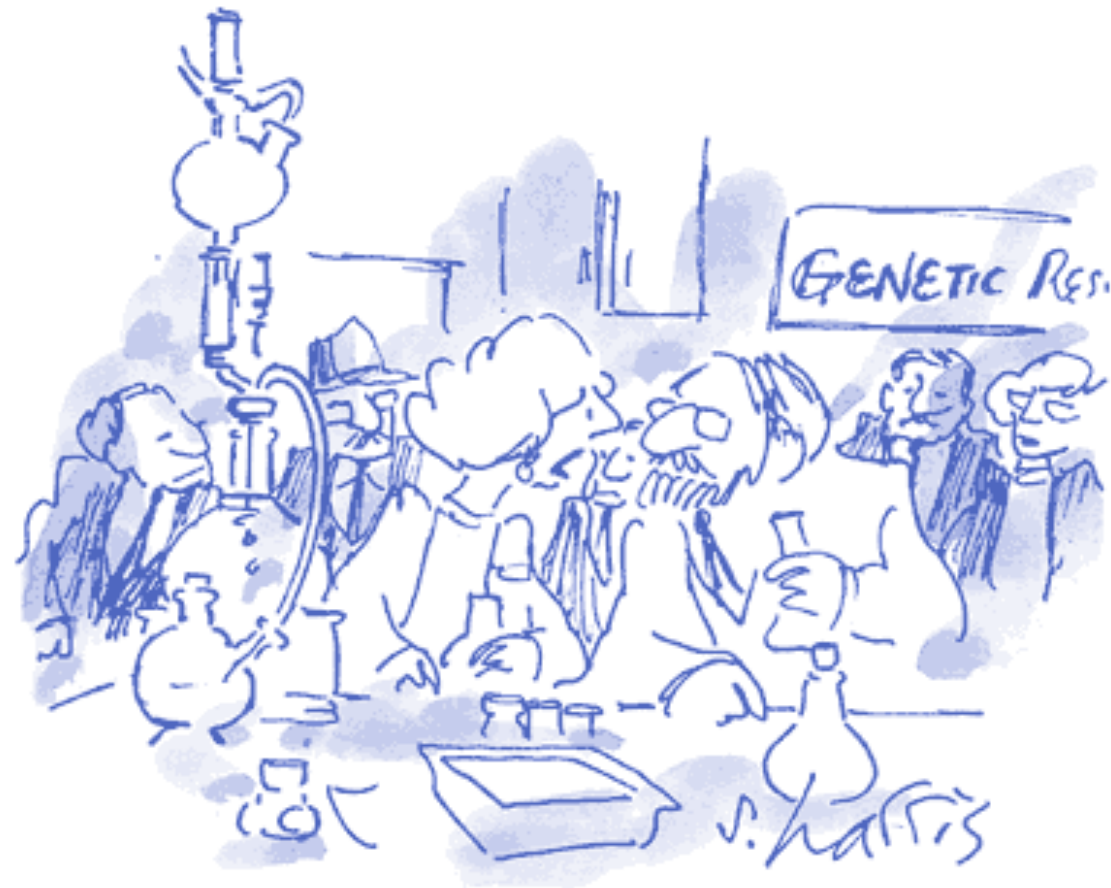




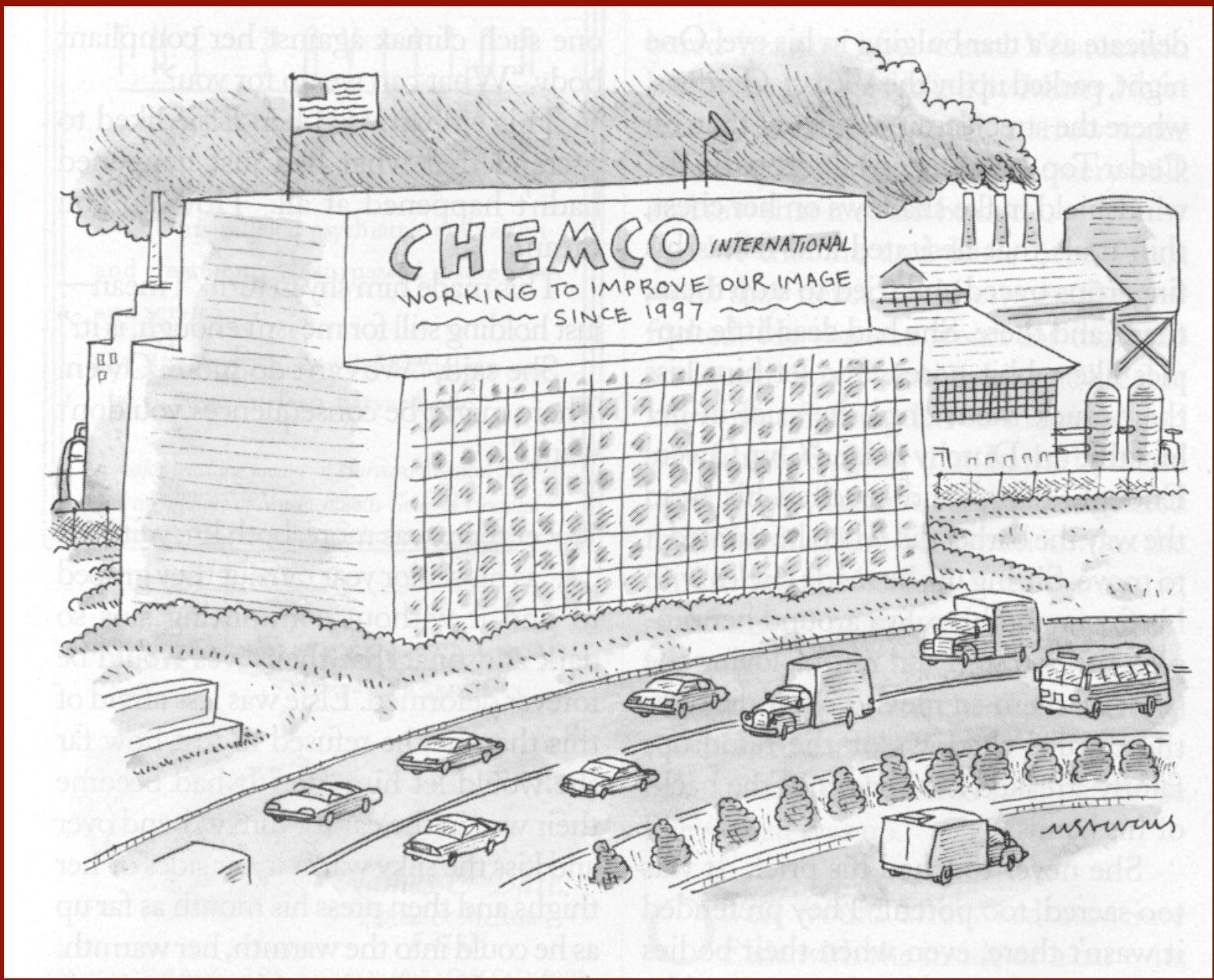
Trials and Tribulations of Protecting Children from Environmental Hazards

Bruce Lanphear, MD, MPH
Child & Family Research Institute
BC Children's Hospital,
Faculty of Health Sciences
Simon Fraser University,
Vancouver, BC



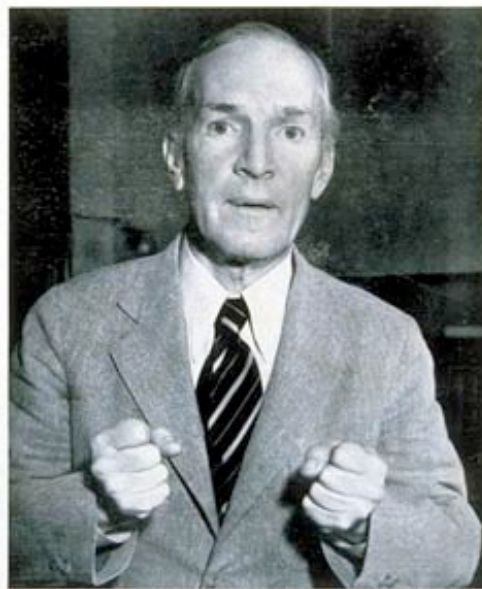
"I FIND IT HARDER AND HARDER TO GET ANY WORK DONE WITH ALL THE ETHICISTS HANGING AROUND."





TIME

The Weekly Newsmagazine



Volume XXIV

UPTON SINCLAIR

*"It falls out in California's special
(See National Affairs)"*

Number 17

“It is difficult to get a man to understand something when his salary depends on his not understanding it”.

Upton Sinclair

Conflict of Interest and Bias



Context

- Many hazards discovered only after widely dispersed in the environment
- Increasing evidence for adverse effects of toxins at levels previously thought to be low
- Toxicity tests not done for majority of chemicals
- Once environmental contamination occurs, there is no systematic plan to evaluate low-level toxicity of persistent hazards

Ethical Dilemmas

- How do we protect children from persistent and prevalent hazards that are widely dispersed in the environment?
- How do we protect children from new chemicals or environmental agents of unknown toxicity?

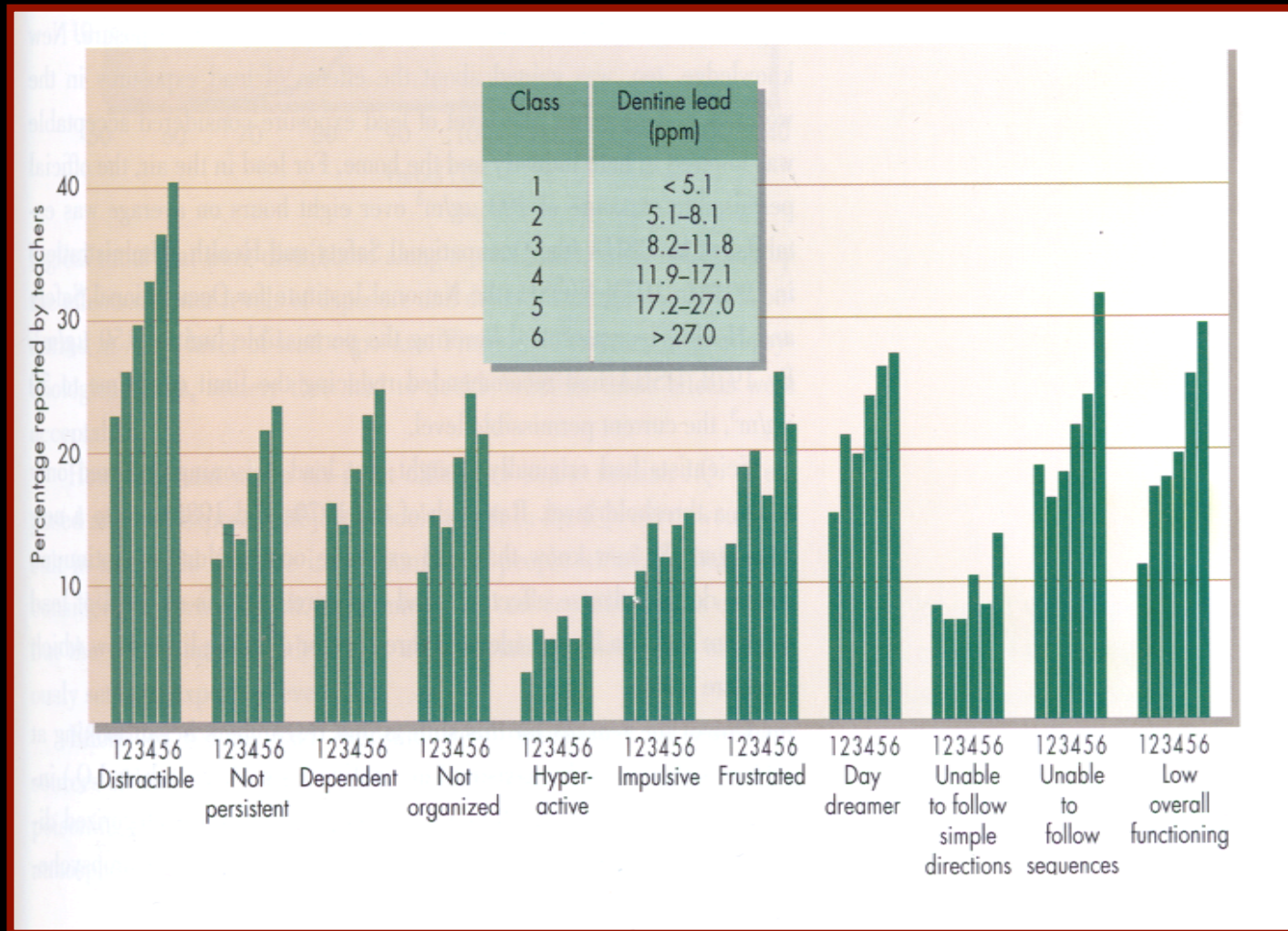


Illustration 22: Dr A.J. Turner, President of the Queensland Branch of the British Medical Association, 1906

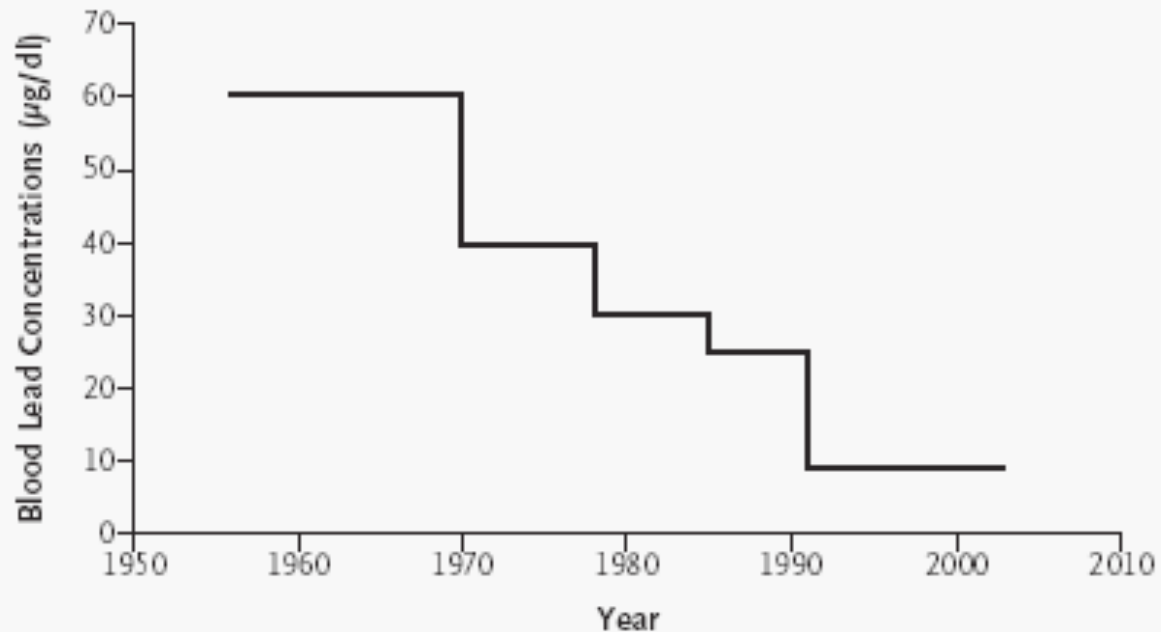
“Prevention is easy. Paint containing lead should never be employed ... where children, especially young children, are accustomed to play”

A.J. Turner, 1908

Lead-associated Behavioral and Emotional Problems in Children by Tooth Lead Concentration



Needleman HL, et al. N Engl J Med 1979;300:689-95.

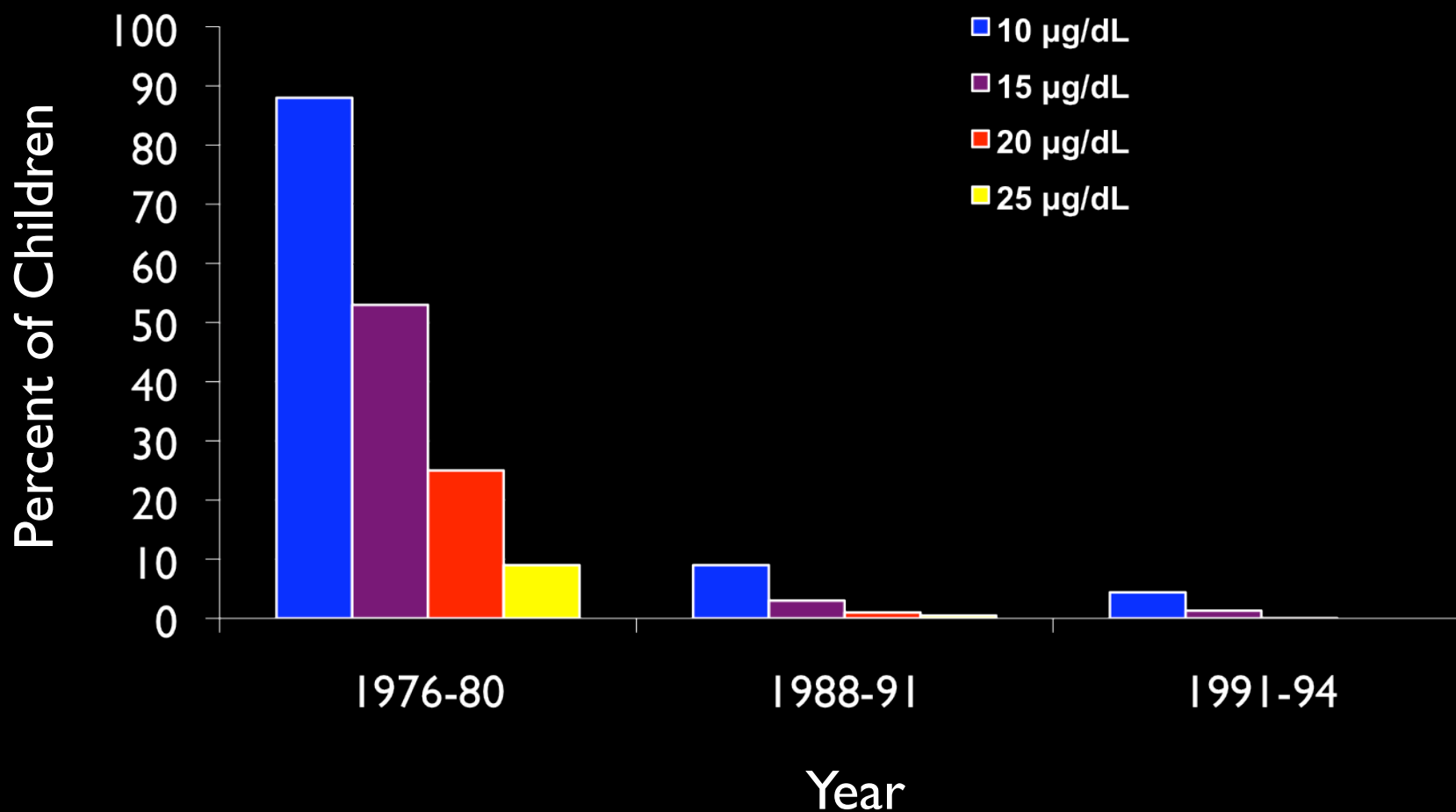


Blood Lead Concentrations Considered to Be Elevated by the Centers for Disease Control and Prevention.

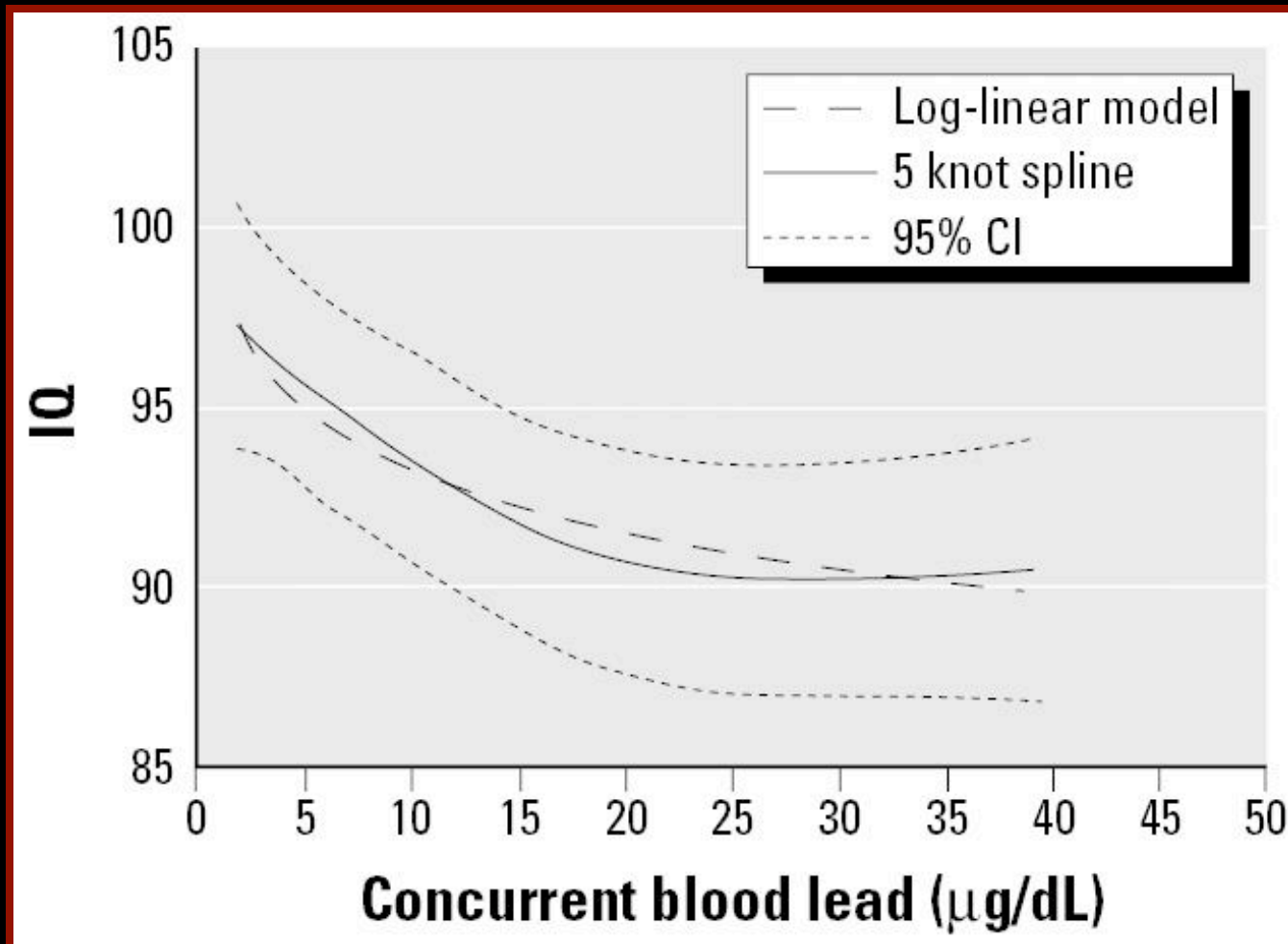
To convert the values for blood lead concentrations to micromoles per liter, multiply by 0.0483. Data are from the Centers for Disease Control and Prevention, 1991.¹

Binder S, Falk H. Strategic plan for the elimination of childhood lead poisoning. Atlanta: Centers for Disease Control, 1991.

Percent of Preschool Children Exceeding Selected Blood Lead Levels, NHANES II - III

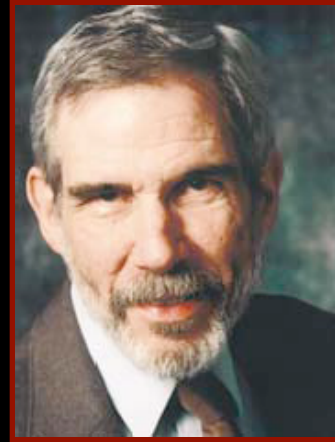


The Ongoing Search for a Threshold of Low-Level Lead Toxicity



Research Supporting Adverse Cognitive Effects at Blood Lead Levels < 10 µg/dL

- Chiodo LM, et al. Neurodevelopmental effects of postnatal lead exposure at very low levels. *Neurotoxicol Teratol* 2004;26:359-371.
- Kordas K, et al. Deficits in cognitive function and achievement in Mexican first-graders with low blood lead concentrations. *Environ Res* 2006;100:371-86.
- Tellez-Rojo MM, et al. Longitudinal associations between blood lead concentrations lower than 10 µg/dL and neurobehavioral development in environmentally exposed children in Mexico City *Pediatrics*. 2006;118:e323-30.
- Hu H, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. *Environ Health Perspect* 2006;114:1730–1735.
- Sarkin PJ, et al. Neuropsychological function in children with blood lead levels below 10 µg/dL. *Neurotoxicology* 2007;28:1170-1177.
- Solon O, et al. Associations between cognitive function, blood lead concentration and nutrition among children in the Central Philippines. *Journal of Pediatrics* 2008;152:237-243
- Chiodo LM, et al. Blood lead levels and specific attention effects in young children. *Neurotoxicol Teratol* 2007;29:538-546.
- Chandramouli K, et al. Effects of early childhood lead exposure on academic performance and behavior of school age children. *Arch Dis Child* 2009;94:844-848.
- Min MO, et al. Cognitive development and low-level lead exposure in poly-drug exposed children. *Neurotoxicol Teratol* 2009;31:225-231.
- Jedrychowski W et al., Gender specific differences in neurodevelopmental effects of prenatal exposure to very low-lead levels: the prospective cohort study in three-year olds. *Early Hum Dev*. 2009;85:503-510.



“Canfield et al. (2003) suggested a 7.4-point IQ effect (roughly one half standard deviation) as lifetime average BLL went from 1 to 10 μ g/dL—more than twice as strong a relationship as shown by most estimates at higher exposures. It may reasonably be asked whether such a strong relationship is plausible, particularly as there are no directly relevant animal or *in vitro* studies that demonstrate a steeper slope for adverse effects of lead exposure at lower BLLs than observed at higher levels. ... New studies using designs that exclude or control potential confounding by pica, which can indicate an underlying developmental delay, or by environmental hygiene, indicating more widespread lead contamination, would be especially helpful in assessing these low-level effects.”

Brown MJ, Rhoads GG. EHP 2008;116:A60.

Total Costs and Benefits of Lead Control

	Conservative estimate	Optimistic estimate
Total benefit from lead reduction	\$192.38	\$270.45
Total cost of lead control	\$11.02	\$1.22
Total net benefit	\$181.37	\$269.23
Cost–benefit	1–17	1–221

All costs and benefits are in billions of 1996 dollars.



The Conquest of Lead Toxicity

A Pyrrhic Victory

A Pattern of Pathology



Ethical Dilemmas

- How do we protect children from persistent and prevalent hazards that are widely dispersed in the environment?

Potential Solutions?

- Accept that many will inevitably be harmed before we have “evidence” of toxicity
- Revise definition of sufficient evidence based on observational studies
- Increase use of experimental trials in public health research

Are Randomized Controlled Trials Always Necessary?

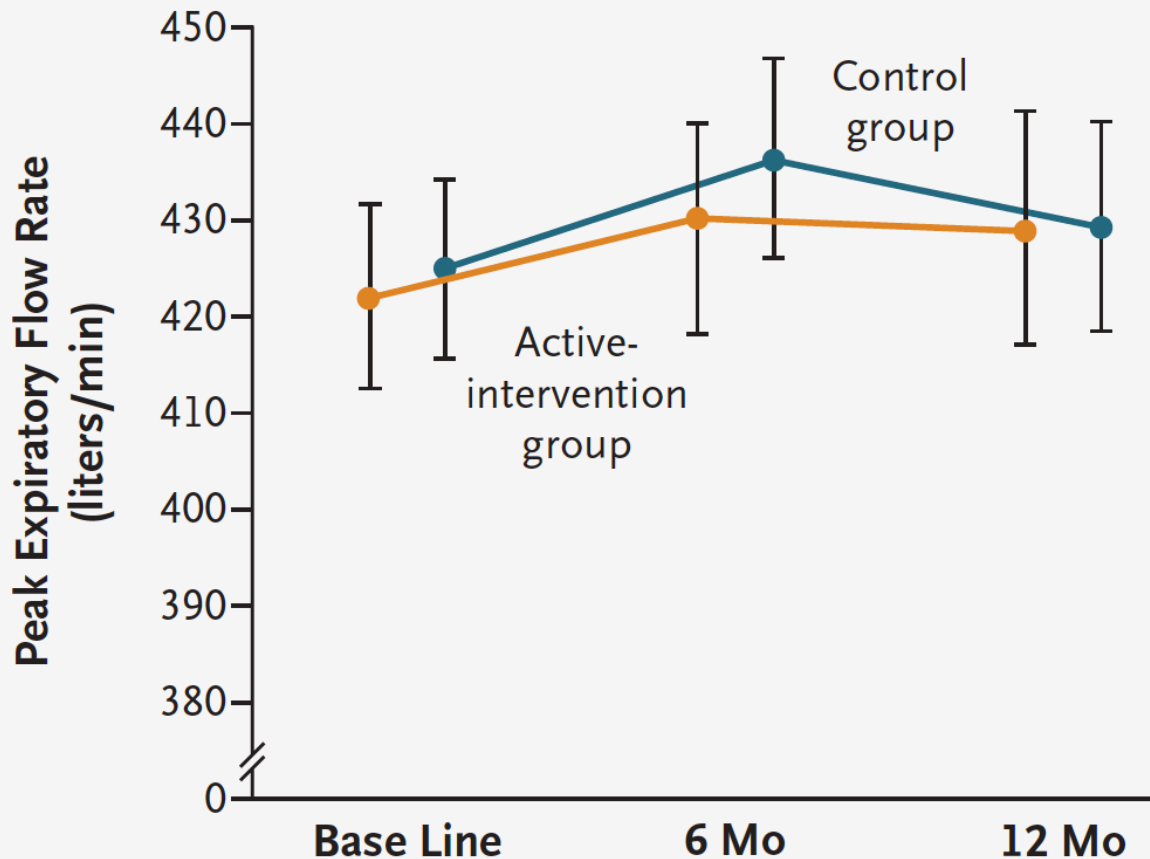


Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

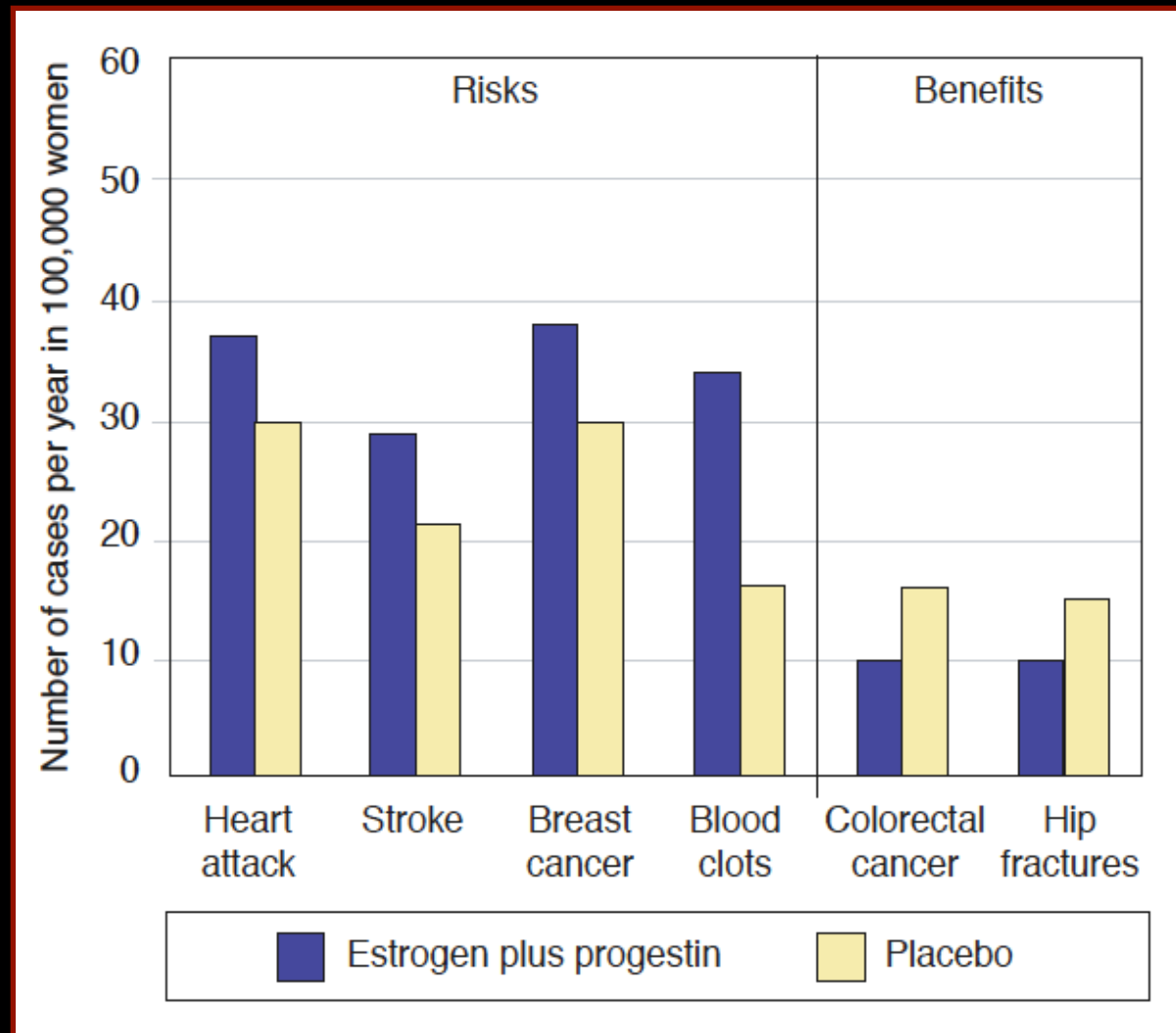
HULTON/GETTY

Mean Morning Peak Expiratory Flow Rate in Mite-Sensitive Patients by Group Assignment

B Mite-Sensitive Patients



The Vanishing Promises of Hormone Replacement



Science 2002;297:325-326.

When to Use Experimental Trials

- Prevalent and persistent toxin or hazard
- Uncertainty about safety or efficacy of treatment (clinical equipoise)
- Causal relationship is unclear

Context for the HOME Study

- Increasing evidence for adverse effects of lead exposure at levels previously thought to be safe
- The trigger to reduce residential lead hazards is a child with lead poisoning (i.e., a blood lead level consistently >15 mcg/dL)
- There is uncertainty about the safety and efficacy of lead hazard controls

HOME Study

- Community representation involved with study design and included on advisory board
- Expanded to include broader diversity of racial and ethnic groups.
- Added an intervention for families in the comparison group so that all children would have the prospect of direct benefit
- IRB approval

The New York Times

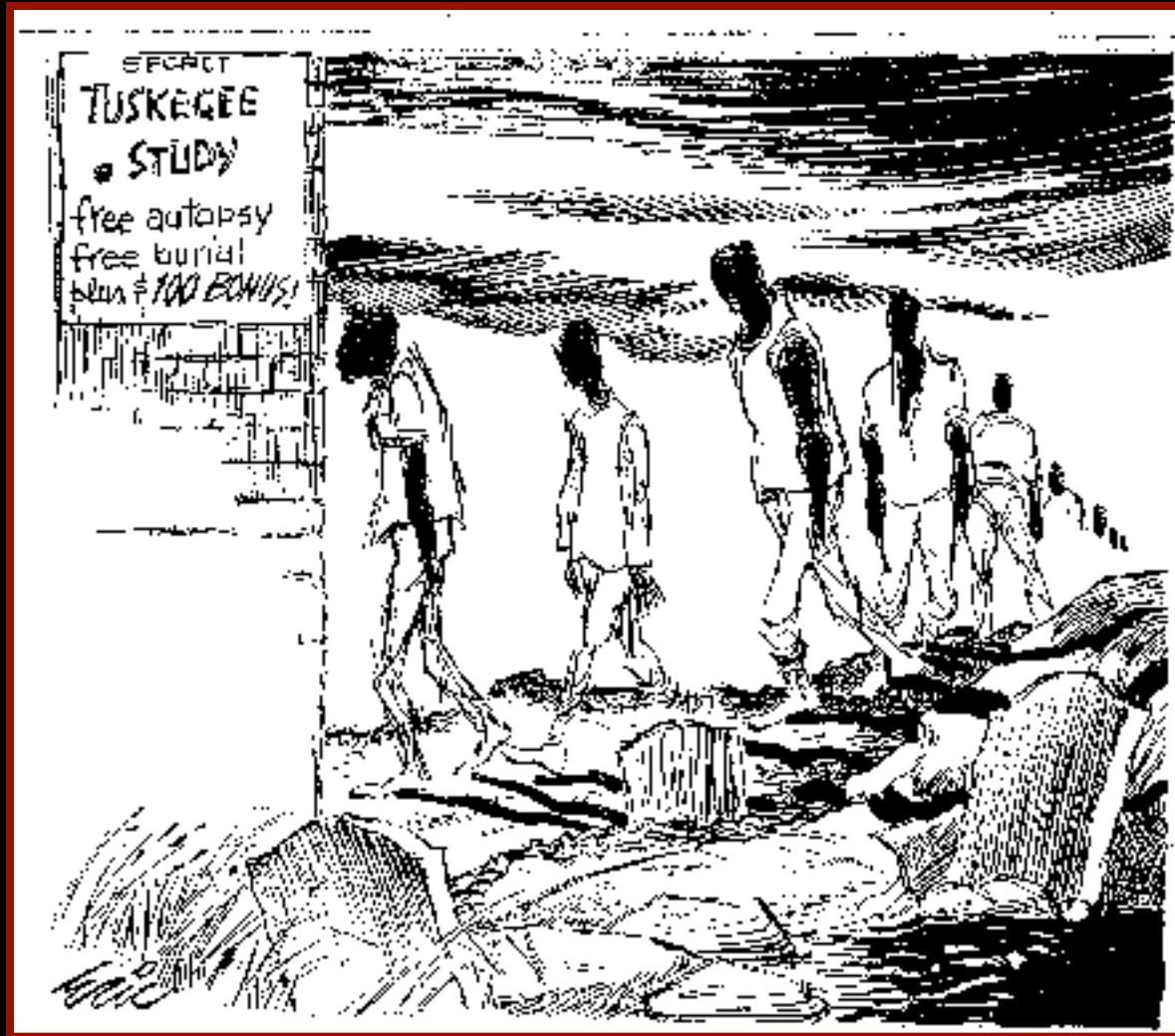
August 24, 2001, Friday

By TAMAR LEWIN (NYT); National Desk

Amid growing concern about the safety of medical research involving humans, the Department of Health and Human Services opened an investigation on Wednesday into a lead-paint study in Baltimore overseen by Johns Hopkins University.

The study was criticized last week in a decision by the Maryland Court of Appeals, which likened it to the infamous Tuskegee syphilis study decades ago.

Uses and Abuses of Tuskegee



Fairchild AL, Bayer R. Science 1999;284:919-921.

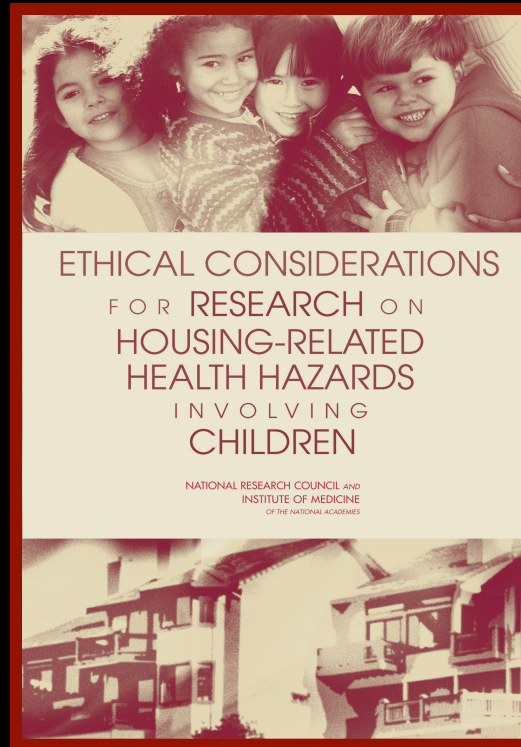
Tuskegee Study

- Participants were not told they had syphilis infection.
- Participants deprived of a known, efficacious and affordable therapy for syphilis.
- Researchers thwarted participant's attempts to get treatment elsewhere.
- Participants were from a vulnerable population

Kennedy-Krieger R & M Study

- Families were told their children were at risk for lead poisoning.
- The safety and efficacy of lead hazard controls were (and still are) uncertain.
- Families were not thwarted in their attempts to relocate to new housing, but federal standard required that abated housing would preferentially be made available to children.
- Children with lead poisoning received > community standard and treatment, if indicated.
- Participants were from a vulnerable population

Ethical Considerations for Research on Housing-Related Health Hazards Involving Children



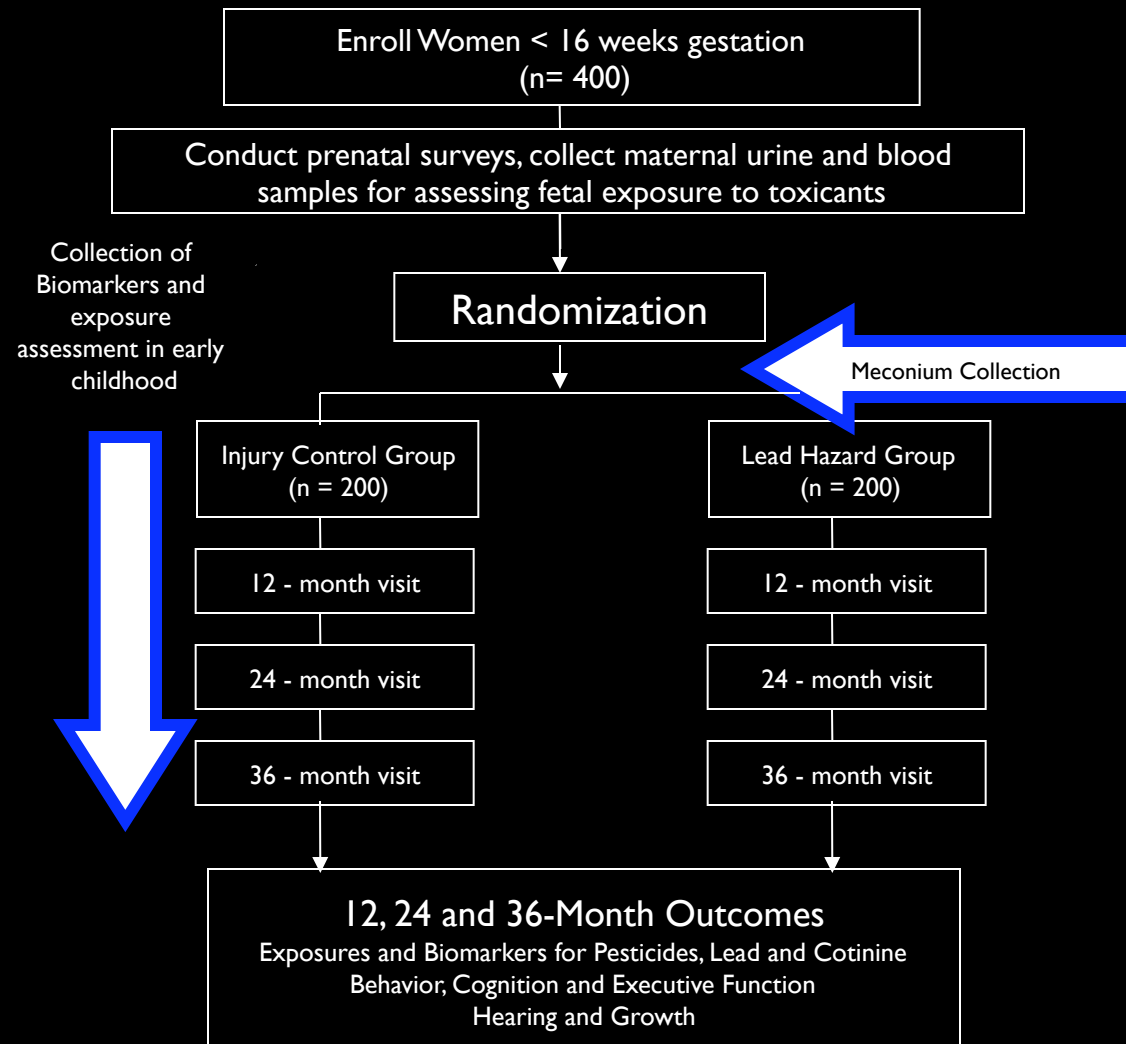
NATIONAL RESEARCH COUNCIL AND
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Use Innovative Study Designs

Researchers designing intervention studies on housing health hazards involving children should consider using innovative designs in which all subjects receive a prospect of direct benefit.



Home Study of Prevalent Toxins

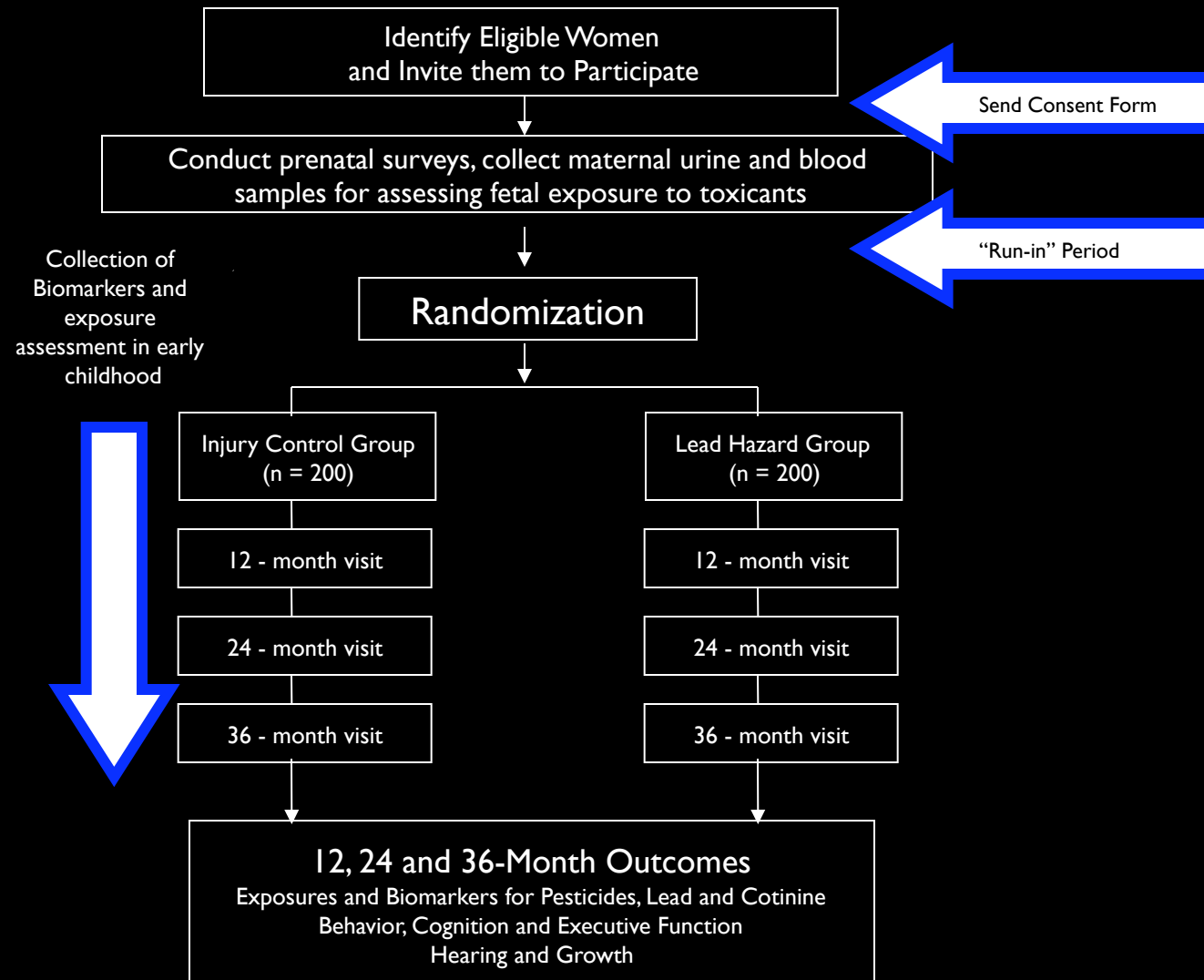


Ensure Parents are Informed

Researchers who carry out intervention studies or longitudinal cohort studies on housing health hazards with children should implement a process of informed parental decision making by discussing the planned consent process with community representatives and considering their input and ensuring that parents of child subjects understand the essential elements of the research.



HOME Study



HOME Study Checklist

Assessment of Informed Consent

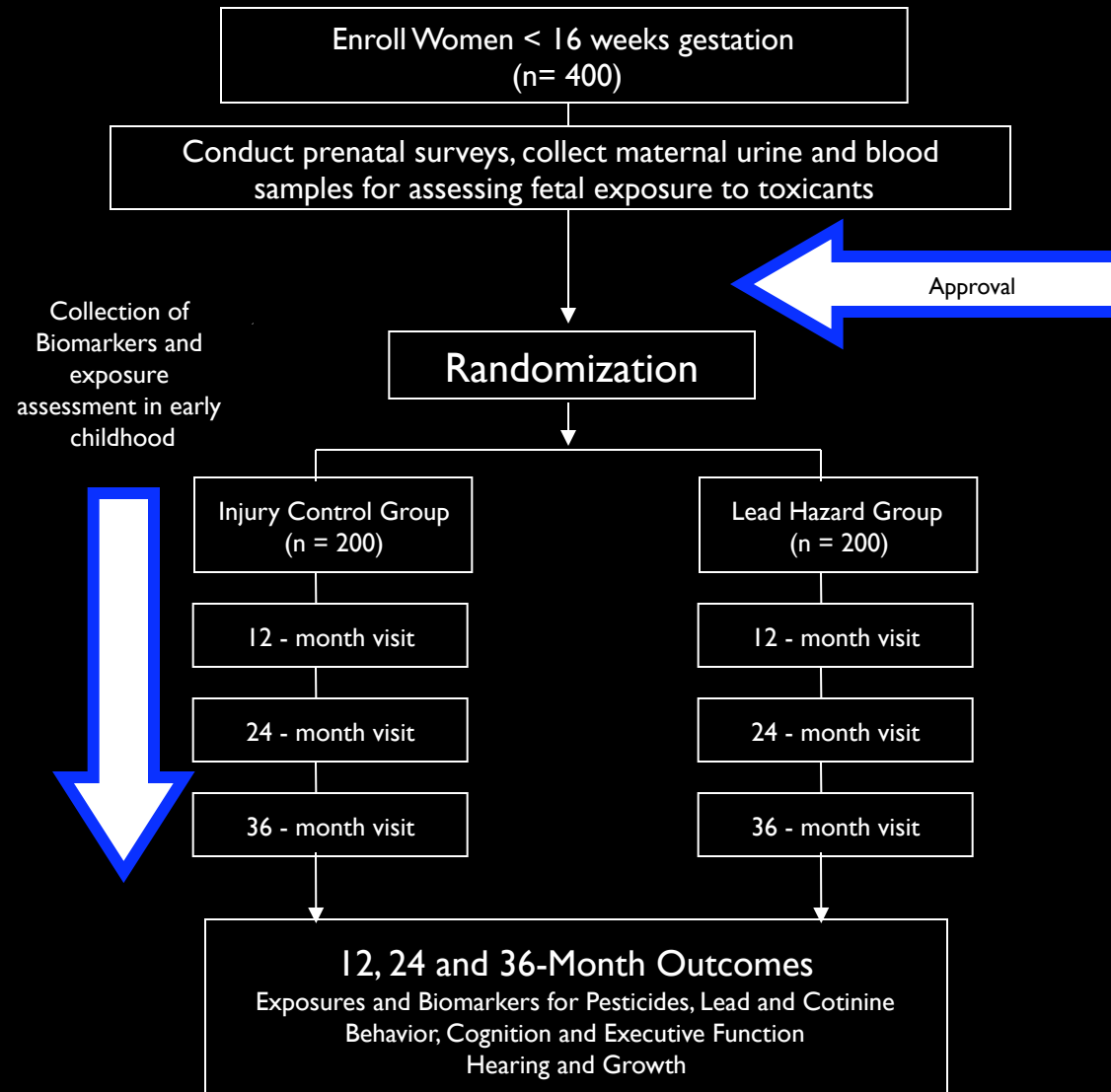
1. How old will my child be at the last visit for the study?
 - 1 year old
 - 3 years old
 - 10 years old
2. Am I able to choose if my family is in the lead repair group or the injury repair group?
 - Yes
 - No
3. Is it possible that the study team may repair certain areas of my home or install devices in my home?
 - Yes
 - No
4. When will the study team make visits to my home?
 - During my pregnancy
 - Shortly after my child's birth
 - When my child is one, two and three years of age
 - At all of these times
5. Is it possible that my family may have to stay in a hotel while the repairs are being done to my home?
 - No, my family will not have to stay in a hotel.
 - Yes, my family may have to stay in a hotel.
6. Will blood be collected from my child at each of the clinic visits, starting when he or she is 1 year old?
 - Yes
 - No
7. What kinds of topics will I be interviewed about?
 - My reasoning skills
 - My mood
 - My eating habits
 - All of the above
8. I have the right to withdraw from the study:
 - At any time
 - Only at certain times
 - Never
9. During the study, my child's blood lead level:
 - Will go up
 - Will go down
 - It is not known – this is what is being tested.

Consider Obligations to Third Parties

Researchers carrying out research on housing health hazards involving children should discuss in their protocol and IRB submissions their legal and ethical obligations to potential third parties affected by their research.



HOME Study



Consider Other Risks in Home

Researchers designing research on housing health hazards to children need to anticipate the risks and behaviors that may be observed in the home, including observations that are not part of the research protocol, develop anticipatory plans that specify how to assess and respond to risks when they are identified, and educate staffs about the plan.

Potential Risks in HOME Study

- Evidence of child abuse
- Imminent hazards in the home
- Risk for landlord eviction
- Maternal depression with suicidal ideations
- Child with lead poisoning
- Insufficient staff training

HOME Study

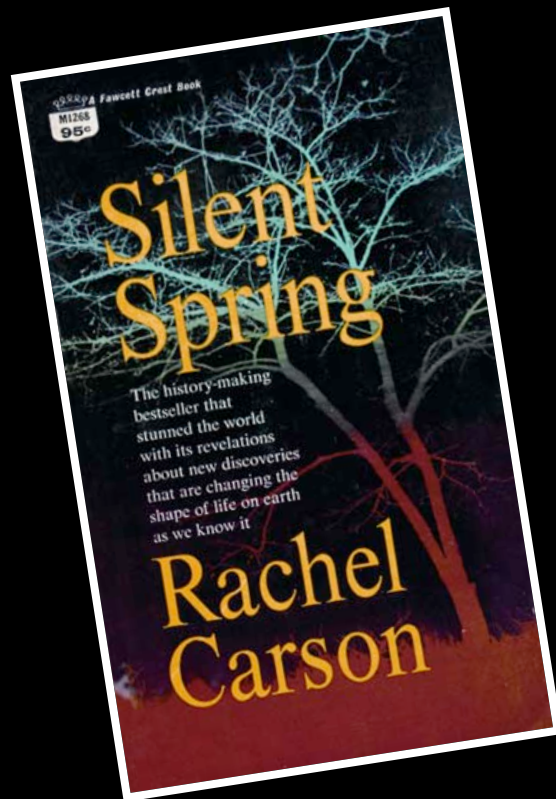
- Expanded to include broader diversity of racial and ethnic groups
- National, independent IRB committee
- Extensive informed consent with checklist
- Add intervention for comparison group so that children in both groups potentially benefit
- IRB approval and COC from NIH, CDC, CHMC, UC, Good Samaritan and Christ
- Established data safety monitoring board
- Community representation on advisory board

Guidelines for Ethical Conduct of Research in Environmental Hazards

- Guidance on remuneration, recognizing large burden on participants
- Guidance for use of experimental trials in study of environmental hazards
- Clarify whether DSMB should routinely be used in trials of environmental interventions
- Guidance for reporting individual test results of environmental contaminants

Ethical Dilemmas

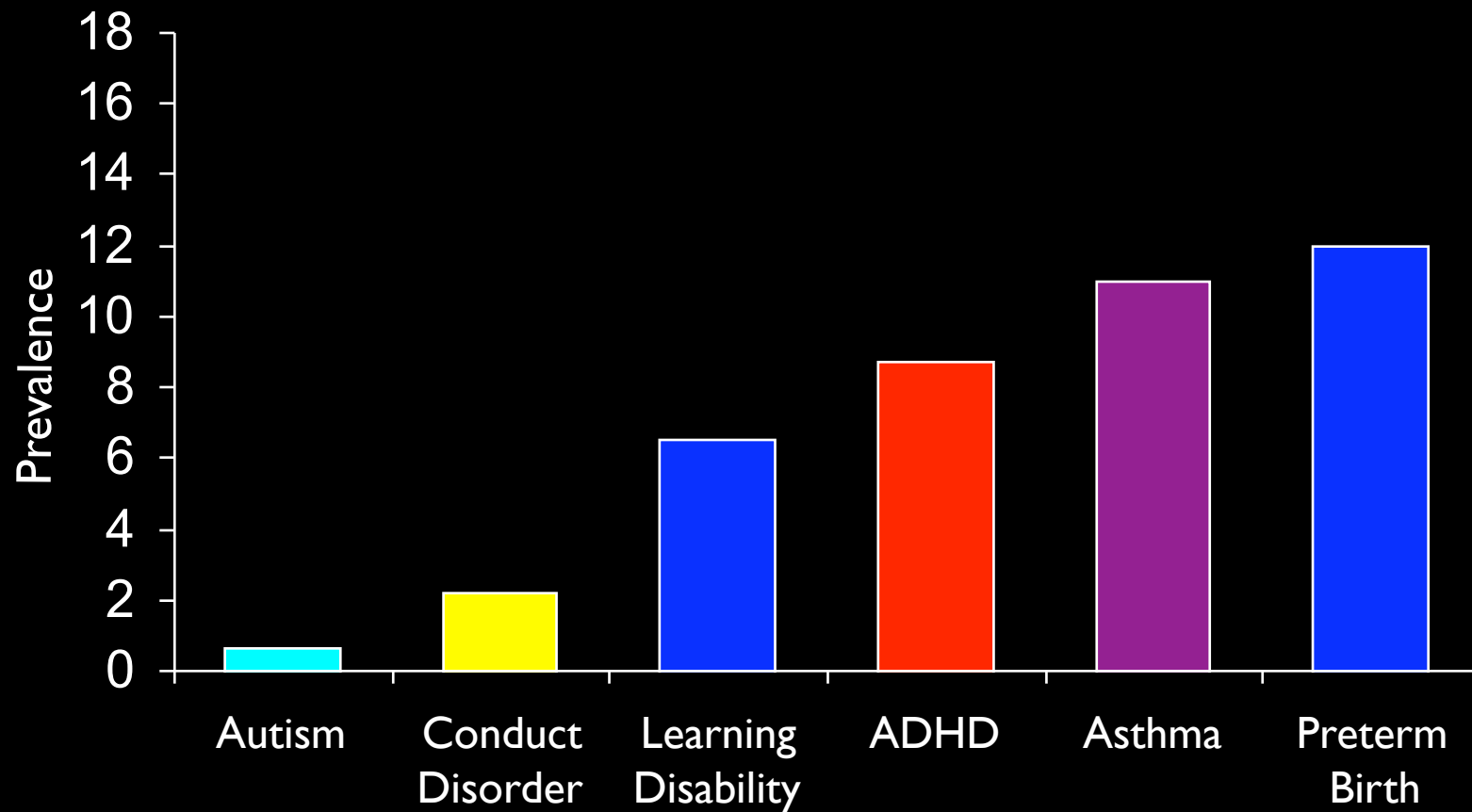
- How do we protect children from new chemicals or environmental agents of unknown toxicity?



In the lower Mississippi, fish have been dying from a cause as yet undetermined. In Oklahoma, quail are not hatching their full clutches of eggs... . In Washington, representatives of a chemical company that makes endrin have testified that no "substantial" amounts of the poison enter the Mississippi from the company's plant, but, as Miss Carson pointed out in her last book, no one can yet say what a "substantial" amount of a modern poison really is.

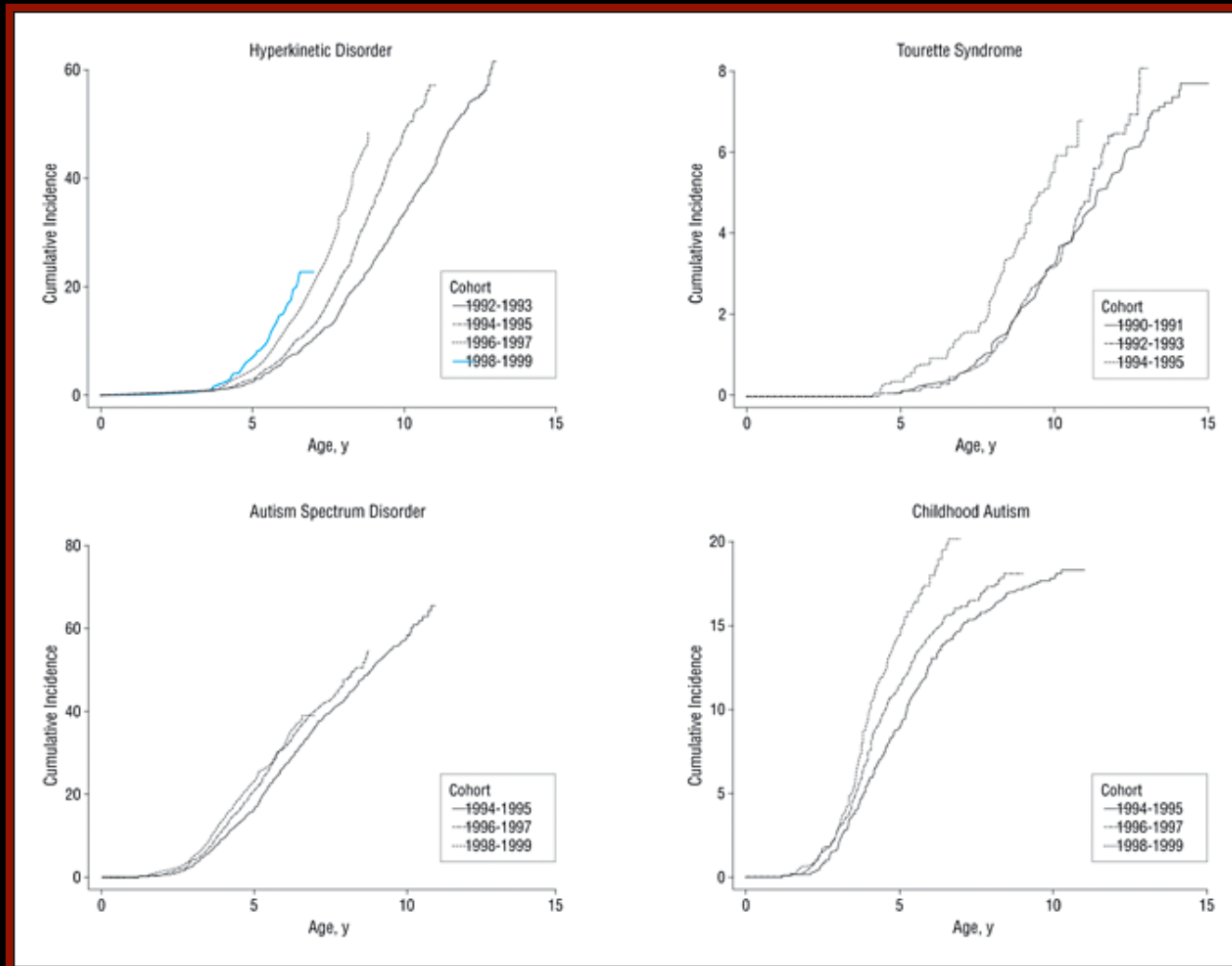
E.B. White, *The New Yorker*

New Morbidities of Childhood

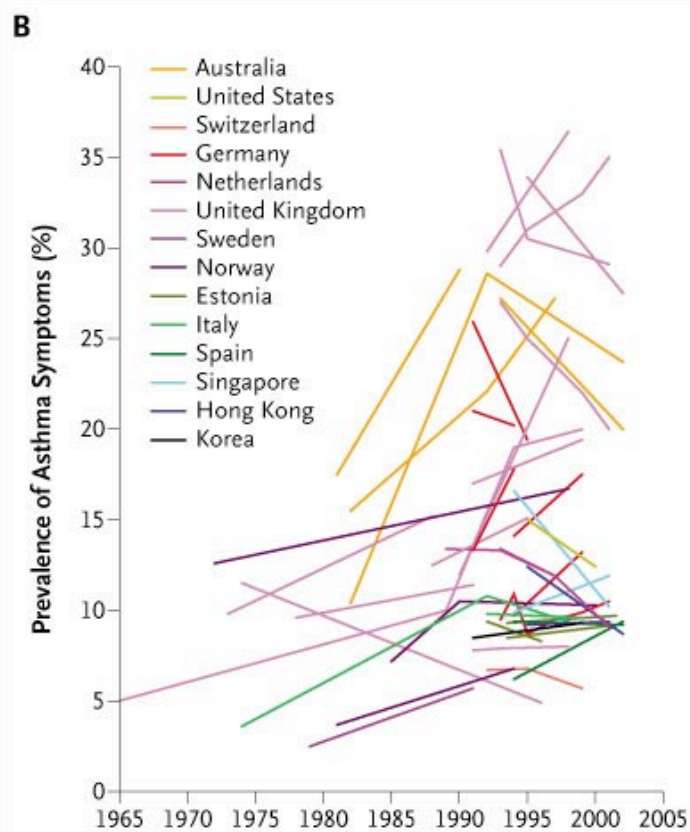
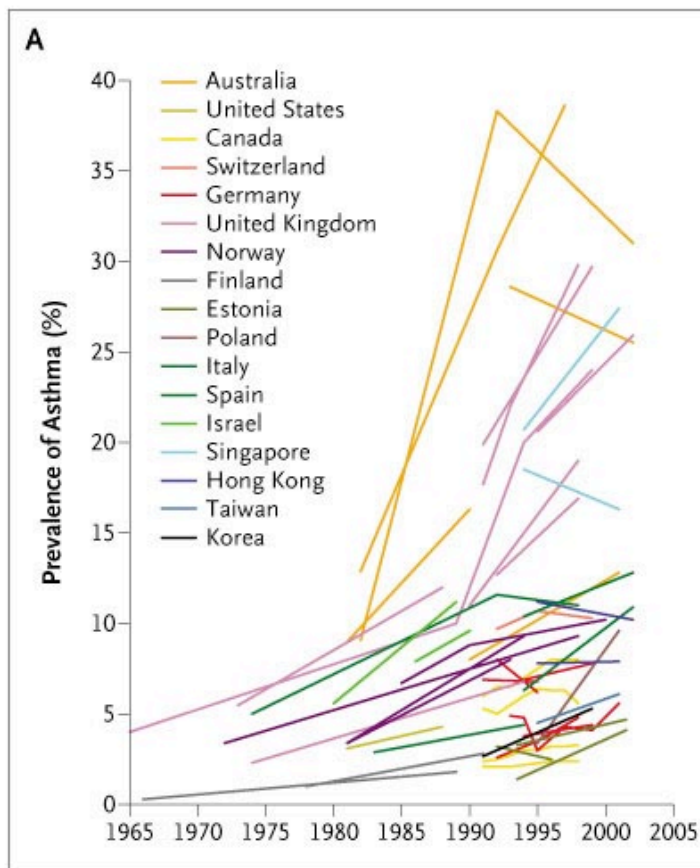


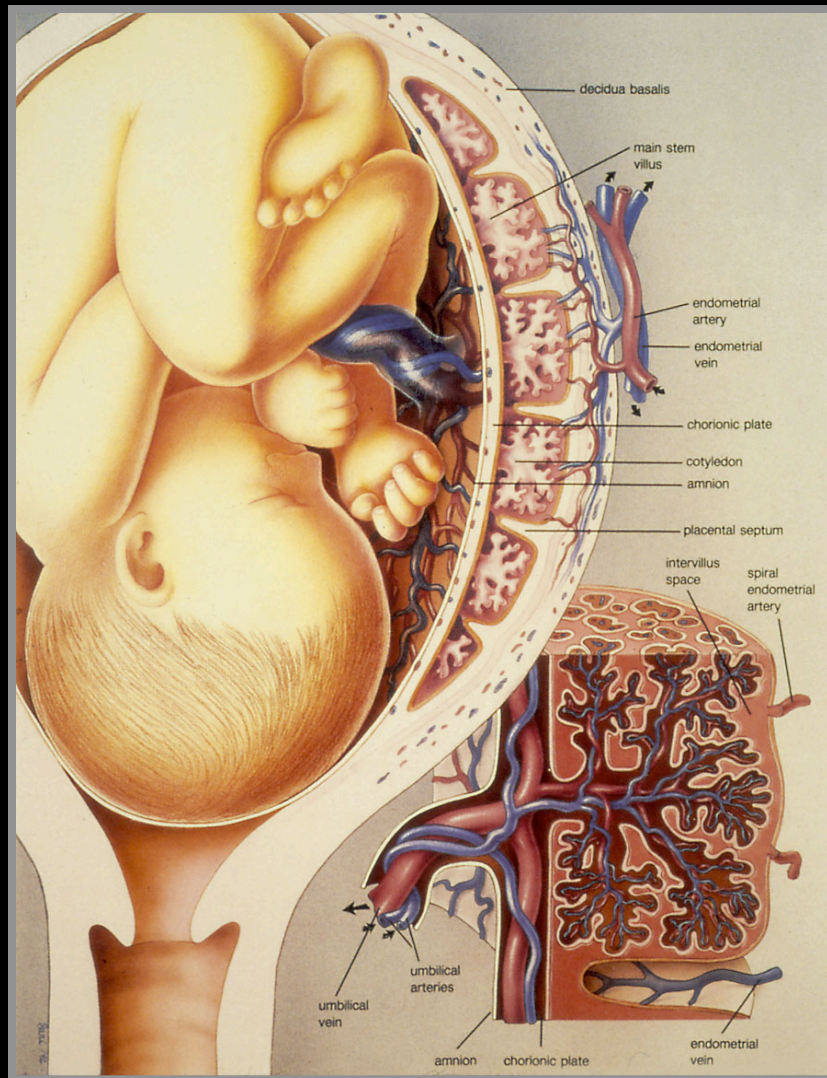
Boyle C, et al. Pediatrics 1994;93:399-403; Branum AM, et al. Paediatr Perinat Epidemiol 2002;16:8-15; Hedley AA, et al. JAMA 2004;291:2847-50. Lanphear BP, et al. Pediatrics 2001 e98. Froehlich T, et al. Arch Ped Adolesc Med 2007;161:857-864; Braun J, et al. Environ Health Perspect 2008;116:956-962.

Trends in Neuropsychiatric Disorders among Children in Denmark (per 10,000), 1990 to 1999 Birth Cohorts



Worldwide Prevalence of Asthma and Asthma Symptoms





Environmental Risk Factors for Chronic Disease

- Inadequate Nutrition
- Infections
- Social Disparities
- Built Environment
- Environmental Toxicants

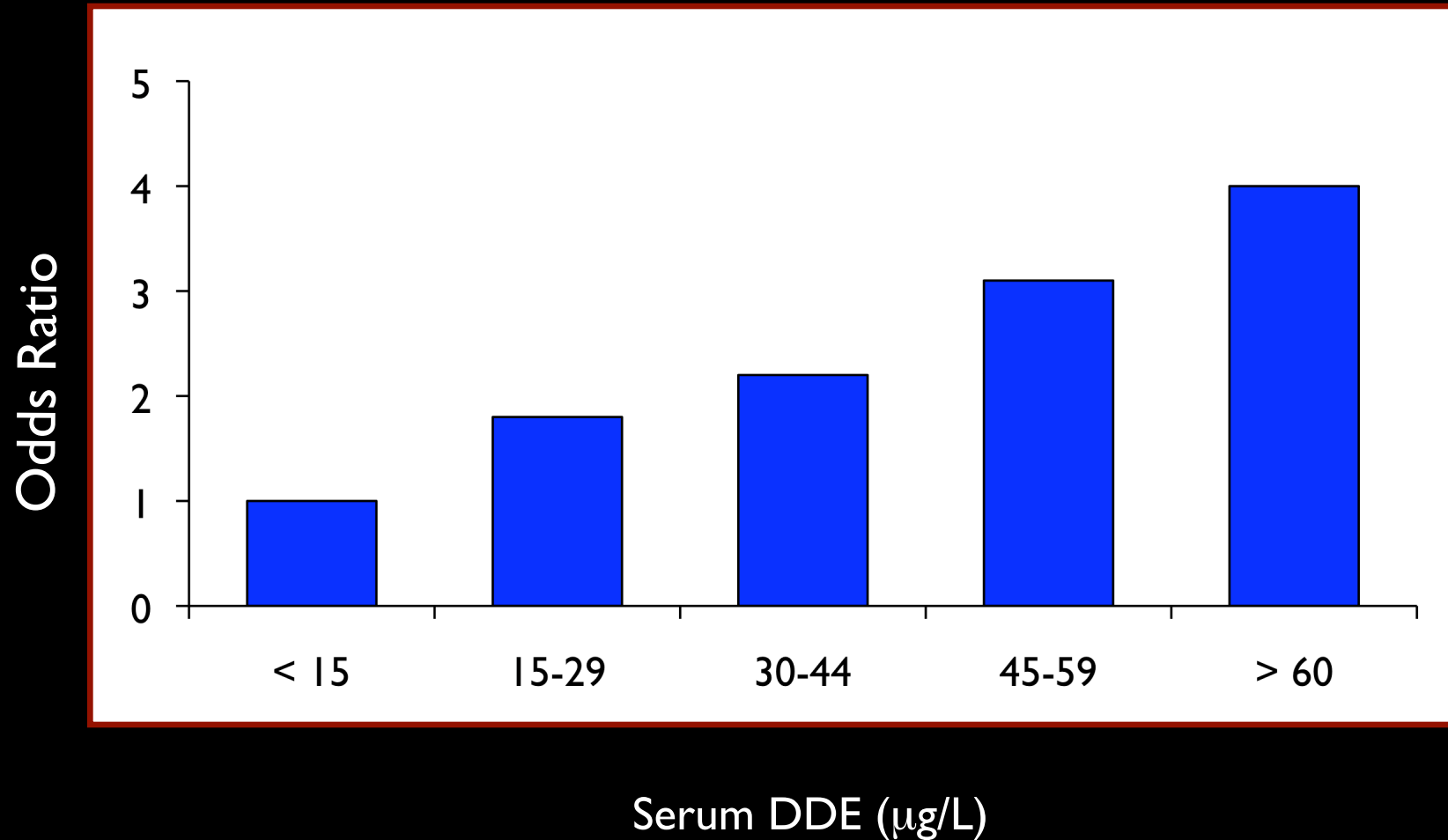
Environmental Toxicants

- Most recognized toxicants were discovered only as a result of an environmental disaster
- Increasing evidence linking toxicants with disease and disability at levels previously thought to be innocuous or safe
- Failure to regulate exposures to suspected toxicants or chemicals of uncertain toxicity

Environmental Disasters

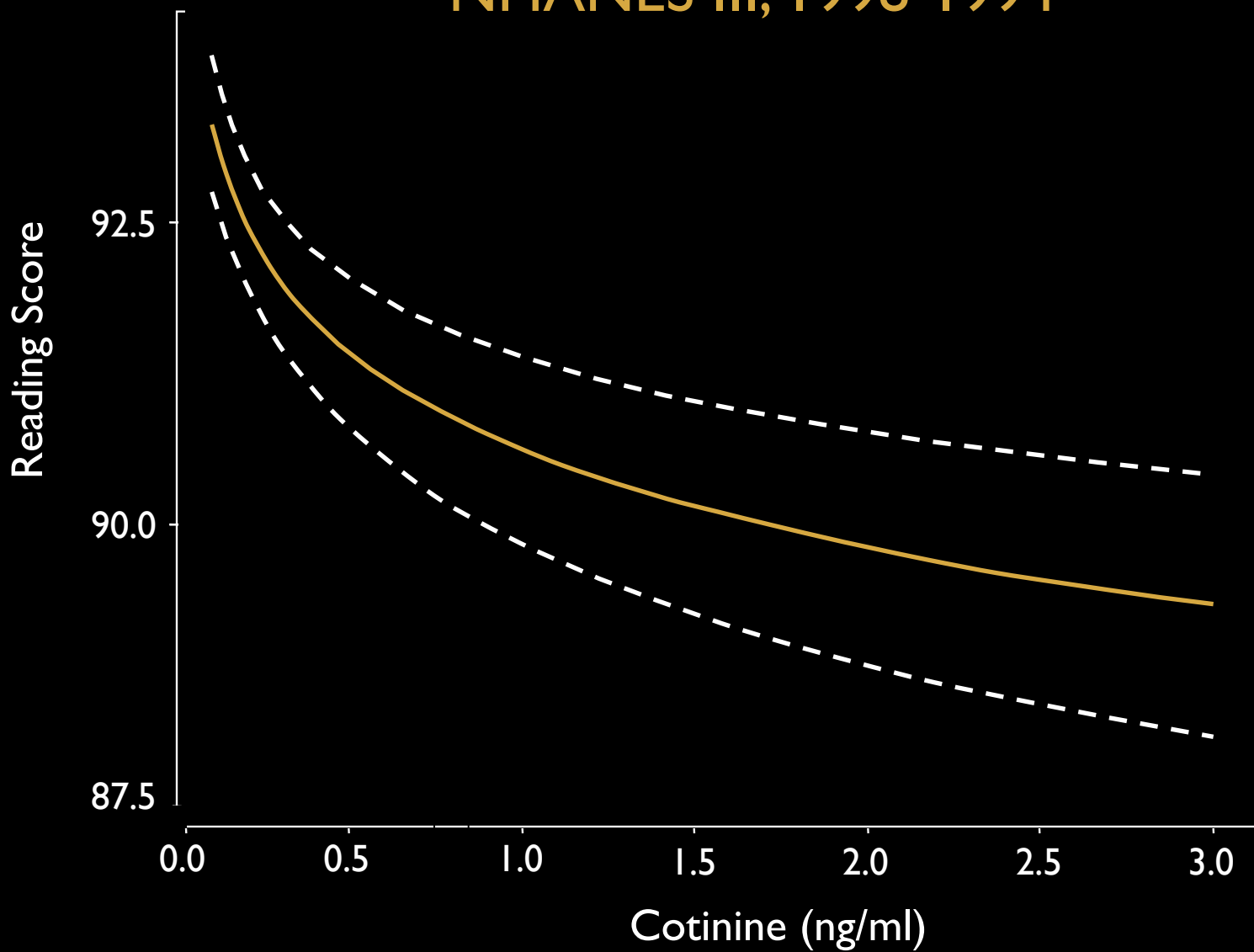


Adjusted Odds Ratio for Preterm Birth by Maternal Serum DDE

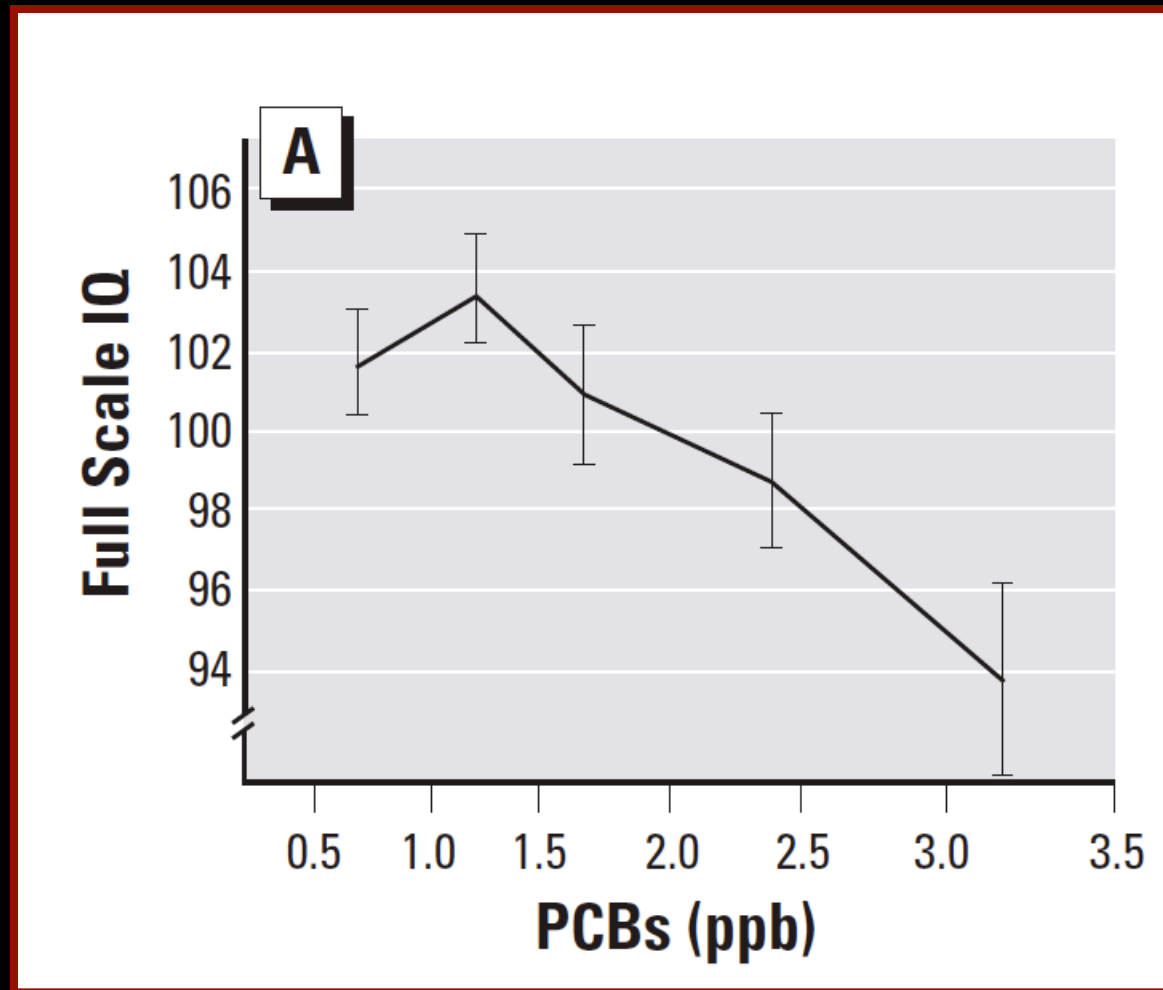


Longnecker M, et al. The Lancet 2001;358:110-114.

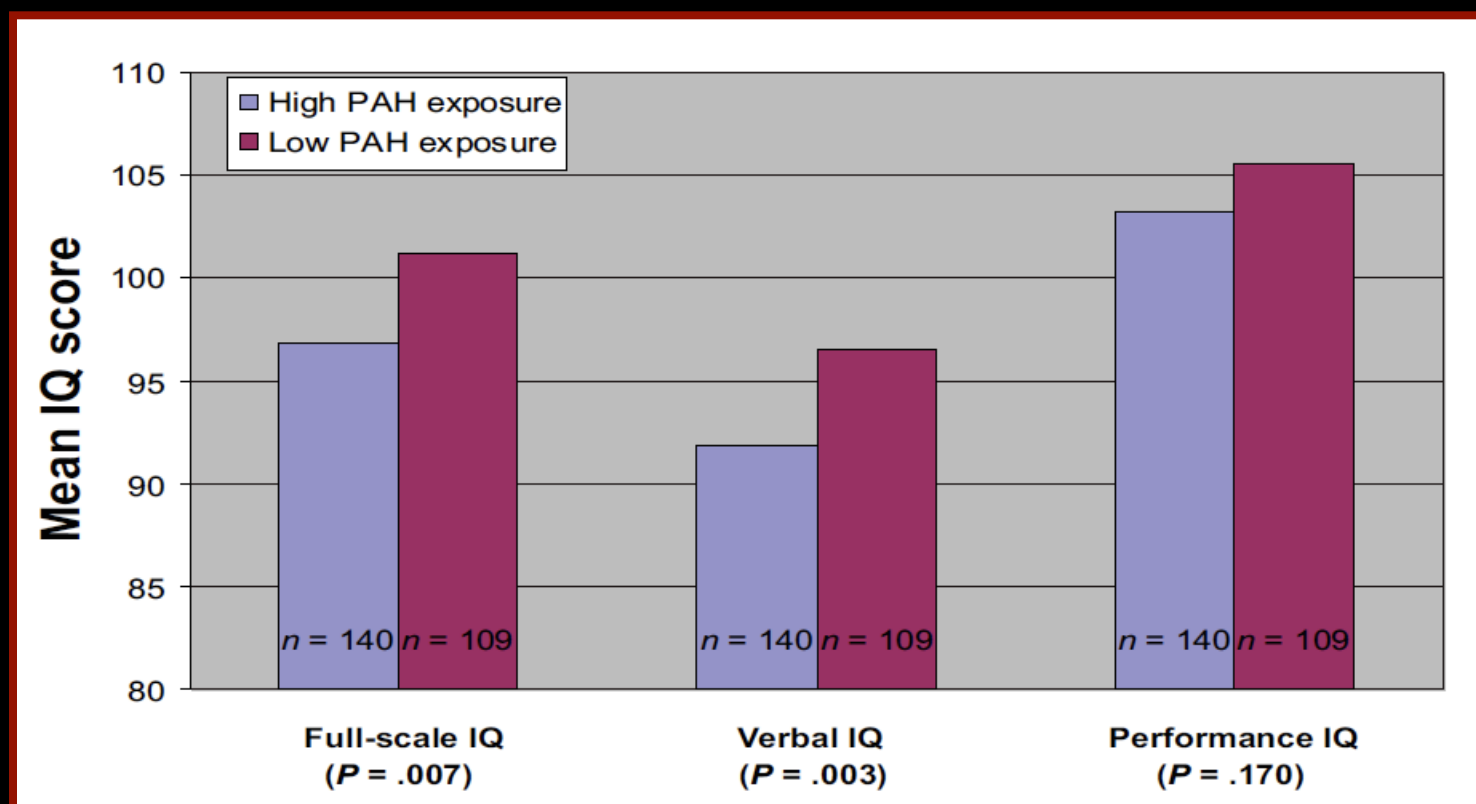
Reading Scores by Serum Cotinine in US Children, NHANES III, 1998-1994



Prenatal PCB Exposure and IQ Scores in 9-year old Children, Oswego, NY

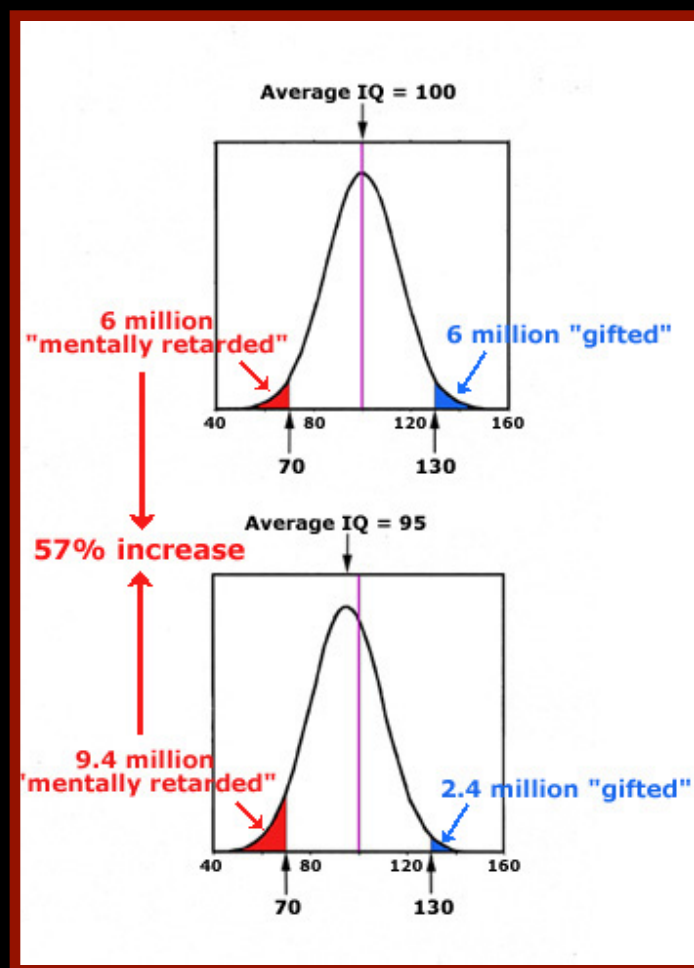


Differences in IQ Scores among 5-year old Children by Prenatal PAH Exposure



Perera F, et al. Pediatrics 2009; 124:e195-e202. Adjusted for prenatal ETS exposure, child's gender, ethnicity, maternal IQ score, maternal education level and HOME Inventory

Impact of Reducing IQ by 5 points on Prevalence of Mental Retardation in US Children



Limitations

- Studies did not account for all relevant risk factors (e.g., parental psychopathology)
- Diagnosis of ADHD, wheeze and other disorders used validated surveys based on parent report
- Other exposures, such as tobacco and alcohol, often relied on maternal report

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 17, 2003

VOL. 348 NO. 16

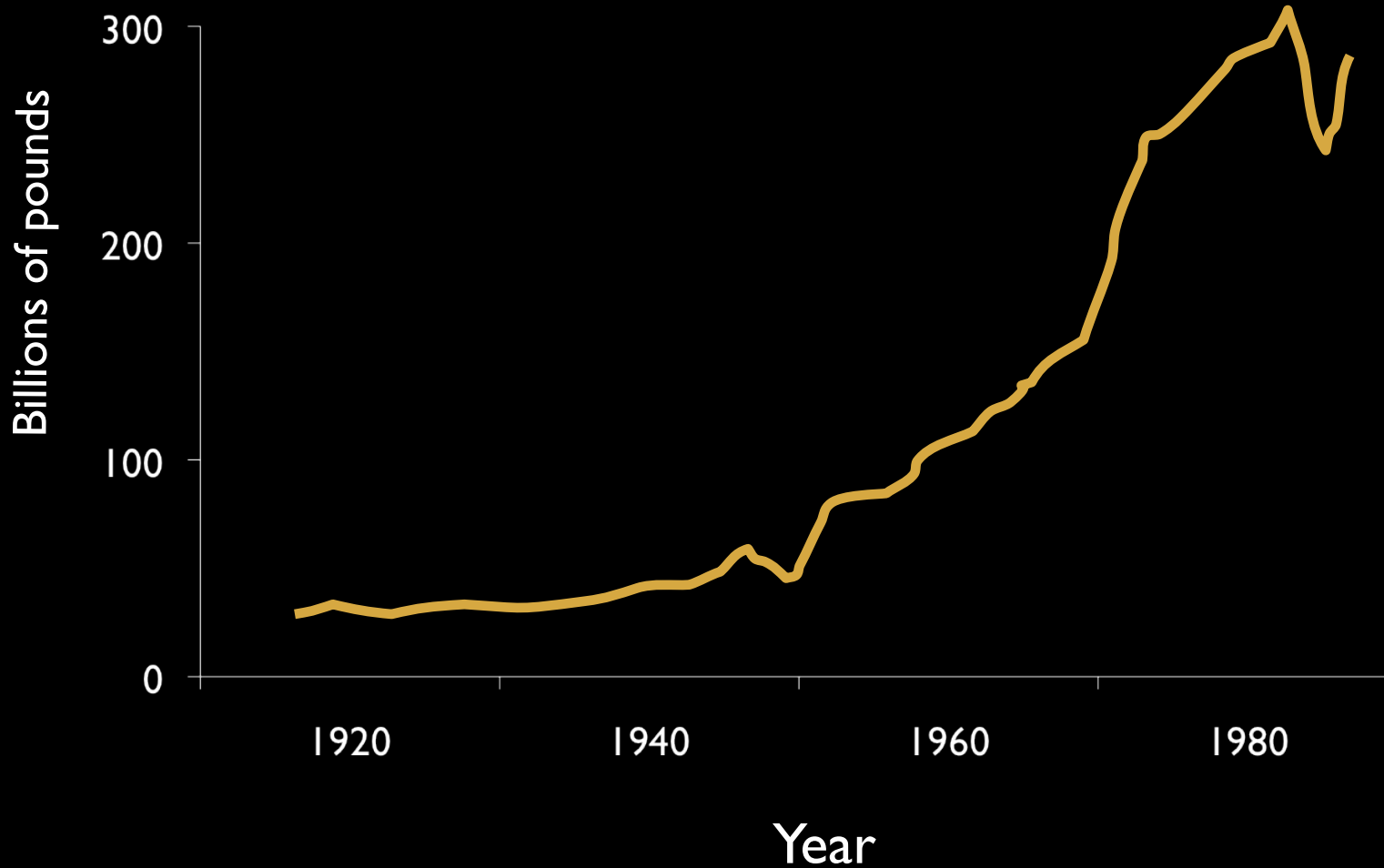
tions of 0 to 10 μg per deciliter. Our findings suggest that when linear estimation from such samples is extrapolated to lower blood lead concentrations, the results do not accurately reflect the greater magnitude of the lead-associated impairment at these lower concentrations.

The larger associations with IQ at lower lead concentrations may appear counterintuitive. Although we did not explore possible biologic mechanisms that could explain this finding, there is evidence that high concentrations of heavy metals may enhance cellular defense mechanisms and thereby lessen the rate at which additional damage occurs.³⁵

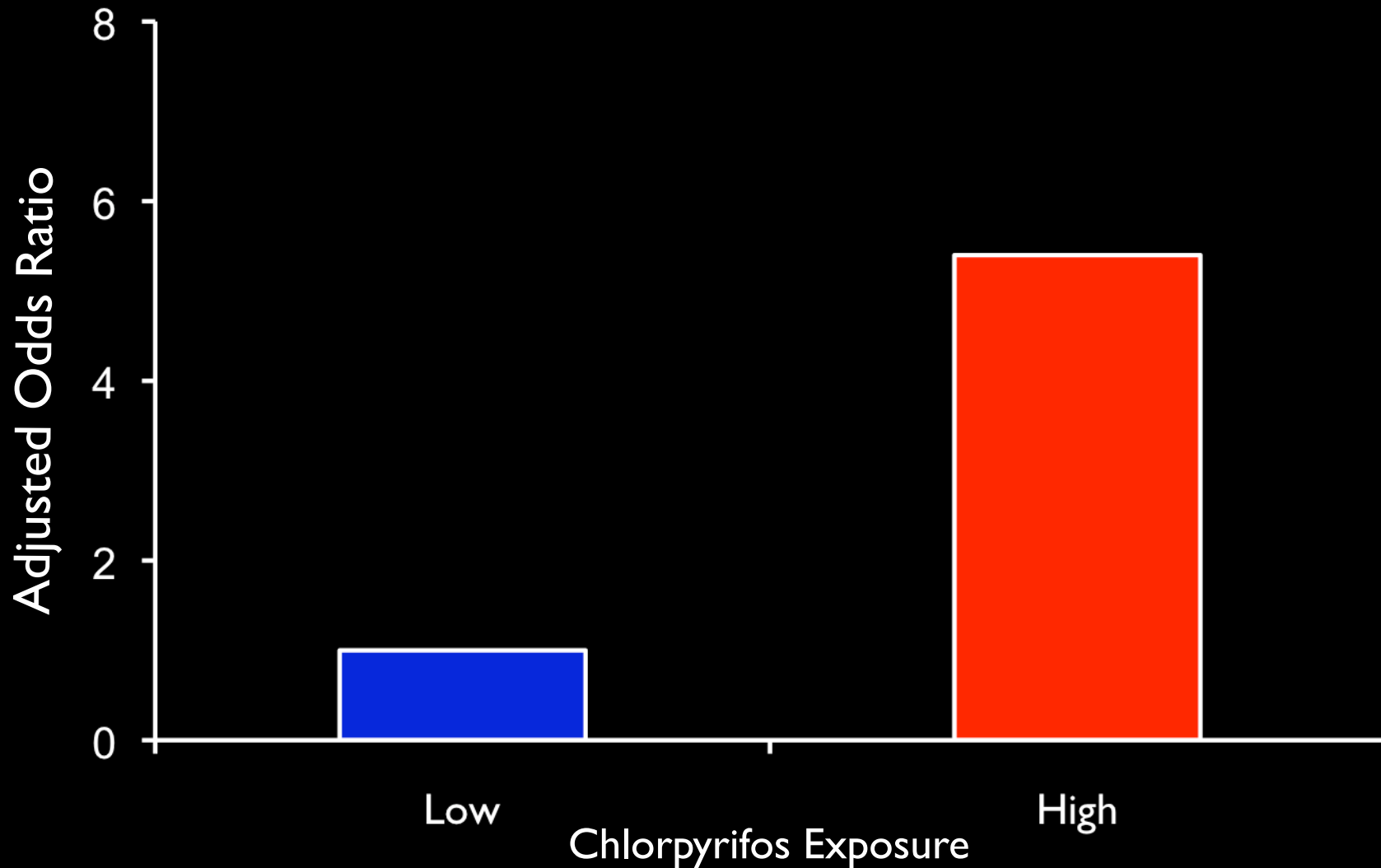
As with any observational study, it is not possi-

ble to draw causal inferences from these findings. Instead, the plausibility of a causal interpretation must be judged by the consistency of findings from numerous epidemiologic studies and the relevant experimental studies in animals.^{7,36,37} An inevitable limitation of the observational design is that it is not possible to control for all potentially confounding variables. However, the available evidence suggests that, in this area of research, a relatively small number of variables (e.g., the Home Observation for Measurement of the Environment score, socioeconomic status, and maternal IQ) are the primary confounders and that including other variables does not appreciably change the estimated

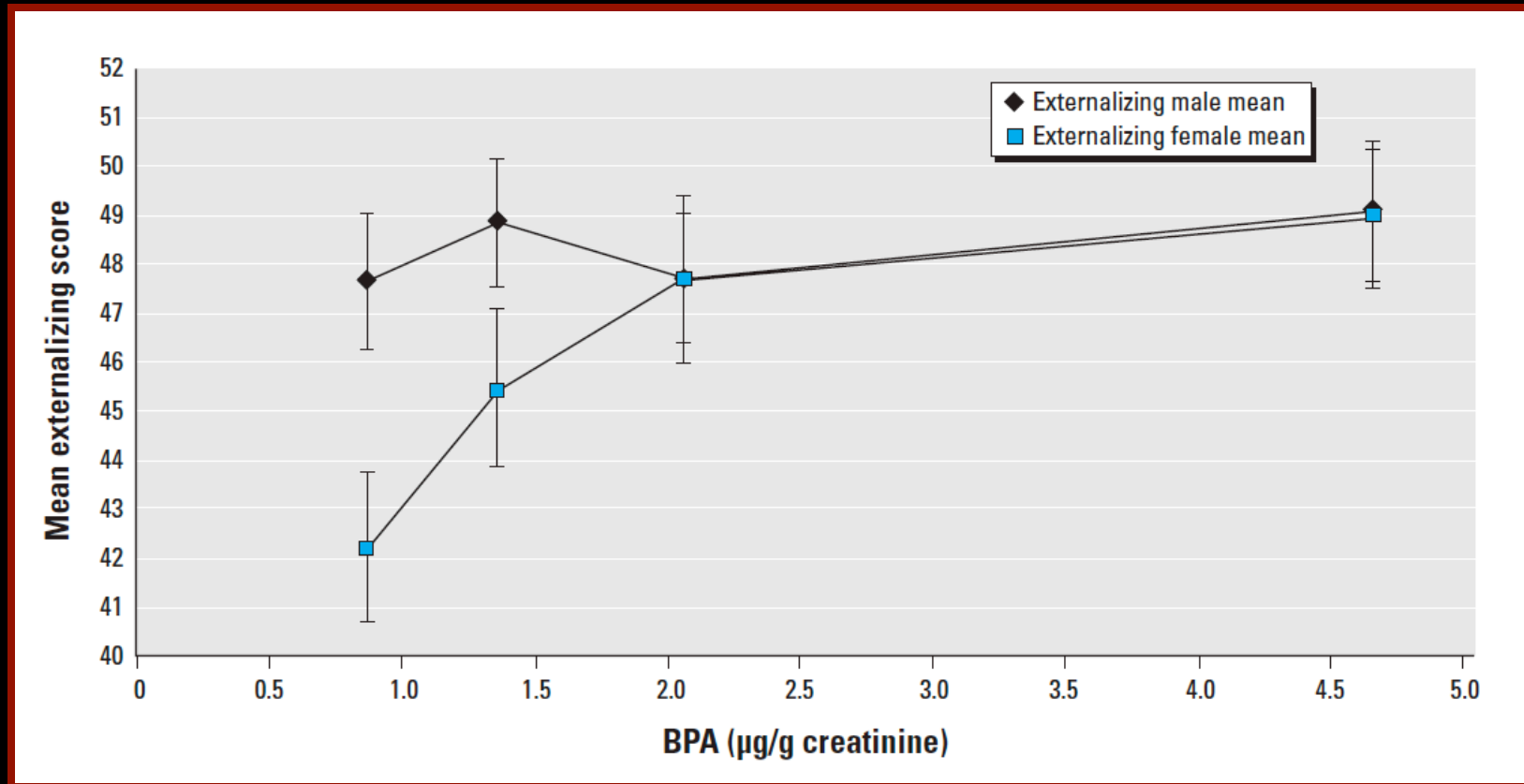
Annual Production of Total Synthetic Chemicals in the U.S.



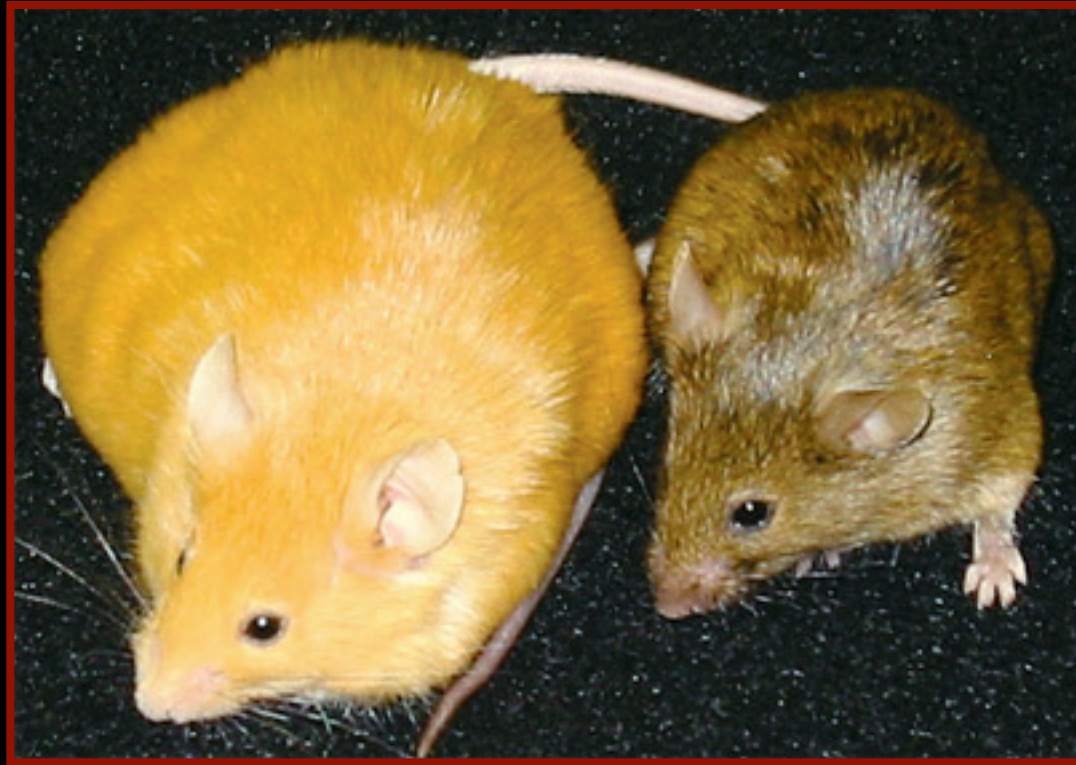
Prenatal Chlorpyrifos Exposure and Pervasive Developmental Disorder in 3-year old Children



Prenatal Bisphenol A Exposure and Externalizing Behaviors - The HOME Study

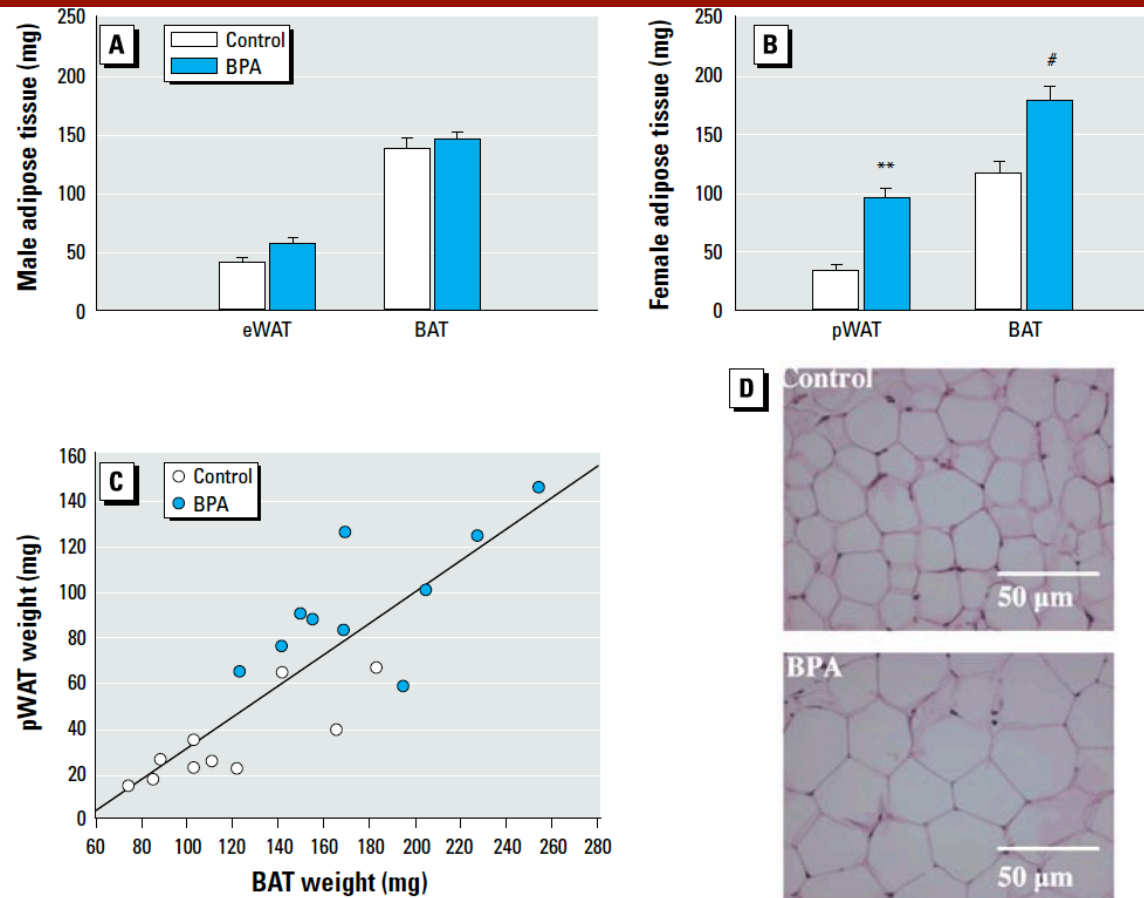


Could Exposure to a Common Chemical, Bisphenol A, be a Risk Factor for the Obesity Epidemic?



Waterland RA, et al. Mol Cell Biol 2003;23:5293-5300.

Effect of Perinatal BPA Exposure on Adipogenesis at Weaning in the Rat



Somm E, et al. EHP 117: 1549-1555. The increase in adiposity was greater in the pWAT (parametrial white adipose tissue) than in brown adipose tissue (BAT).

Failure of Toxicity Testing

- Of the nearly 3,000 high production volume chemicals, 75% lack even the most basic toxicity tests. ¹
- Of the 140 registered pesticides EPA considers to be neurotoxic, the majority have not been tested for developmental neurotoxicity. ¹
- Animal testing may not be sensitive enough to protect humans. ²

1. Claudio L. Toxicol Appl Pharm 2000;164:1-14.

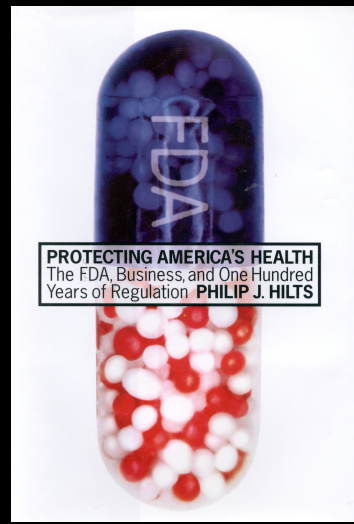
2. Rice D. Env Health Persp 1996;104:205-215.



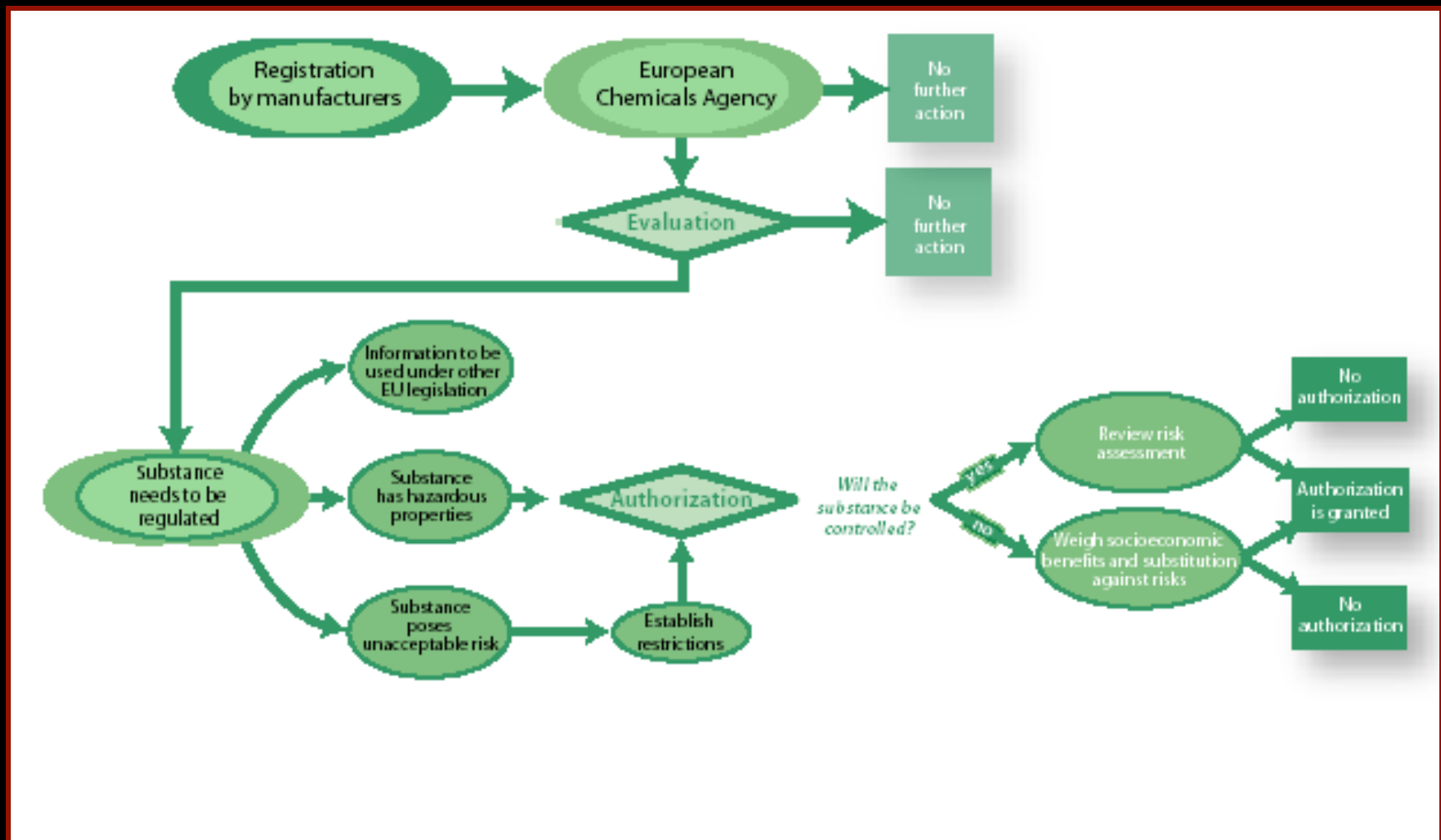
It's all of a piece. Thalidomide and pesticides - they represent our willingness to rush ahead and use something new without knowing what the results are going to be.

Rachel Carson

Lessons from the FDA



Flow Chart of the EU's Regulatory Framework for Regulating Chemicals



Kid Safe Chemical Act of 2010

II

110TH CONGRESS
2^D SESSION

S. 3040

To amend the Toxic Substances Control Act to reduce the exposure of children, workers, and consumers to toxic chemical substances.

IN THE SENATE OF THE UNITED STATES

MAY 20, 2008

Mr. LAUTENBERG (for himself, Mr. MENENDEZ, Mr. WHITEHOUSE, Mrs. CLINTON, and Mr. KERRY) introduced the following bill; which was read twice and referred to the Committee on Environment and Public Works

A BILL

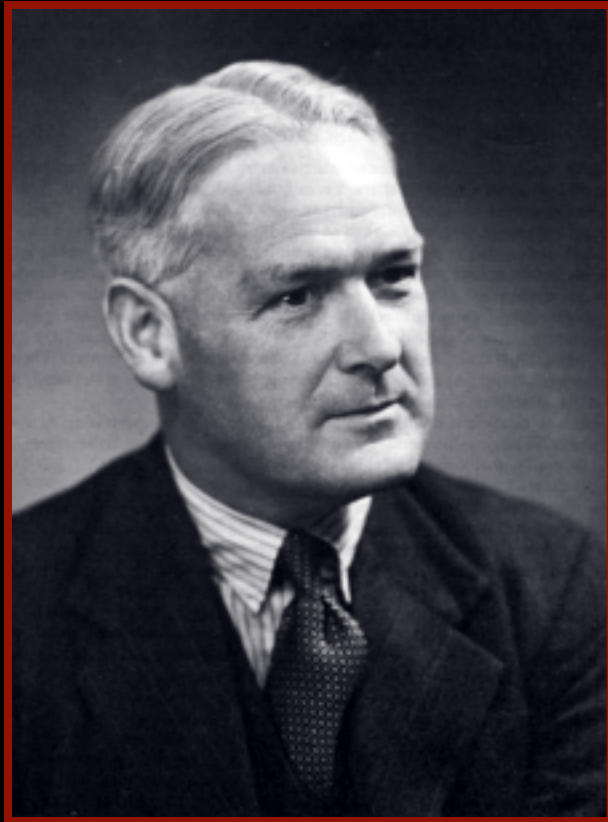
To amend the Toxic Substances Control Act to reduce the exposure of children, workers, and consumers to toxic chemical substances.

Ethical Dilemma

The costs of any adverse health effects, as well as the study, regulation and control of environmental toxicants are socialized, whereas the profits are privatized

Conclusions

- Clarify societal obligations to protect children from environmental hazards
- Require toxicity testing for all high production chemicals before released or marketed
- Require community participation in community-based research
- Expand use of experimental trials to control or understand environmentally-induced diseases
- Design experimental trials to enhance children's potential to benefit



"All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Austin Bradford Hill