern?

• High volume chemical with ubiquitous exposure

• Concern raised in Chapel Hill Statement, 2007 and NTP Report, 2008

• Parallel findings in animal and human studies
  – Reproductive
  – Behavioral
  – Obesity/diabetes
  – Cancer
  – Multiple endocrine systems, not just estrogen
BPA – new research approaches

**CLARITY study**
- Guideline compliant study funded by NTP and conducted by FDA
- Mechanistic studies conducted on animals/tissues from guideline study which ask different questions

**Pharmacokinetic study**
- Deuterated BPA delivered on a cookie; blood and total urine analyzed for 5 days
- Conjugation and elimination is rapid; very low bioavailability
- Elimination of conjugates into urine occurs within 24 hours

**Cashier study**
- Cashiers (78) were tested pre and post shift for BPA, BPS and BPSIP in urine and blood.
- Total urinary BPA and BPS post-shift were significantly higher compared to pre-shift.
Phthalate exposure linked to antiandrogenic activity in mice…

Scott et al. 2008
… and in HUMANS!

Mean AGI (mm/kg) in relation to boys’ age at examination (months).

Mendiola et al. 2011

Swan et al. 2005
Brominated flame retardant exposure: PBDEs increasing in North America 1970–2005

Figure: Shaw and Kannan, *Rev. Env. Health*, 2009

PBDEs: human toxicity

• Neurodevelopmental effects
  – PBDEs-cord blood associated with neurological deficits in children (motor perf., cognition (↓IQ), behavior)
    (Eskenazi et al., 2013; Herbstman et al., 2010; Roze et al., 2009)

• Thyroid homeostasis
  – Altered circulating THs, TSH in adults
    (Meeker et al., 2009; Turyk et al., 2007; Stapleton et al., 2011; Bloom et al., 2008, Chevrier et al., 2010)

• Reproductive development/toxicity
  – Cryptorchidism in infants
  – Early menarche
  – ↓androgens, LH, FSH; ↑inhibin
  – ↑estradiol, inhibin in male infants (BDE-154)
  – ↓sperm counts, testis size (BDE-153)
    (Akutsu et al., 2008; Chen et al., 2011; Main et al., 2007; Meeker et al., 2009; Meijer et al., 2012)
Brominated flame retardants: HBCD health effects

• Two generation rat study showed decreased T4, increased TSH, reproductive effects, altered histology of ovary, decreased viability of pups (Ema et al., 2008)

• Liver hypertrophy: enzyme inducer (CAR/PXR), doses increased liver weight, liver enzyme activity (Germer et al., 2006)

• Mild acute toxicity, irritation, sensitization, mutagenicity (EU Commission, 2008)

• Decreased learning, memory, and behavior

• Anti-androgen, aromatase inhibitor, interact with steroid hormone receptors in vitro
Brominated flame retardants: TBBPA health effects

Toxicity:
- Immunotoxic: Inhibits T cell activation
- Hepatotoxic: destroys mitochondria, causes membrane dysfunction in hepatocytes
- Neurotoxic: oxidative stress, inhibits dopamine uptake, generates free radicals, increases calcium

Endocrine Disruption:
- May inhibit estrogen metabolism via SULT1E1
- Disrupt androgen signaling to increases testis and pituitary weight
- Thyroid: receptor agonist/antagonist
- AhR receptor: weak ligand

Gosavi et al., 2013
Climate change exposures and human health

• Largest NIH portfolio of research on climate change impacts: focus on vulnerable populations, modeling
  – Cardiac vulnerability, esp. elderly
  – Asthma and heat effects on children in NYC
  – Pre-term delivery
  – Acute morbidity among Chickasaw in OK
  – Oceans and Human Health grants: methylmercury

• Co-lead group that coordinates Federal efforts on climate change and human health
  – Climate Change and Human Health Assessment Draft for public comment at
    http://www.globalchange.gov/health-assessment

• Development and use of data tools: Climate Resilience Toolkit https://toolkit.climate.gov
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)

• *In utero*, infants, childhood, adolescence, pregnancy, old age
Lifelong effects of early-life exposures
Endocrine disruptor action is life-stage specific

**Developmental Effects**
(Organizational)
- Most sensitive exposure window
- Persistent effects
- Latent periods

**Adult Effects**
(Activational)
- Usually higher doses
- Effects as long as EDC present
- Can augment developmental effects

A bad start…lasts a lifetime!
Exposures and neurodevelopment

• Neurodevelopmental disorders are becoming more prevalent
  – About 1 in 88 children in the U.S. have a form of autism spectrum disorder (ASD)
  – Among children aged 4-17 years, 9.5%, representing 5.4 million children, have Attention Deficit Hyperactivity Disorder (ADHD)

These disorders may be linked to environmental components.
Air pollution and the growing brain

• Traffic-related air pollution during pregnancy and during first year of life is associated with autism.

• Autism risk in children was also elevated in association with prenatal exposure to several airborne toxics and solvents, including lead, formaldehyde, and 1,3-butadiene.

• Maternal exposure to urban air pollutants, known as PAHs, can adversely affect a child’s IQ.

• Decreased neurodevelopmental performance was associated with prenatal and postnatal woodsmoke exposure.
ADHD and pesticide exposure associated with lower IQ, increased ADHD, and autism

• In animal models, researchers are investigating pesticide exposure as a possible risk factor for ADHD.

• In humans, researchers found that higher maternal urinary levels of organophosphate metabolites were associated with ADHD, decreased IQ, and behavioral issues in children.

UC Berkeley; Marks et al., 2010; Eskenazi et al., 2013
Prenatal pesticide exposure lowers child IQ

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


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
Heavy metal exposure in children

Real-world exposures to metals often consist of low doses

• Very low levels of arsenic exposure (5-10ug/L) in drinking water are associated with lower IQ scores in 3-5 grade children. Wasserman et al., Environ Health (2014)

• Children exposed to mercury show decreased visuospatial processing and memory. Grandjean et al., Neurotoxicol Teratol (2014)

• Exposure to manganese is associated with poorer memory and attention in children, even at low levels commonly encountered in North America. Oulhote et al., EHP (2014)

• Very low levels of lead exposure (below 10 μg/dL) are associated with lower IQ scores in children ages 3 and 5 years old. Canfield et al., NEJM (2003)
In utero and childhood arsenic exposure and cancer (Cancer diagnosis age >25yrs)

Lung cancer

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Bladder cancer

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Childhood and prenatal exposures to phthalates and asthma
Exposures across life-stage and breast cancer, puberty

- Environmental exposures throughout life may predispose women to breast cancer or affect puberty.
- Women exposed to solvents before the birth of their first child may have an increased risk of developing breast cancer.
- Onset of breast development found to occur earlier among white, non-Hispanic girls than observed 10-20 years ago.
- Association of breast feeding with age of onset of girls’ puberty varied by environment.
- Polyfluoroalkyl compound serum concentrations higher in young girls in Cincinnati vs. San Francisco suggesting water treatment systems are effective at reducing exposure.
- CYP19A1 biomarker used to assess risk of early puberty.
Important questions to ask of environmental chemicals

• Are new or “replacement” chemicals safer than the chemicals they are replacing?

• How long are these chemicals going to remain in the environment after they are banned or no longer used in commerce?

• Can exposure to certain chemicals hurt me or my family? How can I protect myself?
Improvements in evaluating environmental health questions: systematic review

• Address the breadth of relevant data
  – Wide range of human study designs (e.g., clinical, observational)
  – Animal studies
  – Mechanistic studies (in vitro and other relevant data)

• Approach to reach hazard identification conclusions

• Procedure to integrate evidence streams
Better tools for research

- In 2014, researchers at Oregon State University developed a silicone bracelet that monitors a wide range of environmental exposures.

- Scientists at University of Cincinnati developing personal ultrafine particle counter.

- Field test indicated highest exposures at bus stop when worn by a child.
Prevention is the key

• Genetic and environmental factors contribute and interact with each other to increase risk;

• The impact of exposures can vary based on timing of the exposure within critical windows of exposure;

• Identifying the hazards associated with chemicals to which humans are exposed is critical; and

• *Environmental factors are more readily identified and modified than genetic factors and therefore present a tremendous opportunity to prevent non-communicable disease.*

You can’t change your genes, but you can change your environment!
Thank you!