Proof, causation, and scientific uncertainty: What do we do?

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Precautionary principle

- What do we know?
- What are we uncertain about?
- What do we do?

Why confront uncertainty?

- We regularly live with uncertainty
- Ethical dimensions
  - Responsibility to current AND future generations
  - Duty to foresee [to see, to look ahead, predict], forestall [to prevent from happening]
  - Justice: distribution of costs and benefits
- Economic: prevention is usually cheaper
- Public health: Primary prevention is a principle of public health practice; requires action based on what we know, despite residual uncertainty

Kinds of uncertainty

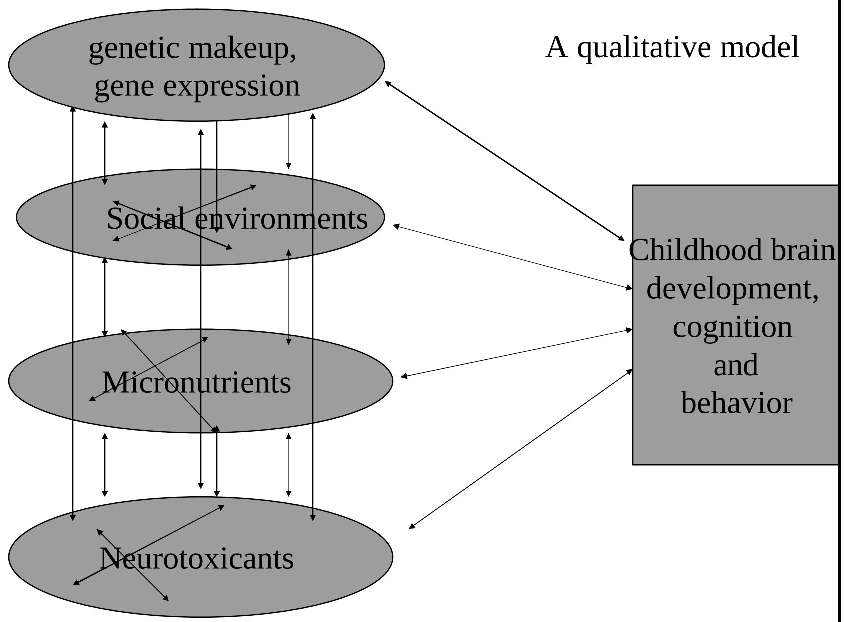
- Statistical
- Model
- Fundamental
- Manufactured

Statistical uncertainty

- Results from not knowing the value of some variable at a particular point in space or time, but knowing, or being able to determine, the probability of a given value
- Easiest to reduce or quantify
- Examples: mercury levels in fish; particulate air pollution; measure variables; understand their inherent variability

Model uncertainty

- Results from not fully understanding the relationships between variables in a system
- May know that a particular outcome is possible, but probability of that outcome is difficult to predict; may be indeterminate.
- Example: Impacts of maternal mercury or lead exposure on child neurological development



Modified from: Hubbs-Tait et al. Psychological science in the public interest

Fundamental uncertainty

- Increasing indeterminacy
- Partially results from ignorance
- Ignorance of ignorance a big problem (we don’t know what we don’t know)
- Fail to ask the right questions
- Example: Consequences of promoting continuous economic growth as an overarching goal (how will it play out)

Manufactured uncertainty

- Created to serve a particular purpose, often political, economic, or ideological
- Obfuscates
- May depend on lack of “proof”
- Examples: health effects of tobacco, lead; climate science

Science and the precautionary principle

- Kinds of errors and error bias
- “Proof”
- What do we need to consider in order to say that something “causes” something else?
- The limits of science

Kinds of errors when assessing "safety"

- Type 1 (false positive)—conclude that something is harmful when it is not
- Type 2 (false negative)—conclude that something is safe when it is not
- Type 3—the right answer to the wrong question

Error bias

- Scientific studies are usually interpreted to favor type 2 over type 1 errors
- This is because we have chosen not to conclude that evidence is "significantly positive" without it being "strong"
- ? Should the interpretation of "science" for establishing policies to protect public environmental health favor Type 1 errors?
- Who should decide?

How do we think about "causation" of diseases or other adverse outcomes?

- Hume (1700s)—we don't perceive or see causes; we observe sequences and events and infer causes
- Infectious diseases—one set of criteria (Koch)
- Epidemiology—another set of criteria (Hill)
- Ecology—even more complex

Bradford Hill: on criteria for causation in epidemiology

- "None of my criteria can bring indisputable evidence for or against a cause and effect hypothesis and none, except for time sequence, can be required as a *sine qua non*"
- "All scientific work is liable to be upset or modified by advancing knowledge. <u>That does not confer upon us a freedom to ignore the knowledge that we already have, or to postpone the action that it appears to demand at a given time</u>."

Cigarettes and lung cancer—evidence for causation

- 1945—Ochsner—Incidence rises together
- 1950—Doll & Hill—case-control study
- 1953—Wynder—tar causes cancer in mice
- 1954—Follow up studies show association, and that greater exposure > greater risk
- 1990s—biological mechanism(s) described (genetic factors; mutations)

"Proof"

- Scientific "proof" depends on the kind of study and the criteria that "we" agree upon to establish proof.
- "Proof" and "level of proof" required to take some action integrate a mixture of scientific, social, and political factors; e.g. civil vs. criminal charges
- Intuitively we rely on "weight of evidence" to make decisions (evidence from multiple sources).
- Safety is not provable because it is not possible to "prove" that something will not happen.

When is “proof” of causation difficult to establish?

- “Webs of causation”—e.g. complex interactions among chemical exposures, genetics, nutrition, social circumstances, etc.
- Non-specificity—many diseases have multiple “causes”; e.g. heart disease (genes, diet, blood pressure, smoking, air pollution, arsenic, mercury, etc.)
- Long lag time between exposure and disease

Effect modifiers: “What” do we blame?

- For some risk factors, the magnitude of hazard depends on the levels of other variables (i.e. effect modifiers).
- Example: lead exposure, dietary iron deficiency, and poverty independently impair normal brain development of children
- They also interact, so that lead exposure or iron deficiency is WORSE in the presence of the other

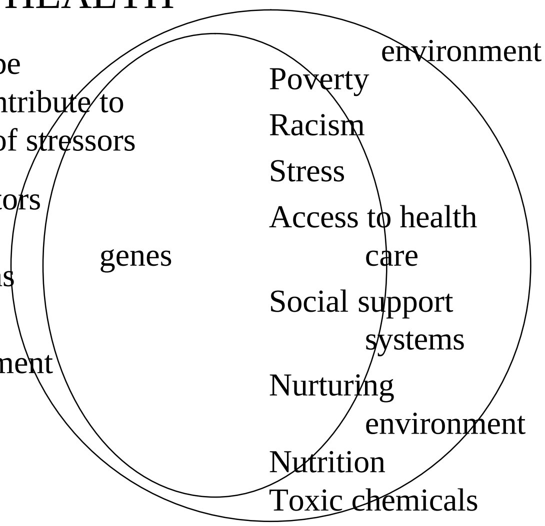
CHILDREN'S HEALTH

Environment can be supportive and contribute to resilience, or full of stressors

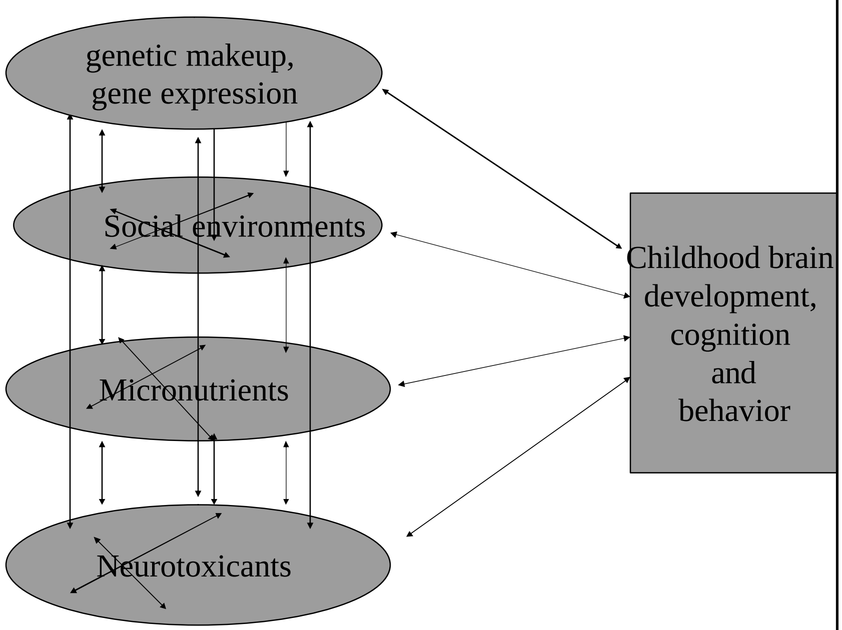
Environmental factors can directly impact cells, tissues, organs

Genes and environment are in continuous conversation

Environmental factors can alter gene function, gene expression



- Poverty
- Racism
- Stress
- Access to health care
- Social support systems
- Nurturing environment
- Nutrition
- Toxic chemicals
- Radiation
- Infections
- Physical agents



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The scope of the problem

Prevalence of Learning and Behavioral Disabilities

Total: 17%, 12 million children

- Learning disabilities: 5-10%
- ADHD: 3-5%
- Autism: ?? 0.5 % (5 per 1,000)?

Cellular Events in Neurodevelopment

In vivo and in vitro testing: each of these events is subject to disruption by environmental agents

- Division
- Migration
- Differentiation
- Formation of synapses
- Pruning of synapses
- Apoptosis
- Myelination

Active throughout childhood & adolescence

Organophosphate Pesticide (OP) Effects in Laboratory Animals

- Small single dose on day 10 (neonatal)
- Permanent decrease in cholinergic receptors in the brain
- Permanent hyperactivity (Ahlbom, 1995)
- Gestational exposures: coordination and motor disorders, decreased brain weight

Prenatal OP Exposures: The Urban Environment

Meconium assays in 20 newborns (Whyatt 2001):

- diethylphosphate (DEP); diethylthio-phosphate (DETP)
- Metabolites of chlorpyrifos, diazinon, parathion, organophosphate (OP) insecticides

Detections: Organophosphate residues present in all 20 newborns studied

Umbilical cord blood –correlation with head circumference (Whyatt, et al. EHP, 2003)

Organophosphate effects—human; Columbia study

- Prenatal chlorpyrifos exposure associated with 3.5-6 point decrease in 36-month development scores (Bayley MDI; PDI) in a low-income minority sample
- 5 fold increased risk of developmental delay
- Increased risk of diagnosis of ADHD
- Much less effect after chlorpyrifos restricted

(Whyatt, et al; in press)

Organophosphate exposures in general population

- Organophosphate pesticide residues are present in about 75% of the general public and about 90% of children
- Levels are higher in children than adults
- http://www.cdc.gov/exposurereport/

Organophosphates and the precautionary principle

- Monitor—actively look for exposures and effects
- Heed early warnings—to some extent the ban on residential use of chlorpyrifos is a result, but exposures from agricultural use remain.
- Consider all the evidence—animal and human data
- Consider the boundaries of consequences in time and space—long term impacts on quality of life
- Alternatives

Organophosphate pesticides and the precautionary principle

- <u>Plausibility and nature of harm</u>: impaired brain development; documented exposures
- <u>Scientific uncertainty</u>: e.g., latency period, genetic polymorphisms; dose-response curve(s); multiple exposures; social factors
- What <u>precautionary action</u>? Do we have enough information to act?

Policy questions and implications

- Who decides when evidence is sufficient to trigger action? Do we require "proof" of harm?
- What kinds of "effects" trigger concern?
- How do we deal with multiple interacting factors?
- How much safety testing before a chemical or product can be marketed?
- Do we consider cumulative exposures from multiple sources?
- Who decides?