Characterizing the Public Health Impact of Children's Exposures to Environmental Chemicals

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Two Issues

1. What is the best strategy for expressing, quantitatively, the adverse effects of environmental chemicals on children's health and development at the population level?

2. Are we adequately conceptualizing the scope of the adverse effects that contribute to the total health burden associated with children's exposures to environmental chemicals?

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Failure to apply an explicitly ***developmental perspective*** leads us to omit some critical adverse effects of early-life exposure

1. Issue of Risk Communication to Stakeholders: affected communities, risk assessors, regulators, legislators, journalists

- **Expressing the impact of chemicals on children at the population level**
  - **average impact (e.g., 0.5 IQ point loss per µg/dL increase in blood lead level)**
  - **cost-benefit analysis of preventing/reducing exposure**
    - **bisphenol A: $3 billion/year (Trasande, 2014)**
    - **control of lead in France: net benefit ~€2 billion/year (Pichery et al., 2011)**
  - **aggregate impact on quality-of-life (mortality, morbidity), e.g., WHO Global Burden of Disease approach (GBD)**

Estimating the Global Burden of Disease Due to Chemicals

- **Typical "disease-oriented" approach:**
  burden accumulates if someone dies or meets criteria for a disease with an ICD code

General Approach to Estimating GBD

- identify disease(s) attributable to an exposure (with an ICD code)
- estimate incidence of disease in a population and proportion due to some exposure (PAF)
- determine case fatality rate and age distribution: years-of-life-lost, or YLL
- determine duration of disease and its severity: years lived with a disability and degree of disability, or YLD

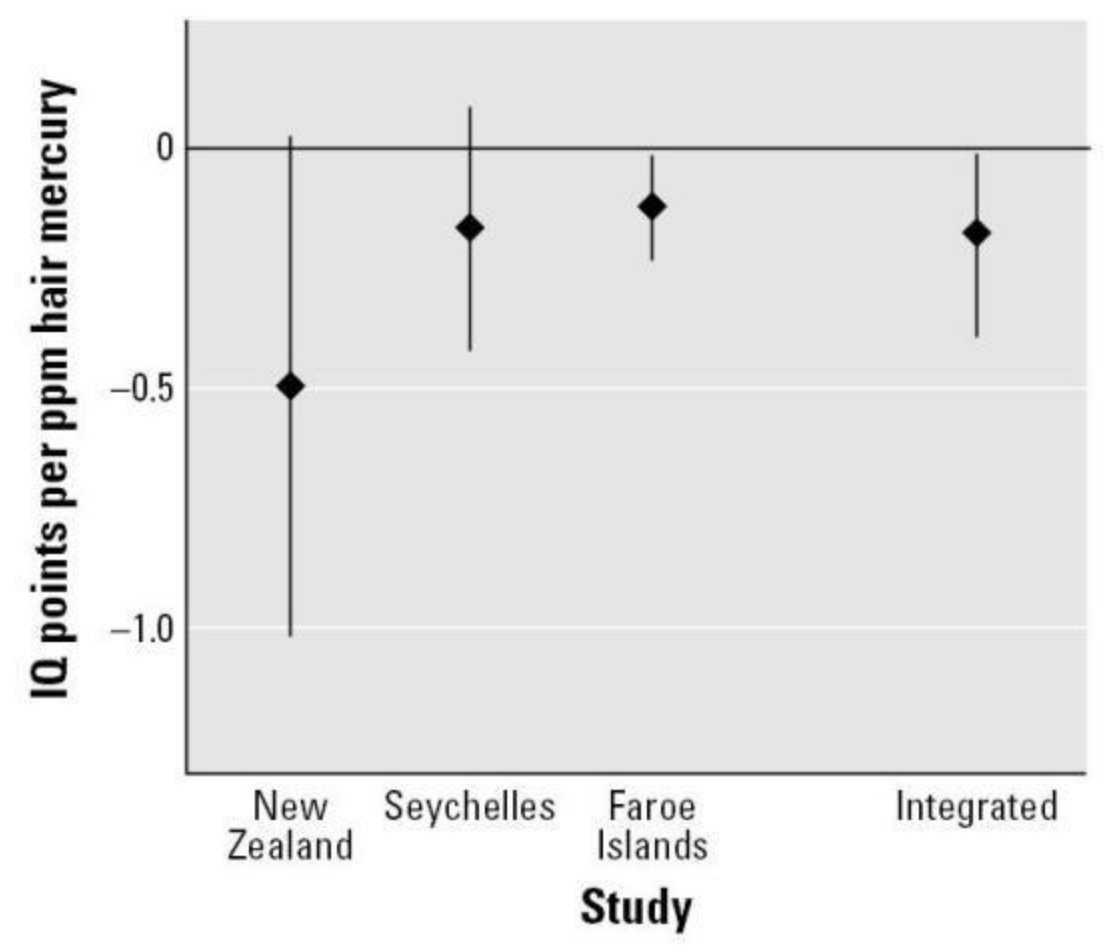
  •Calculate "disability-adjusted life years" (DALYs) by country/region: YLL + YLD

- Sum across countries/regions: global DALYs

Methylmercury

- Linked to adverse effects on many organ systems, but strongest evidence is for impaired cognitive development following prenatal exposure, e.g., reduced IQ

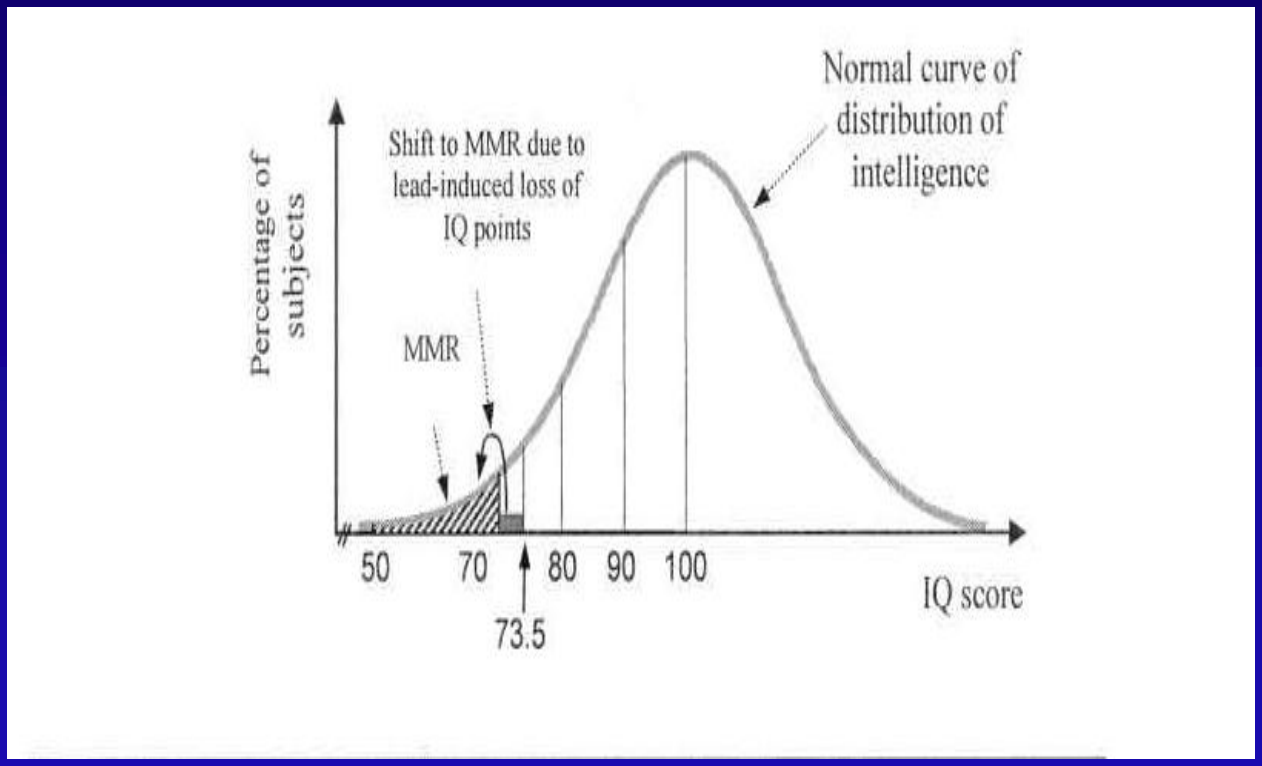
Dose-Effect Relationship for Prenatal MeHg Exposure and IQ reduction in children



Axelrad et al., *Environ Health Perspect* 2007; 115(4): 609–615

IQ Loss and Mild Intellectual Disability (MID)

- **IQ loss not a disease per se, so analysis *only* considers when IQ loss results in MID (i.e., IQ<70)**



Ideally, a country- or region-specific IQ distribution should be used because background prevalence of MID depends on prevalence of other risk factors (e.g., pertussis, meningitis, ascariasis, iodine deficiency, etc.)

Calculating Incidence of MID Attributable to Prenatal Exposure to MeHg

- estimate proportion of population, by country/ region, in each maternal hair mercury interval
- estimate the IQ loss for children within each interval and estimate number of children who will end up with IQ <70

Hair mercury interval (µg/g)	IQ loss
0-2	0.225
2-4	0.675
4-6	1.125
6-8	1.575
8-10	2.025
10-12	2.475
12-14	2.925
18-20	4.275

Highest Incidences of MeHg-Associated MID

Country (WHO Region)	Incidence MID (per 1000 births)
Antigua and Barbuda (AMR B)	19.47
French Polynesia (WPR B)	17.21
Portugal (EUR A)	15.39
Barbados (AMR B)	15.08
Saint Lucia (AMR B)	13.81
Grenada (AMR B)	13.33
Saint Kitts and Nevis (AMR B)	9.90
Brunei Darussalam (WP A)	9.87
Bahamas (AMR B)	9.56
Kiribati (WP B)	9.20
Malaysia (WP B)	8.31
United Arab Emirates (EMR B)	7.92

Disability-Adjusted Life Years

WHO Region	Estimated incidence of MID (per 1,000 births)	Total DALYs
Africa D	17.49	69,122
Africa E	17.46	77,155
Region of the Americas A	2.68	9,512
Region of the Americas B	10.62	51,996
Region of the Americas D	19.59	16,383
Eastern Mediterranean Region B	8.96	14,802
Eastern Mediterranean Region D	13.30	56,862
European Region A	4.82	21,010
European Region B	5.24	11,868
European Region C	2.71	6,359
South-East Asia Region B	5.08	16,746
South-East Asia Region D	4.50	66,480
Western Pacific Region A	4.53	7,188
Western Pacific Region B	13.82	226,396

Limitation of Disease-Oriented Approaches (e.g., GBD) to Estimating Health Burden of a Chemical

- "Health" is a continuum not a dichotomy; clinical disease is only "tip of the iceberg"—what about the contributions to population burden made by people who don't meet clinical criteria?

Is there an alternative approach?

Distinction Between Individual and Population Risk: Organizing Principles

- Most cases of disease arise from the *middle* of the distribution of health index
  - "a large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk" (Rose, 1985)
  - among effect estimates, relative risk, in isolation, can be misleading in assessing risk at population level

- Implies burden attributable to a risk factor not fully captured by focusing solely on extreme tails (i.e., people who meet clinical criteria for a "disease")

- To reduce total morbidity, sometimes might be more effective to focus on exposure at the *population level,* i.e., shift the entire distribution of exposures, not just reduce the number of individuals in the "high risk" tail because it is the *"total dose"* of a risk factor to a population that determines the burden associated with it

Risk of Down Syndrome (DS) by Maternal Age

Maternal age (years)	DS cases/1000 births	Total Births (as % of all ages)	% of Total DS cases
<30	0.7	78	**51**
30-34	1.3	16	20
35-39	3.7	5	16
40-44	13.1	0.95	11
>44	**34.6**	0.05	2
All ages	1.5	100	100

Mortality Rates for Ischemic Heart Disease by Baseline Systolic/Diastolic Blood Pressure

(Prospective Studies Collaboration, Lancet 2002;360:1903-1913)

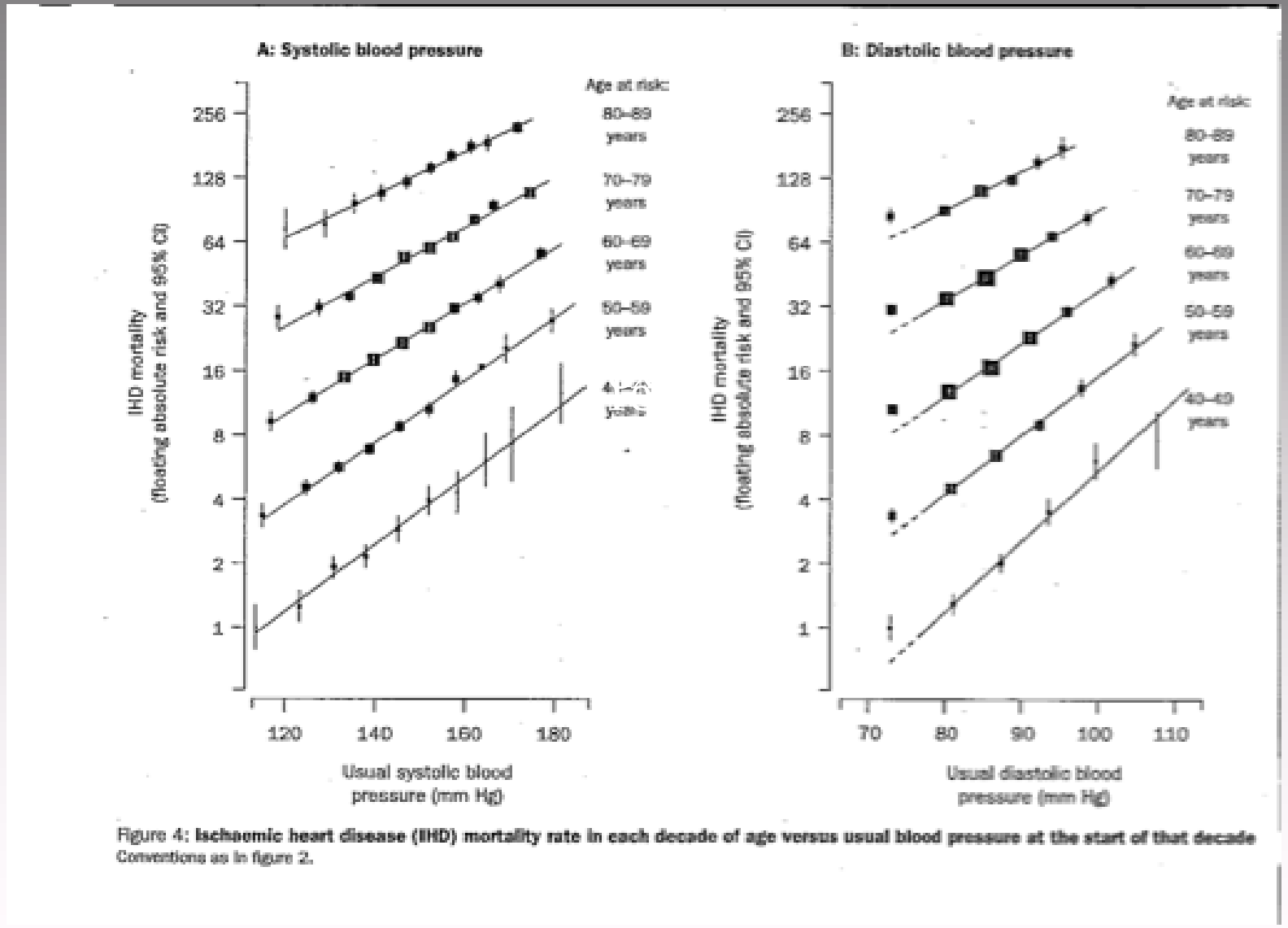
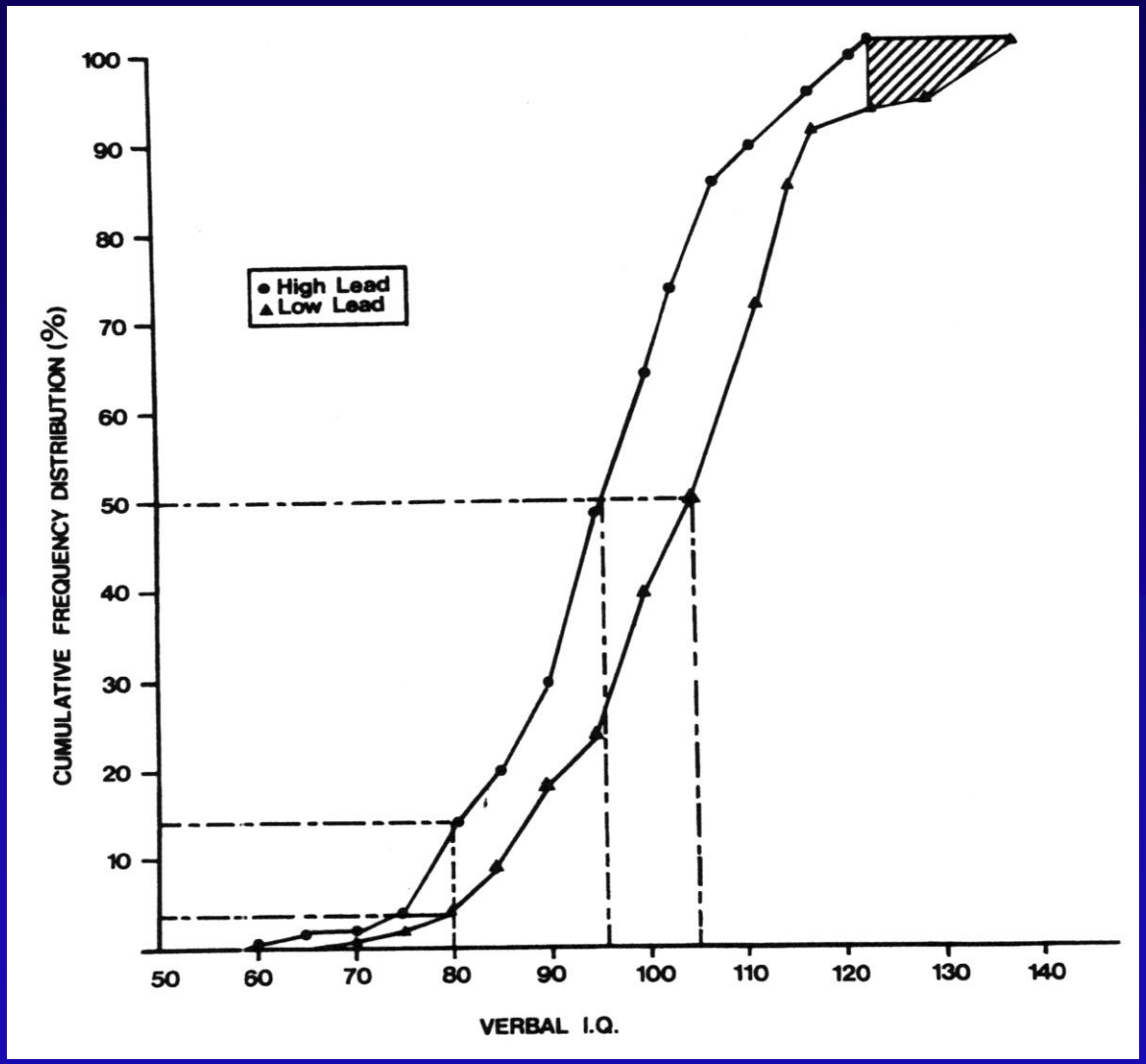


Figure 4: **Ischaemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade**
Conventions as in figure 2.

Cumulative Frequency Distributions of Children's Verbal IQ, Stratified by Tooth Lead Level



Needleman, Leviton, Bellinger *N Engl J Med* 1982;306;367

Challenge

- **Develop an approach that incorporates concept of "total dose" to population, i.e., doesn't focus solely on impact on the most highly exposed individuals**

- **Would consider *both* frequency of an exposure and its associated effect size (mean impact in case of a categorical diagnosis or dose-effect relationship in case of an exposure with a continuous distribution)**

- **Would allow population burden attributable to a chemical to be *compared* to the burdens attributable to other risk factors**
  - **provide an empirical basis for setting priorities for prevention/intervention, identifying where resources should be focused to produce maximum societal benefit**

Neurodevelopmental burden of risk factors in 0-5 year old children in US

- **Endpoint:** Full-Scale IQ

- **Data requirements (preferred):**
  - effect size: an estimate based on a meta-analysis or pooled analysis of multiple studies of an exposure
  - exposure: distribution of the exposure in the population or prevalence/incidence

- **Population:** 25.5 million children 0-5 years old in US (Federal Interagency Forum on Children and Family Statistics, 2011)

Traumatic Brain Injury (Babikian et al., *Neuropsychology* 2009;23: 289-296)

annual cases in USA (0-14 year olds): 475,000

assume: 1/3 events occur in 0-5 year olds, for a total of 791,665 cases in a 5-year cohort

IQ loss by severity (Glasgow Coma Scale):

mild: 80%	4.47 pts (2,830,994)
moderate: 10%	8.99 pts (711,711)
severe: 10%	16.59 pts (1,313,381)

total IQ loss: 4,856,086 points

Total IQ Losses Associated with Medical Events/Conditions, US Children 0-5 Years (Bellinger, *Environ Health Perspect* 2012;120:501-7)

Event/Condition	Total Number of IQ points Lost
brain tumors	37,288
Duchenne muscular dystrophy	68,850
congenital heart disease	105,805
chemotherapy (leukemia)	135,788
type 1 diabetes	185,640
pediatric bipolar disorder	2,203,200
traumatic brain injury	4,856,086
nonorganic failure to thrive	5,355,000
autism spectrum disorders	7,018,563
iron deficiency	9,409,510
ADHD	16,799,400
preterm birth	34,031,025

Prenatal Methylmercury Exposure

Hair Hg levels (µg/g), US women of childbearing age (NHANES 1999-2000) (McDowell et al., *Environ Health Perspect 2*004; 112:1165-1171)

10th	25th	50th	75th	90th	95th
0.04	0.09	0.19	0.42	1.11	1.73

assume IQ decline of -0.465 IQ points/µgHg/g for hair Hg levels >0.58 µg/g (Grandjean et al., 2012); assume value of 1.73 µg/g as midpoint for the 10% of women with values >1.11

total IQ loss: 1,385,785 points

Organophosphate Pesticides

- no meta-analysis but 2 propective studies on prenatal urinary dialkyl phosphate metabolites (DAP) levels and Full-Scale IQ in childhood
  - Bouchard et al., *Environ Health Perspect* 2011;119:1189-95 (N=329)
  - Engel et al., *Environ Health Perspect* 2011;119:1182-8 (N=101)

- weighted effect size over range of 50 nmol/L-500 nmol/L: -0.0134 pts/nmol/L DAP (6.03 points).

- NHANES (2000-2004):
  - median DAP: 65 nmol/L
  - 95th percentile: 483.5 nmol/L

- combining exposure distribution with dose-effect relationship:

total IQ loss: 18,978,019 points

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Childhood Lead Exposure

blood lead distribution, 1-5 year olds (NHANES, 2/2011):

50th	75th	90th	95th	98th
1.43	2.10	2.98	3.80	7.5

dose-effect assumptions (Lanphear et al., 2005):

- **slope over range 2.4-10.0 = -0.51 IQ pts/µg/dL (also assumed for range 0-2.4 µg/dL); -.19 pts/µg/dL over range of 10-20**
- **for children with blood lead level >10, assume mean of 15, and average IQ loss of 6.1 (5.1 + 1)**

IQ loss Attributable to Lead

•50%	0-1.43 µg/dL:	12,750,000 X 0.72 X 0.51 =	4,717,500
•25%	1.43-2.10:	6,375,000 X 1.77 X 0.51 =	5,737,500
•15%	2.1-2.98:	3,825,000 X 2.54 X 0.51 =	4,972,500
•5%	2.98-3.80:	1,275,000 X 3.39 X 0.51 =	2,205,750
•3%	3.80-7.50:	765,000 X 5.65 X 0.51 =	2,203,200
•2%	>7.5:	510,000 X 6.1 =	3,111,000

total IQ loss: 22,947,450 points

Calculation of IQ loss for Lead

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Potential Utility of Approach

- **risk prioritization**
  - **for exposures for which knowledge limited (e.g., PBDEs, BPA), (acknowledging that early studies of a risk factor often report larger effect sizes than later studies)**
- **estimate impact of interventions to reduce exposure or cost of not interveing**
  - **NHANES II (1976-1980) blood lead distribution: 119,990,842 FSIQ pts (to present, savings of ~100 million points)**
- **conduct cross-setting comparisons of relative importance of an exposure**

Cross-Setting Comparison: MeHg Burden

- **US** (NHANES): per capita impact: **0.05 pts/child**

- **Japan:** Yasutake et al. *J Health Sci* 2004;50:120-5 (N=8,665, 9 prefectures)

  hair Hg: 15-49 years

≤1	≤2	≤2.2	≤5	≤10 µg/g
26.3	70.8	75.1	98.3	99.9

  per capita impact: **0.60 pts/child**

- **Brazil**: Oliveira et al. *Ann Hum Biol* 2010;37:629-42

  villagers in Rio Madeira region (N=120)

  mean hair Hg:17.4 (SD 11.5) µg/g

  7% <5, assume 2.5 µg/g

  75% > 10, assume 15 µg/g

  per capita impact: **5.8 pts/child**

2. Two Elements of a Developmental Perspective

1. deficits caused by early-life exposure can initiate developmental cascades, resulting in late pathologies that differ from those initially observed
2. early-life chemical exposure becomes part of the context in which all subsequent development unfolds, sometimes serving as a risk modifier of later events/exposures

Concept of Developmental Cascades

Early-life exposure can:

- **initiate a cascade of events whereby the late outcomes differ from the near-term outcomes**

- **reduce CNS "reserve capacity," accelerating neurodegenerative processes associated with aging or aggravating adverse effects of later neurological insults**
  - **Possible mechanism: epigenetic changes expressed as altered gene expression in adulthood, with epigenetic marks representing "tombstones" of previous exposures no longer evident**

A Developmental Cascade: Lead and Crime

Cincinnati Prospective Lead Study: Adjusted Rate Ratios for each 5 µg/dL increment in blood lead

- **Total arrests:**
  - **prenatal Pb:** **1.40 (1.07-1.85)**
  - **average childhood Pb:** **1.07 (0.88-1.29)**
  - **6-year blood Pb:** **1.27 (1.03-1.57)**

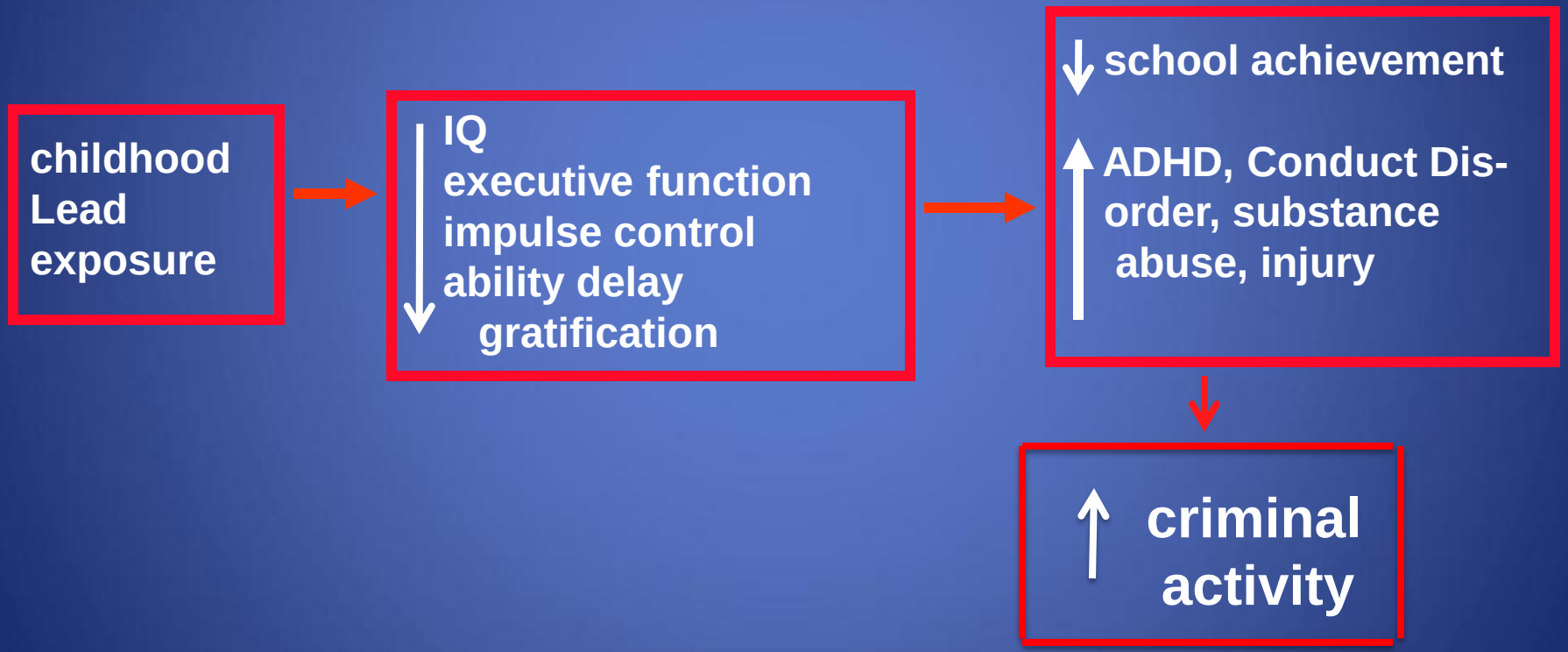
- **Violent offenses:**
  - **prenatal Pb:** **1.34 (0.88-2.03)**
  - **average childhood Pb:** **1.30 (1.03-1.64)**
  - **6-year blood Pb:** **1.48 (1.15-1.89)**

Wright et al. *PLoS Medicine* 2008;5(5):e101

Does Lead Damage a "Crime" Center in the Brain or Is Increased Propensity for Crime the Late Result of Series of Developmental Events?

- Lead-associated neuropsychological deficits
  - reduced IQ
  - reduced ability to sustain attention
  - executive dysfunction
    - poor impulse control
    - reduced cognitive flexibility
    - reduced ability to delay gratification
    - reduced ability to formulate and implement long-term strategies and modify them in response to feedback
- reduced academic achievement and school completion
- behavioral disorders such as ADHD, conduct disorder

Hypothesized Chain of Events Linking Childhood Lead Exposure to Adverse Psychosocial Outcomes in Adulthood



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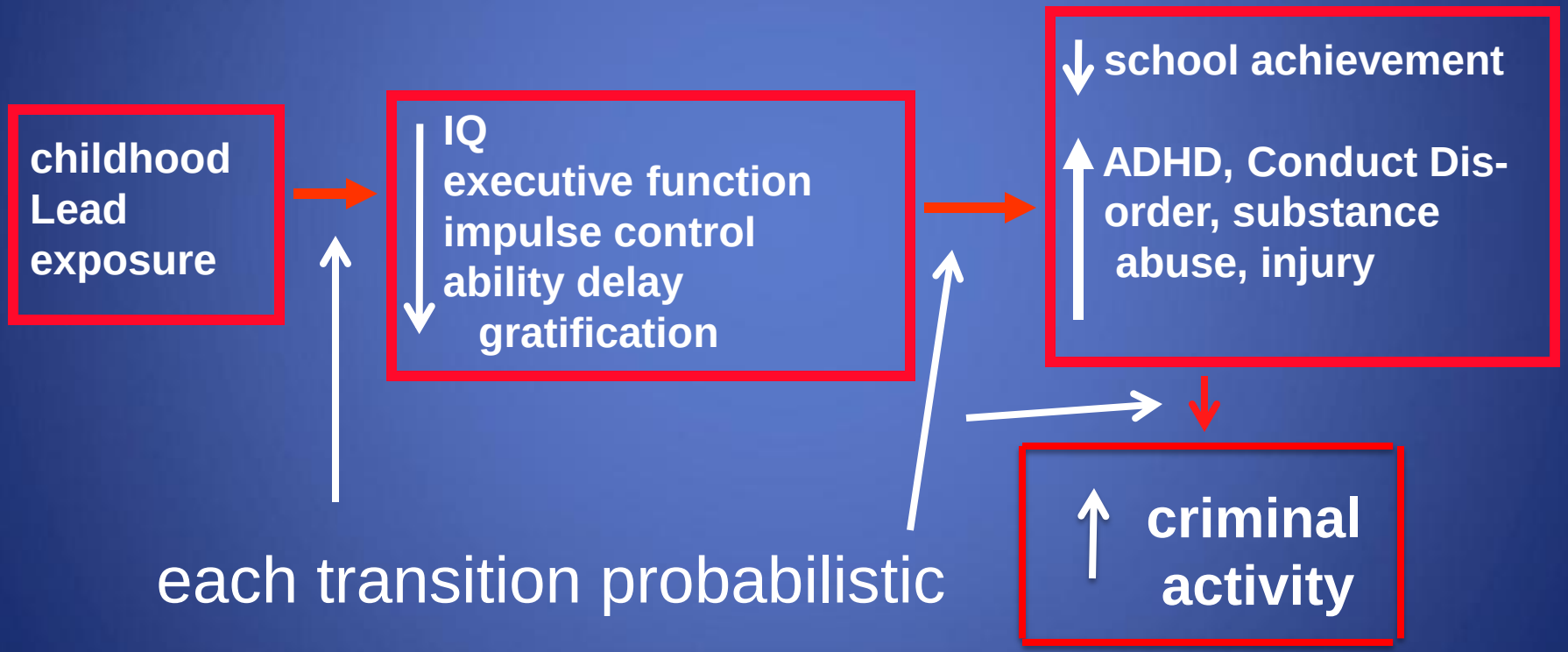


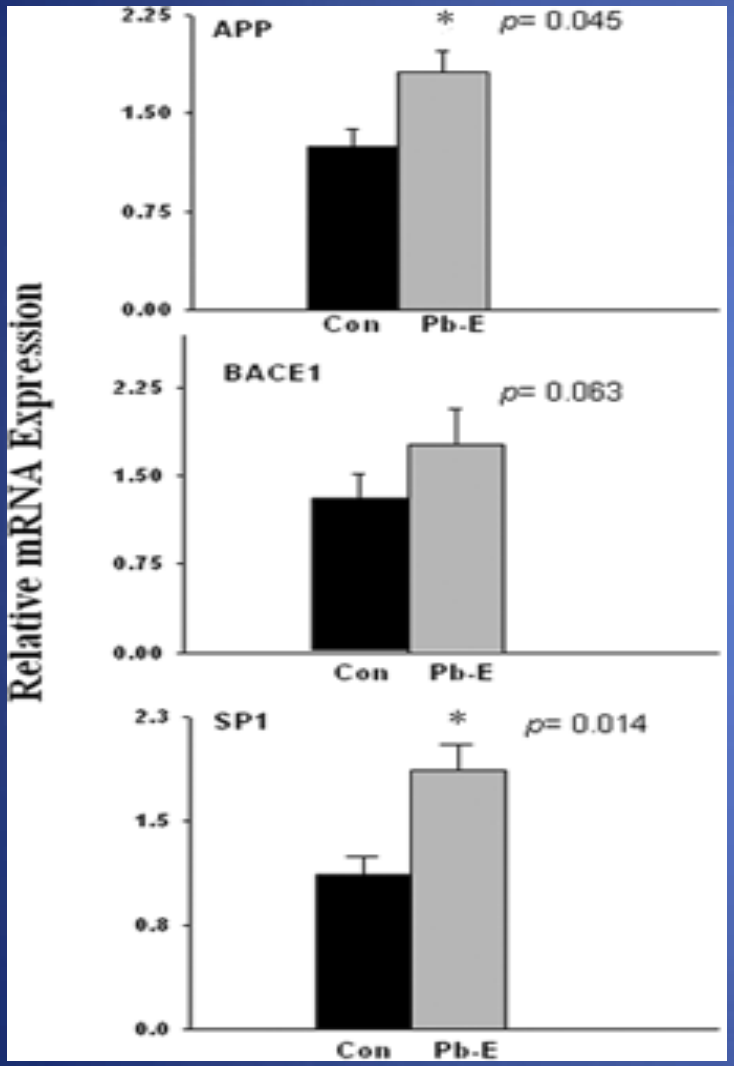
Early Life Exposure and Aging-Related Processes: Rodent Studies of Lead Exposure and Alzheimer's Disease

(Zawia et al. Free Radic Biol Med 2009; 46: 1241-9)

- AD characterized by extracellular deposition of beta-amyloid proteins (Aβ) and intracellular deposition of hyperphosphorylated tau protein

- at 20 months, rats exposed to lead only as newborns showed delayed overexpression, as adults, of gene encoding β-amyloid precursor protein (APP)
- increase in APP gene expression accompanied by elevation in β-amyloid protein in brain tissue.
- changes *not* seen in rats exposed to lead only as adults

Alzheimer's Disease-like Pathology in 23-year-old Monkeys After Developmental Exposure to Lead (Wu et al. *J Neurosci* 2008;28:3-9)



Increased mRNA expression of APP and BACE1 (ß-site APP cleaving enzyme), and Sp1 (transcriptional regulator) in frontal cortex

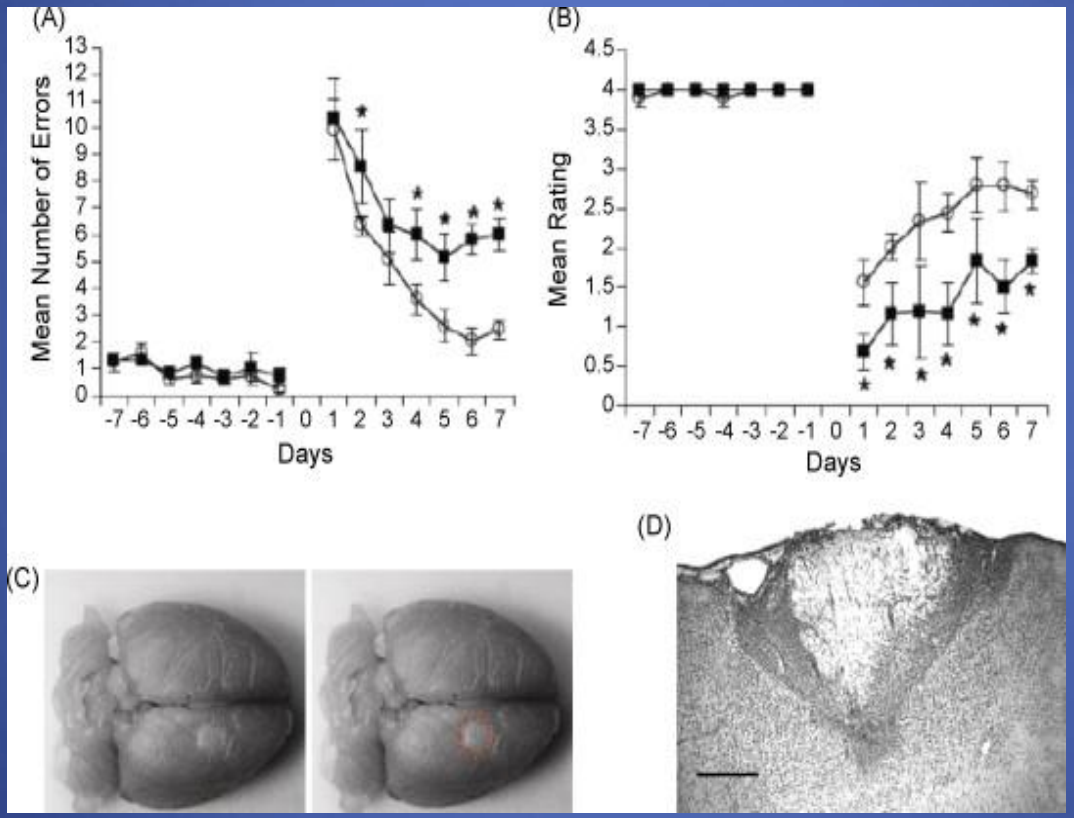
Increased intracellular staining of total Aß and dense core plaques (especially rich in Aß1-42, particularly amyloidogenic species)

20% reduction in activity of DNA methyltransferase 1 (suggesting latent gene expression effects mediated by pathways regulated by DNA methylation)

Higher levels of 8-oxo-dG (biomarker of oxidative DNA damage)

Early-Life Exposure as a Risk Modifier of Later Insults

Recovery from a Photothrombotic Stroke in Hind Limb Parietal Sensorimotor Cortex



Squares: Lead-exposed rats; A: beam walking; B: proprioceptive limb placing

Schneider JS, Decamp E. *Neurotoxicology* 2007;28:1153-1157

Lead exposure and development of columnar processing units in neocortex

- Early-life lead exposure associated with:
  - dose-related reduction in area of barrel field cortex; mean barrel field area in the highest exposure group decreased 12% versus controls; total cortical area in the same sections not significantly different (Wilson et al., *PNAS* 2000;97:5540-5545)
  - impaired reorganization of barrel field cortex following whisker ablation, leaving clusters of denervated neurons active but useless

Conclusions

- **Estimation of population impact of early-life exposure *should not* be based on:**
  - **single endpoints, such as IQ, viewed in isolation and as independent, unchanging**
  - **clinically-defined outcomes; burden associated with "subclinical" impacts can account for more of the overall burden**
- **exposure-related adversities evident in childhood reflect only earliest stage of their unfolding; full accounting requires a lifespan developmental perspective, and include outcomes along the probabilistic cascade of events that begin with early-life exposure**
  - **Also must include morbidities that early-life exposure to a chemical contribute to as a risk modifier, forming part of the context that determines the impacts of later pathologic (and perhaps physiologic) CNS events**