WHAT CAUSES AUTISM?

THE CASE FOR AN ENVIRONMENTAL CONTRIBUTION

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The Heinz Endowments
Environmental Links to the Incidence of Autism
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Definition of Autism

- A complex, serious, biologically based disorder of brain development
- First described in 1943 by Kanner.
- Most commonly becomes evident in early childhood.
- Characteristic features: Social deficits, abnormalities in communication, repetitive behaviors, and cognitive inflexibility.
- Diagnosis is based on clinical and behavioral assessment. There is no specific biochemical indicator or distinct neuroanatomical abnormality that defines autism.

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Clinical Presentation of Autism is Heterogeneous

- Severity ranges from mild to profound
- 70% of children with autism also have MR
- Some have increased brain size
- One in three develops epileptic seizures
- One in two have speech impairment
- Yet some have unique skills, e.g., some children with Asperger's syndrome

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Autism Spectrum Disorder (ASD)

- A term that reflects the heterogeneity of clinical presentation
- ASD encompasses:
  - Autistic Disorder (DSM 299.00)
  - Asperger's syndrome (DSM 299.80)
  - Pervasive developmental Disorder – Not Otherwise Specified (DSM 299.80)

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Epidemiology of Autism

- Current prevalence in US is 6-7 cases per 1,000 children (or 1 in 150)
- This is substantially higher than reported prevalence a decade ago
- No racial differences in prevalence
- 3-5 times more common in boys

- Key question: Has a true increase occurred in incidence of autism?

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Genetic Contribution to Autism

Genetics clearly plays a role in causation

- 70% concordance in identical twins
- Families may contain children with frank autism as well as children with "autistic traits"
- Autism may co-occur with numerous inherited syndromes – Fragile X syndrome, Down syndrome, Cohen syndrome, Angelman syndrome, and Rett syndrome

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Strategies for Genetic Research in Autism

- Family-based and case-control evaluations of candidate genes
- Cytogenetic studies
- Genome-wide screens. These have identified copy number variations (CNVs), deletions and micro-duplications associated with autism

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Shortcomings of a Purely Genetic Explanation for Causation of Autism

- None of the genetic findings account for more than 1-3% of cases of autism.
- Taken together, the genetic factors identified to date account for no more than 20-25% of cases
- Difficulty in explaining occurrence of sporadic cases, discordant development of autism in identical twins, variations in expression within families, rise in incidence of autism (if real)

These shortcomings raise the possibility of an environmental contribution to autism

Gene-environment interactions are likely

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Plausibility for an Environmental Contribution to Autism: Three Key Arguments

- Evolving knowledge of the vulnerability of the developing human brain to environmental toxins
- Direct evidence that chemicals can cause neurodevelopmental toxicity in the developing brain
- Direct evidence that certain prenatal exposures can cause autism

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Vulnerability of the developing human brain to environmental toxins

- Children today are surrounded by a large and increasing number of chemicals. Some are highly beneficial - e.g., foodstuffs, antibiotics and disinfectants. But others are toxic and known to cause disease
- Measurable levels of several dozen industrial chemicals have been detected in the bodies of nearly all persons in industrially developed countries, including breast milk and cord blood of newborn infants

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Industrial Chemicals and Children - The Failure to Test

- 80,000 + chemicals in commerce
- 3,000 produced in quantities of 1 million pounds or more per year (high production volume [HPV] chemicals)
- No basic toxicity information is publicly available for about half of HPV chemicals
- Information on developmental toxicity is publicly available for fewer than 20% of HPV chemicals

--EPA: Chemical Hazard Data Availability Study, 1998

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Why Children Are Especially Vulnerable to Toxic chemicals

- Greater exposure proportionate to body mass– *7 times more water per Kg per day; Hand-to-mouth activity*
- Diminished ability to detoxify many chemicals
- Heightened biological vulnerability
- More years of future life

National Academy of Sciences, 1993

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The Exquisite Vulnerability of the Fetus to Toxic Chemicals

- Phocomelia in infants exposed in the womb to thalidomide.
- Cancer of the reproductive organs in girls exposed in the womb to di-ethyl stilbestrol (DES)

These tragic cases destroyed forever the myth of the invulnerable placenta

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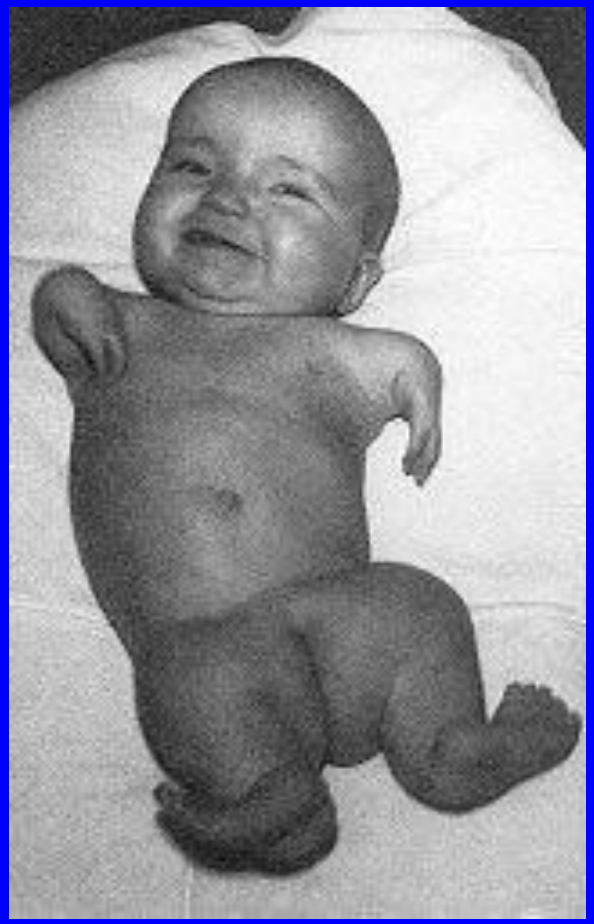
Chemicals Can Cross the Placenta to Injure the Fetus



Phocomelia Following Fetal Exposure to Thalidomide

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Exquisite Vulnerability of the Fetal Brain to Toxic Chemicals

- First documented at Minamata, Japan

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A child massively exposed to mercury in the womb – Minamata, Japan, 1960

No visible damage to the mother

Minamata showed that the fetal brain is far more vulnerable than the adult brain to industrial chemicals

This vulnerability is a consequence of the brain's extraordinary complexity, and is greatest in early life

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Chemicals currently known to cause injury to the developing brain

- Lead
- Methyl Mercury
- Polychlorinated Biphenyls (PCBs)
- Arsenic
- Manganese
- Organic solvents, e.g., Ethanol and Toluene
- Organophosphate pesticides - Chlorpyrifos
- Organochlorine pesticides

- *Another 201 industrial chemicals are known to cause neurotoxicity in adults, but developmental toxicity is untested.*
- *An additional 1,000 are neurotoxic in animal species.*

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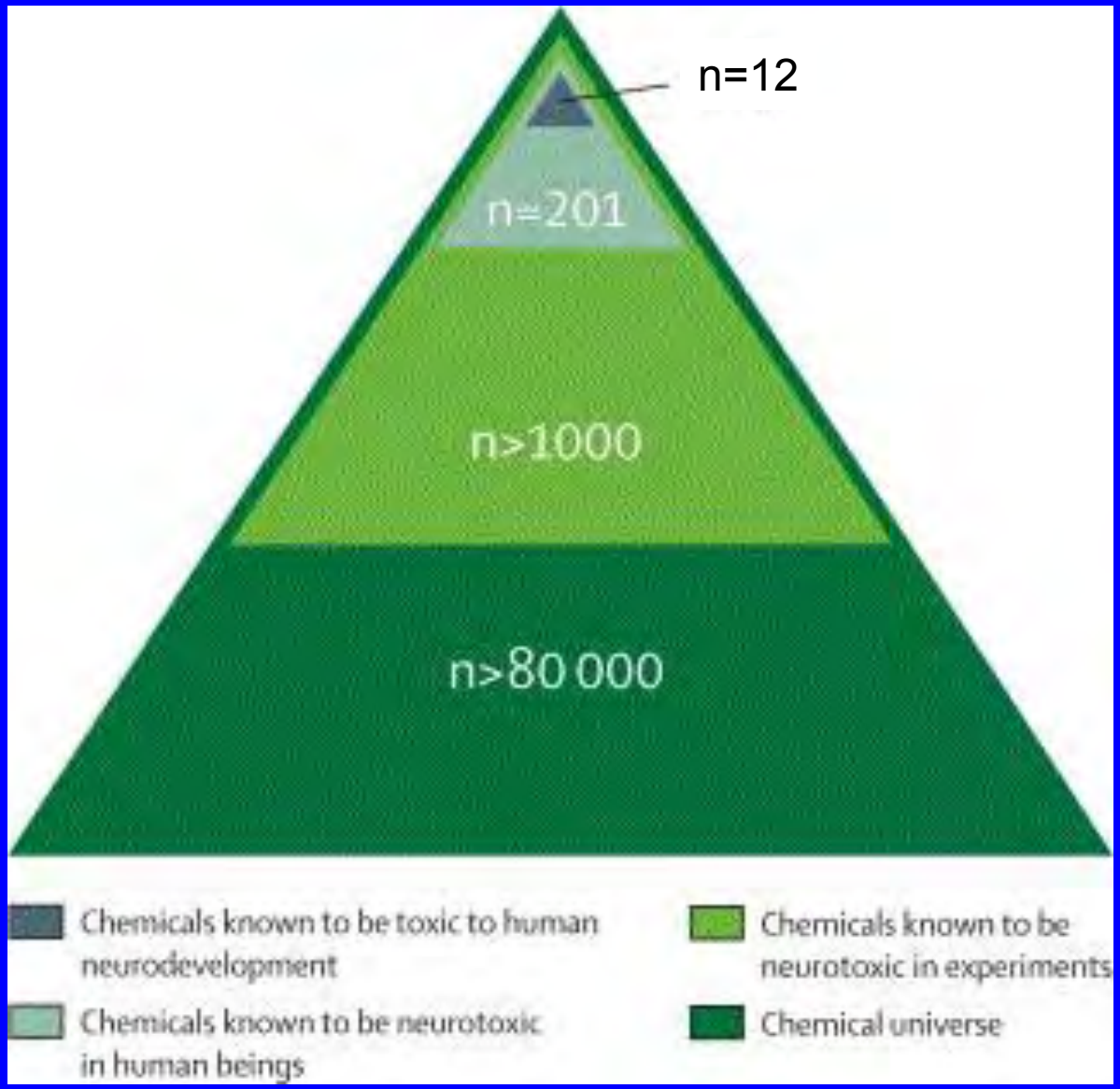
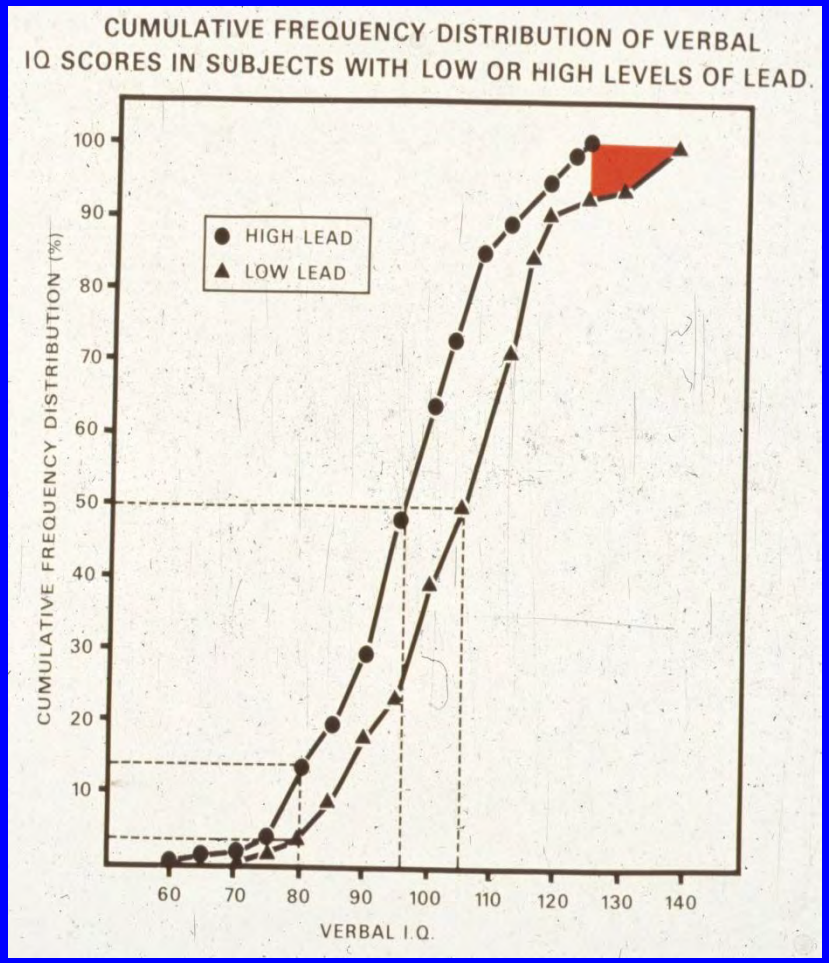
Are there additional developmental neurotoxicants not yet discovered?



Grandjean & Landrigan, *The Lancet*, 2006

Subclinical Toxicity - The Needleman Study

Apparently healthy children with increased lead levels have lower IQ



Needleman HL et al. *NEJM*, 1979

The Concept of Subclinical Toxicity -

- The underlying premise is that there exists a continuum of toxicity, in which clinically apparent effects of lead have their asymptomatic, subclinical counterparts. Relatively low dose exposure may cause harmful effects to health that are not evident with a standard clinical examination.
- Subclinical toxicity is now recognized to pertain to all chemicals that are toxic to the brain
- Timing of exposure is critically important

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Societal impact of 5-point loss in IQ score

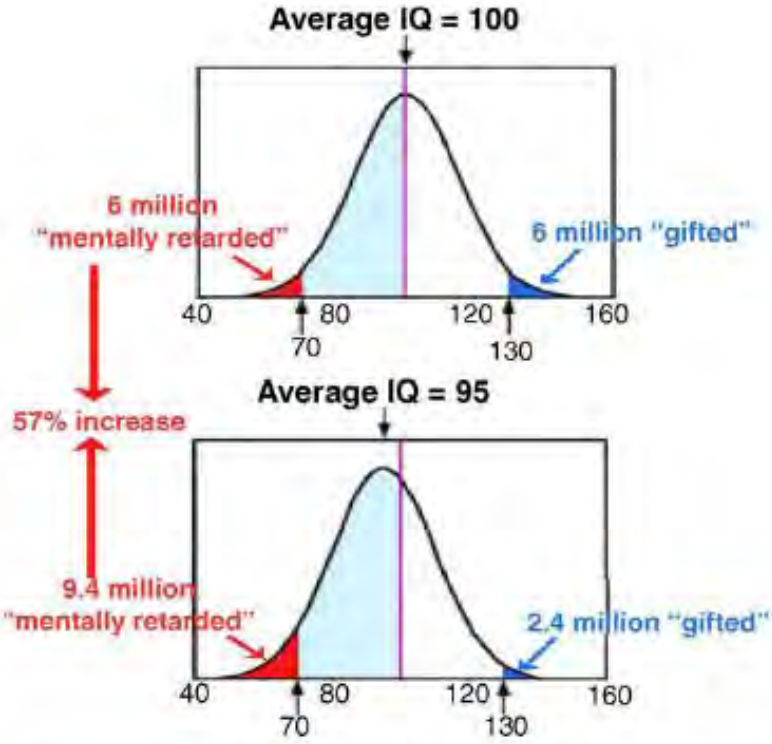

Fig. 3. Losses associated with five-point drop in IQ on a population of 100 million. Based on Weiss (1988) and modified by http://www.ourstolenfuture.-org/NewScience/behavior/iqshift.htm.

Lead and Behavior – Lead Affects Domains beyond Intelligence

- At age 7, Needleman found an association between lead levels and aggression, delinquency and social problems
- By age 11, increased delinquent and aggressive behavior were clearly evident in children with higher lead levels
- By age 18, young adults with higher lead levels at age 7 were more likely to be dyslexic and to have quit school

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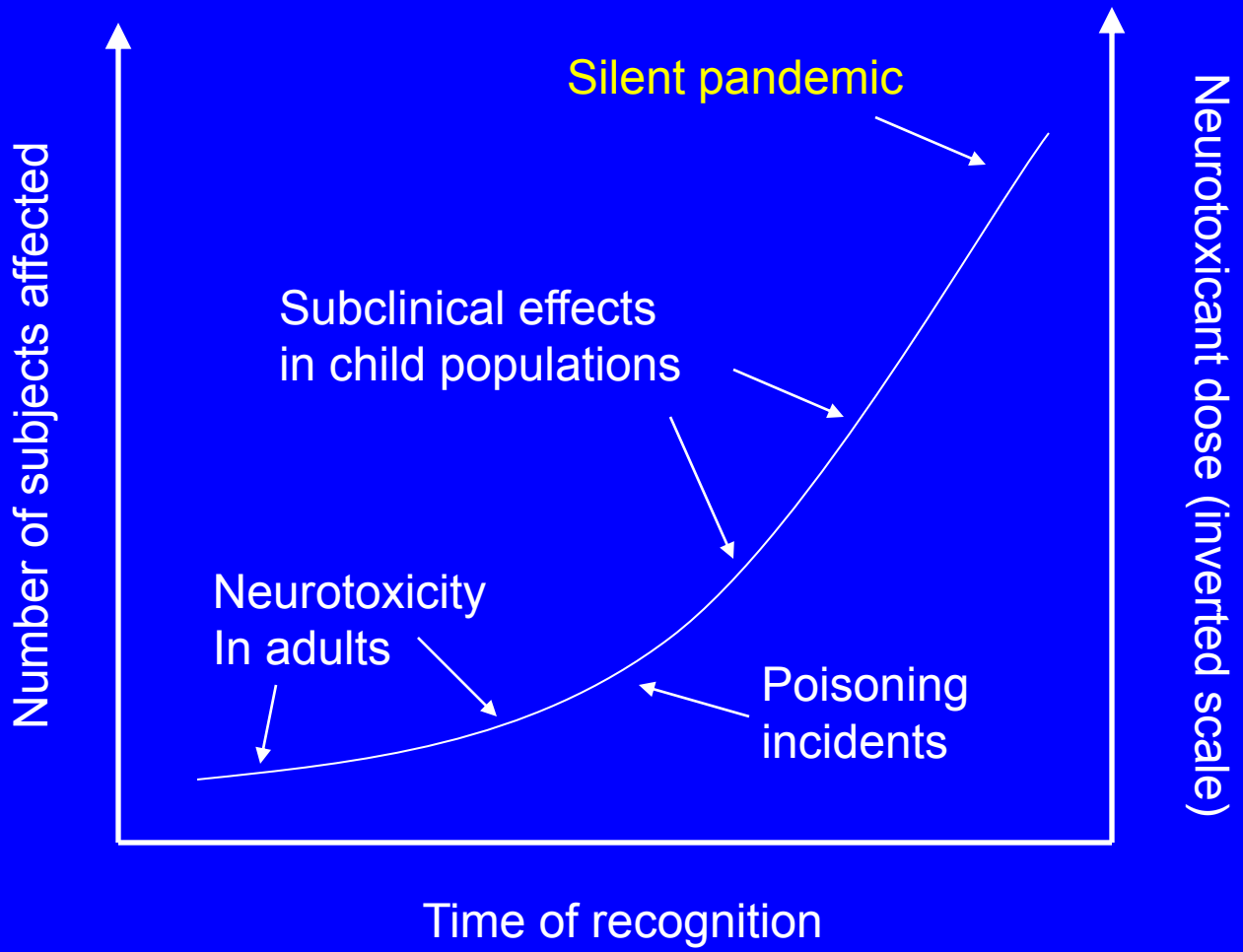
Time course of recognition of developmental neurotoxins



Grandjean & Landrigan, *The Lancet,* 2006

Prenatal Exposures and Autism

The strongest "proof of concept" evidence for an environmental contribution to autism

- A small number of environmental exposures are convincingly linked to autism
- Each of these exposures appears to have occurred prenatally, and indeed to have occurred very early in gestation at a time in embryologic development when the fundamental architecture of the brain is being established

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Chemicals and other environmental exposures known to cause autism

- Thalidomide
- Misoprostol
- Prenatal rubella infection
- Valproic acid
- Organophosphate insecticides - chlorpyrifos

Are there additional environmental causes of autism yet to be discovered?

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Additional Collateral Support for an Environmental Contribution to Autism

- The US National Academy of Sciences has concluded that 28% of all developmental disorders in children are caused in part by environmental factors – 3% by environmental exposures alone, and 25% more through gene-environment interactions

- Recent epidemiologic studies indicate that prenatal exposures to tobacco smoke (maternal smoking) and lead are associated with ADHD

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There is No Evidence that vaccines Cause Autism

Studies in multiple countries have failed to find an association:

- UK
- California, USA
- Yokohama, Japan
- Denmark
- Finland
- Avon, UK
- USA (CDC)

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The Autism Discovery Project

Progress in identifying the environmental causes of autism can be achieved by a three-pronged strategy:

- Enhanced testing of chemicals for developmental neurotoxicity

- Neurobiological research that that emphasizes the importance of timing of exposure.

- Epidemiologic studies of children – especially multi-year prospective studies of birth cohorts that incorporate careful measures of chemical exposures and of genetic susceptibility-
  - The Mount Sinai Cohort Study
  - The Cord Blood Repository
  - The National Children's Study

The Ultimate Goal: Adoption of a more explicitly precautio approach to exposure prevention

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The Mount Sinai Cohort Study

- Following 400 children in East Harlem, NY from early in pregnancy through puberty
- Goals: To examine impacts of prenatal chemical exposures on brain development and reproductive development
- Findings: Prenatal exposure to chlorpyrifos reduces brain growth and increases risk for PDD
- Continuing research: Examining effects of exposures to endocrine disruptors

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The Cord Blood Repository

- A novel tissue bank that will collect and bank 2,000 samples of cord blood and placental tissue per year.
- Each mother will provide an exposure history and informed consent
- Samples will be analyzed for multuple chemicals
- Samples will be analyzed genetically
- Babies will be followed longitudinally including detailed developmental assessments

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Research

The US National Children's Study

- The "Children's Framingham Study".
- A multi-year prospective epidemiological study that will examine the influences on health of exposures in early life -chemical, physical, social and behavioral exposures.
- 100,000 children to be followed from early in pregnancy to at least 18 years of age
- Will launch in 2008
- Linked through WHO to similar studies in many nations

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Epidemiological Research:
The National Children's Study

http://www.nationalchildrensstudy.gov/

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Critical Research Questions for the National Children's Study

- What are the contributions of indoor and ambient air pollution to the origins of asthma?
- What are the environmental causes of learning disabilities, autism and attention deficit disorder?
- What are the environmental causes of birth defects
- What are the environmental causes of cancer?

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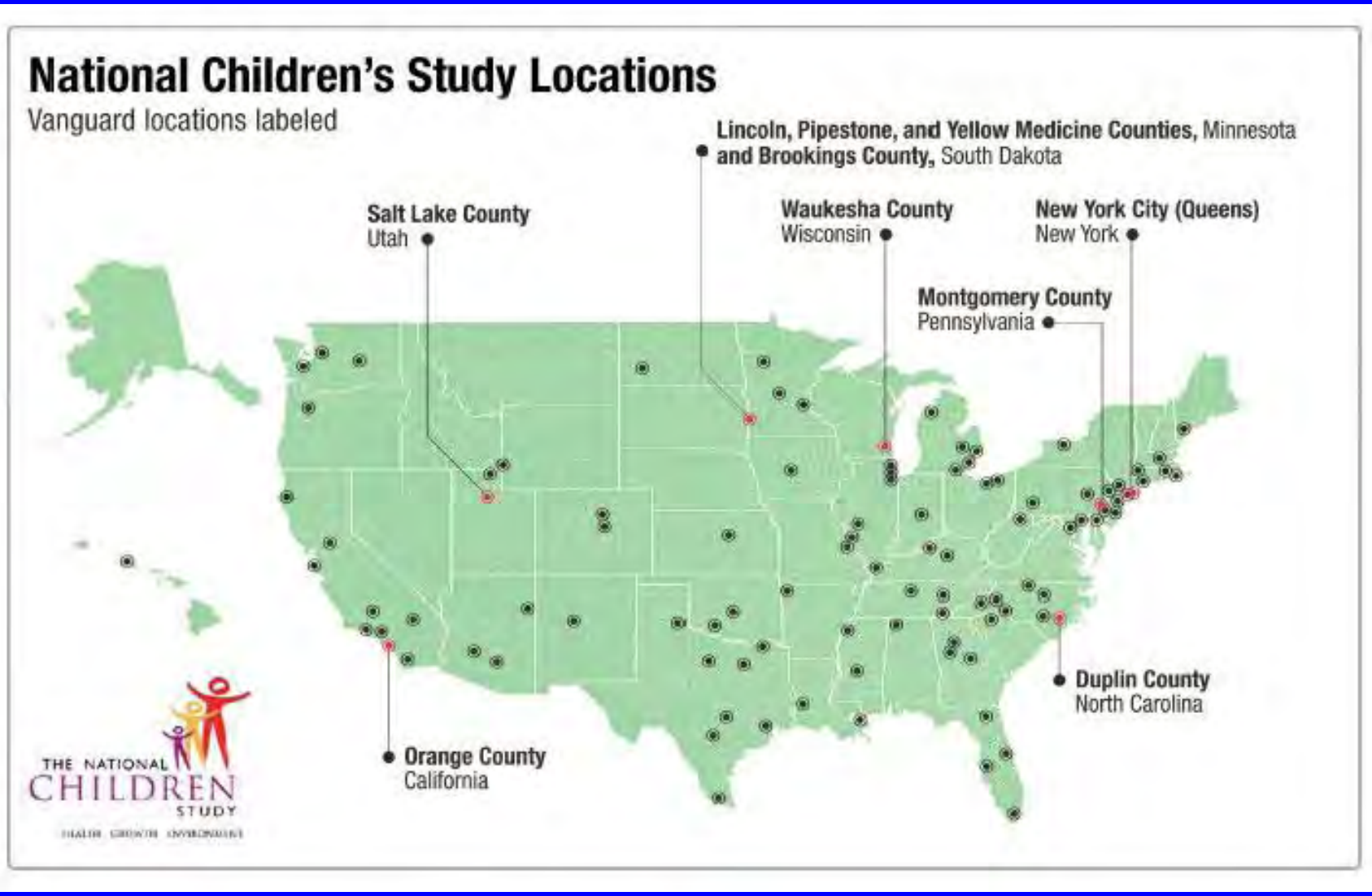
The National Children's Study



Who will be enrolled?

- Household recruitment
  - Women who are in the first trimester of pregnancy
  - Women who are planning a pregnancy
  - Women of child-bearing age who are not planning pregnancy but could become pregnant during the enrollment period
- Supplemental recruitment
  - Prenatal care providers
  - Community based recruitment of eligible women

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The Model for the National Children's Study
The Framingham Heart Study

Rates of Heart Disease, Stroke and Lung Cancer Exploded after World War II. To find out why, US public health authorities launched the Framingham Heart Study.

The Framingham Heart Study

Identified the major risk factors for cardiovascular disease:

- Cigarette smoking
- High cholesterol
- Hypertension
- Sedentary life style
- Diabetes

The Result: Development of a blueprint for prevention

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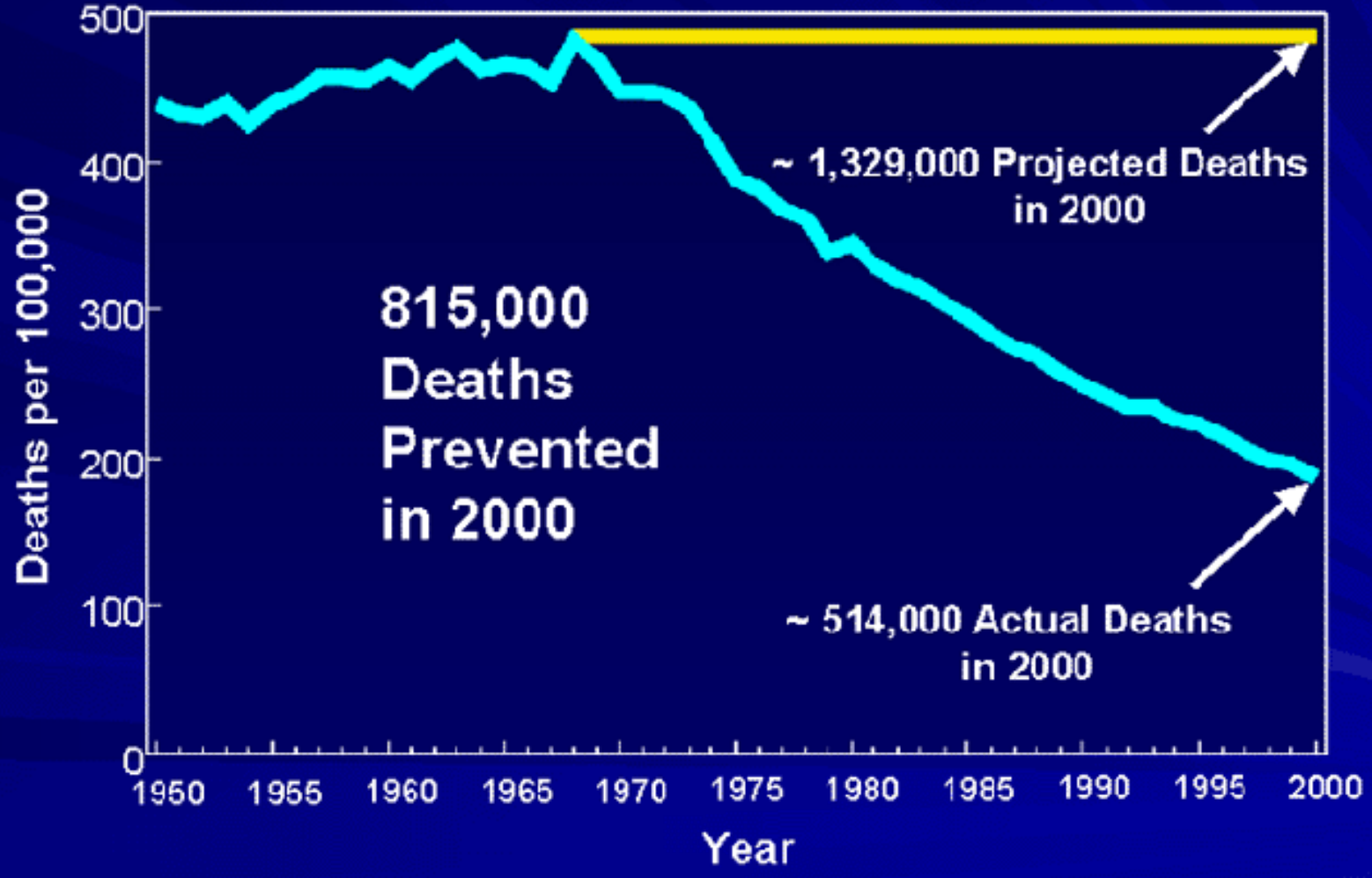
Coronary Heart Disease

Age-Adjusted Death Rates: Actual and Expected
United States, 1950-2000



The Good News: Progress is Possible

Studies showing environmental harm to children are powerful drivers of progress

- Declining use worldwide of leaded gasoline
- Decline in exports of toxic and banned pesticides under international treaty

Removal of lead from gasoline as a case study

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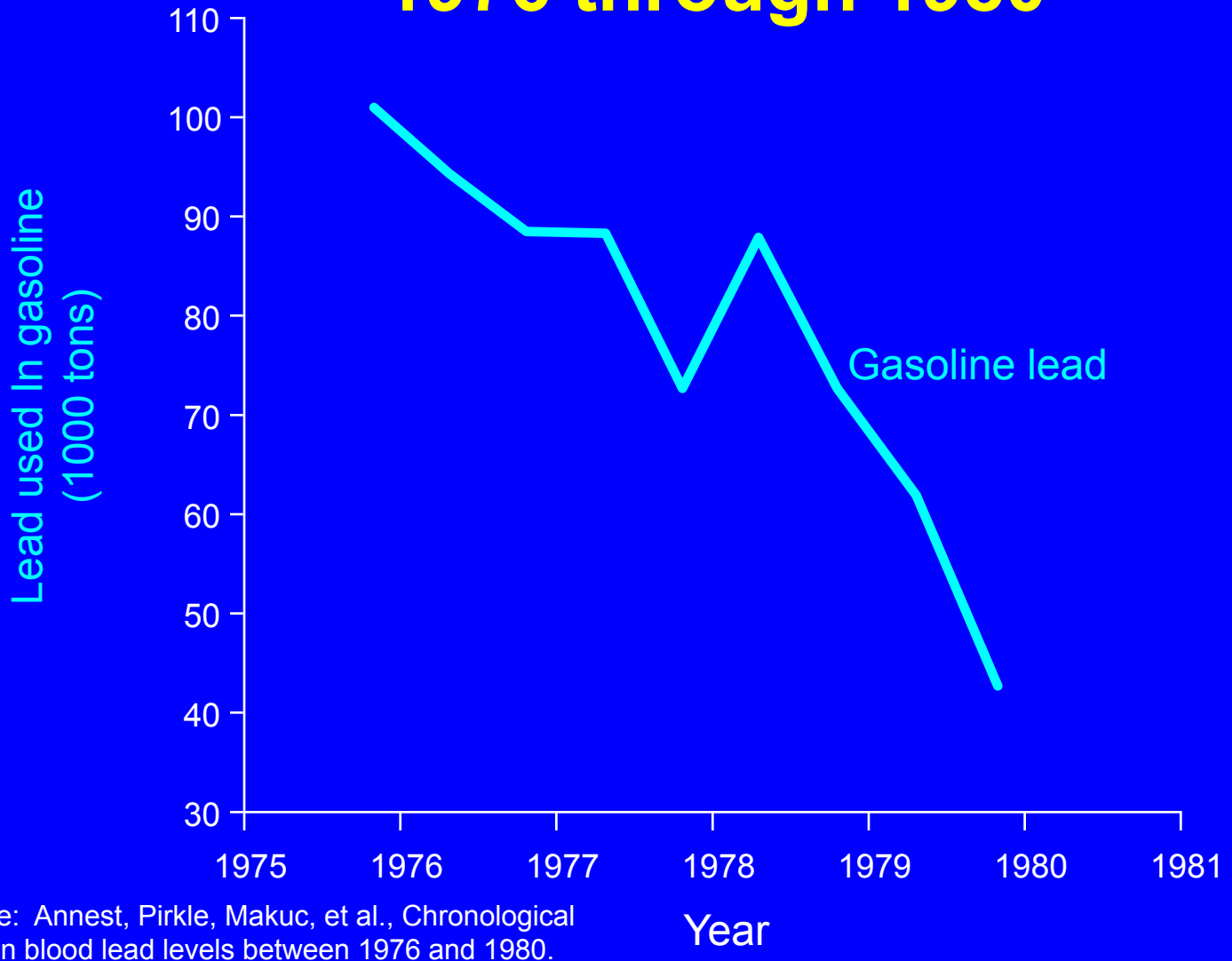
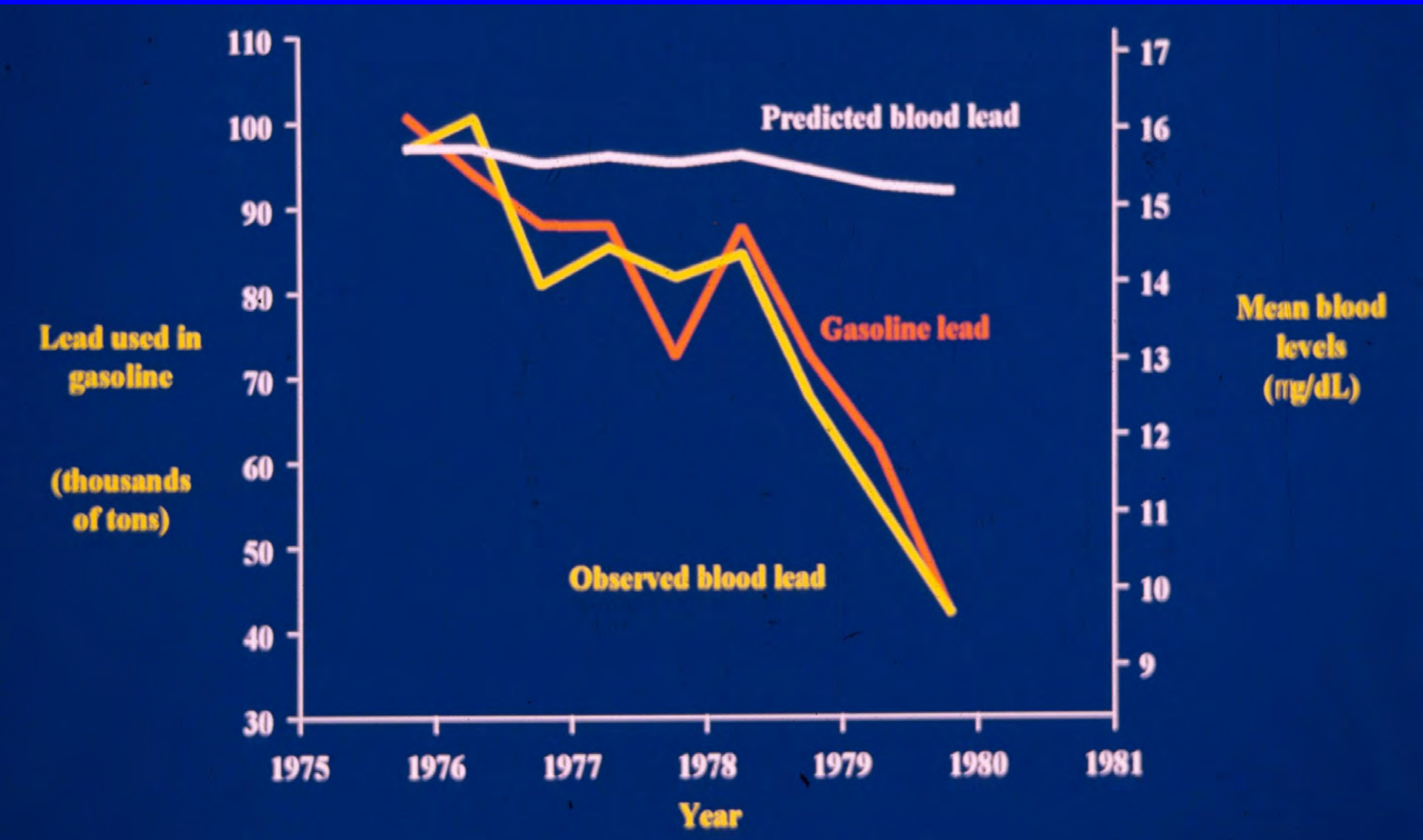
Lead use in gasoline in USA declined from 1976 through 1980



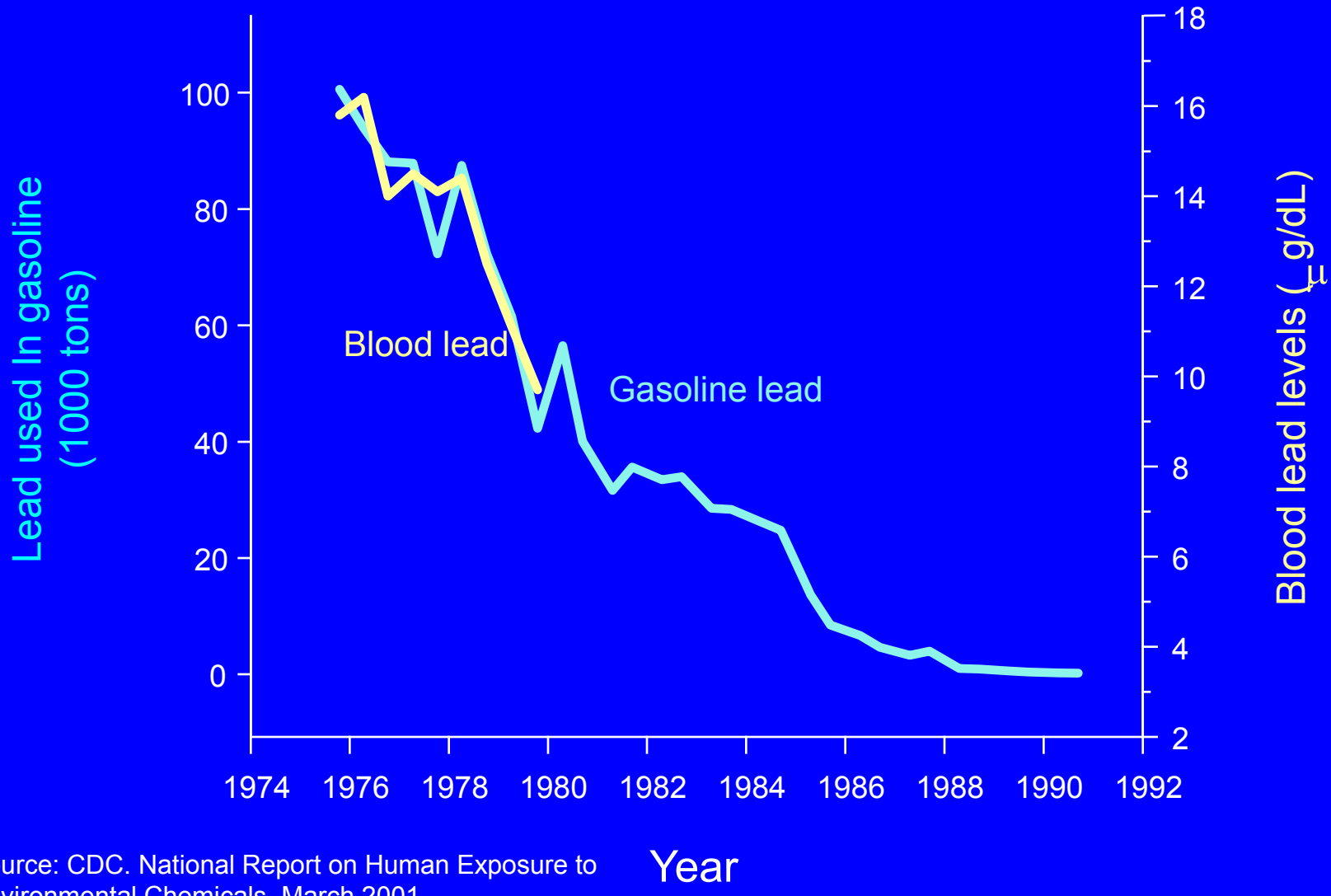
Source: Annest, Pirkle, Makuc, et al., Chronological trend in blood lead levels between 1976 and 1980. NEJM 1983; 308;1373-7.

The EPA Decision on Lead in Gasoline:

Decline in Blood Lead Levels Greatly Exceeded Expectation



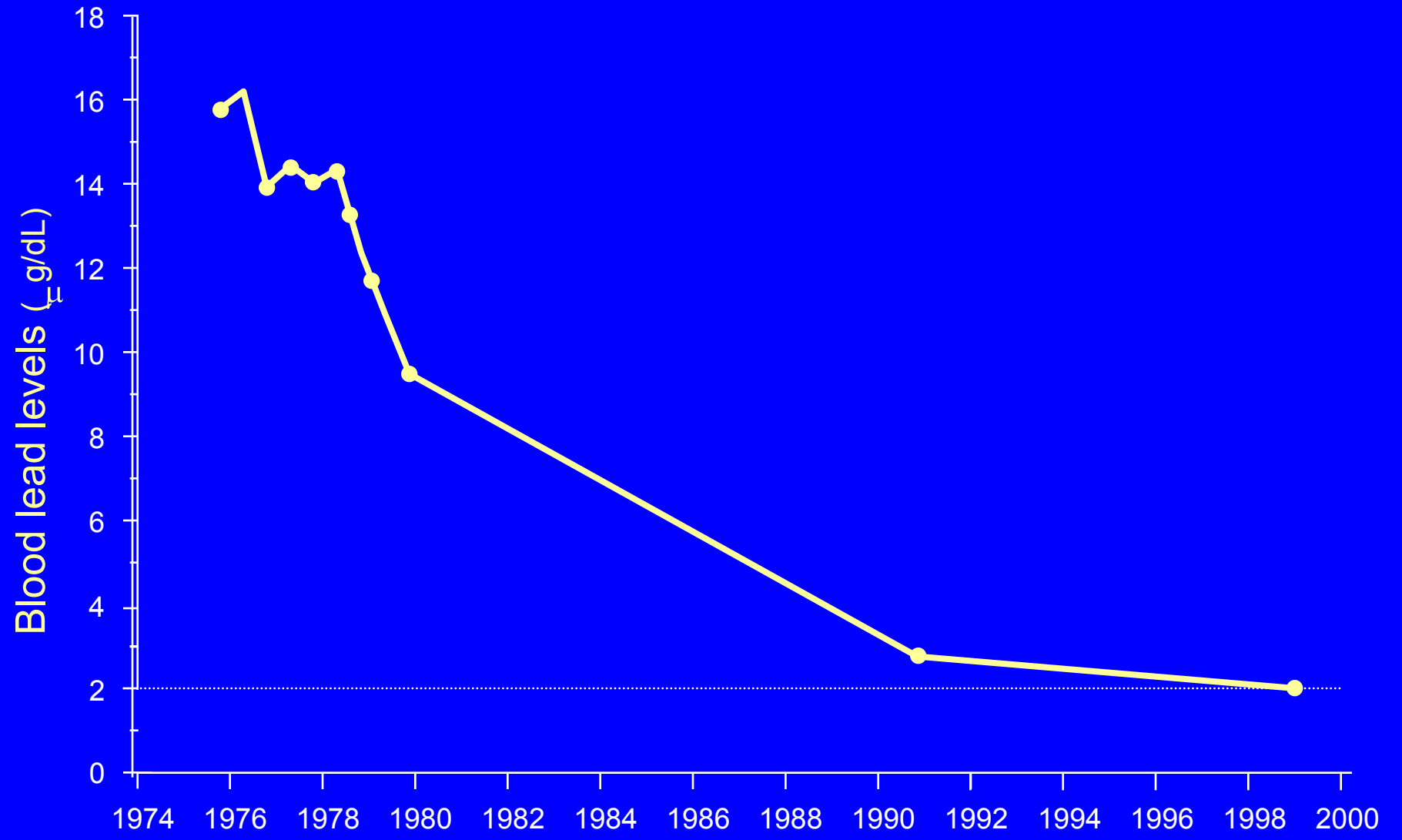
Beginning in 1980, EPA further restricted lead use in gasoline. Gasoline lead levels continued to decline through 1991



Source: CDC. National Report on Human Exposure to Environmental Chemicals, March 2001

Blood lead levels in the U.S. population 1976 -1999

NHANES II, III, 99+



Source: CDC. National Report on Human Exposure to Environmental Chemicals, March 2001

Conclusion - Children Represent the Future of our Societies

- Protecting the health of children and ensuring that children live in safe environments will allow them to reach their full potential.
- We are becoming more aware that children and the developing fetus are especially vulnerable to some chemicals in the environment.
- Governments and stakeholders have a responsibility to prevent toxic chemical exposures during preconception, and throughout gestation, infancy, childhood and adolescence.
- Prevention is possible.

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Thank You!

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Protecting Children against Environmental Threats to Health