

Low-level Exposure to Environmental Toxins

Much Ado About Nothing?

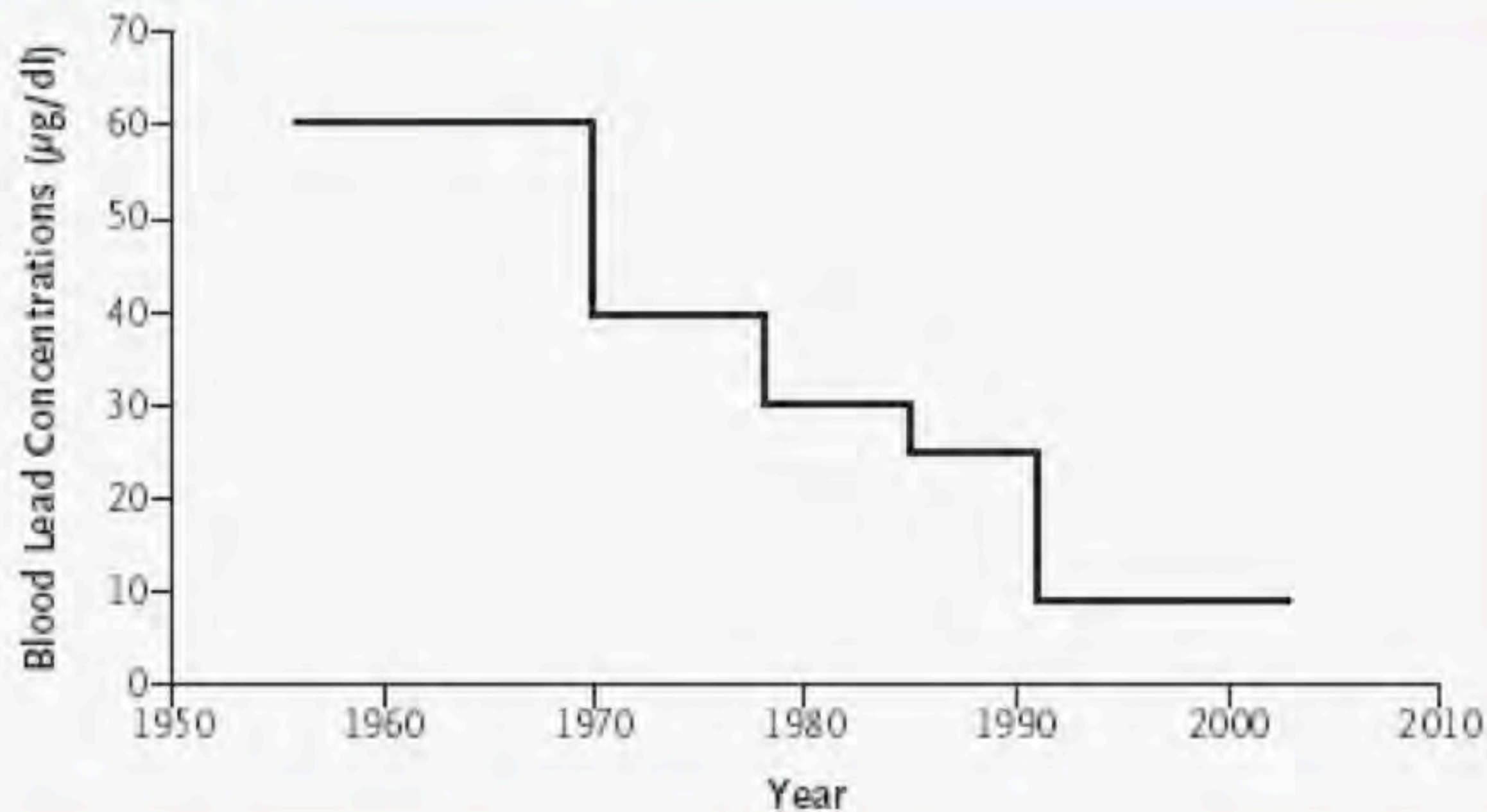
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Faculty of Health Sciences, Simon Fraser University

IQ Deficits Linked with an Increase in Blood Lead from 10 $\mu\text{g/dl}$ to 20 $\mu\text{g/dl}$

<u>Study</u>	<u>Estimated Loss</u>
Hawk (1986)	2.6
Hatzakis (1987)	2.7
Fulton (1987)	2.6
Yule (1981)	5.6
Bellinger (1992)	5.8
Dietrich (1992)	1.3
Baghurst (1992)	3.3
Silva (1988)	1.5

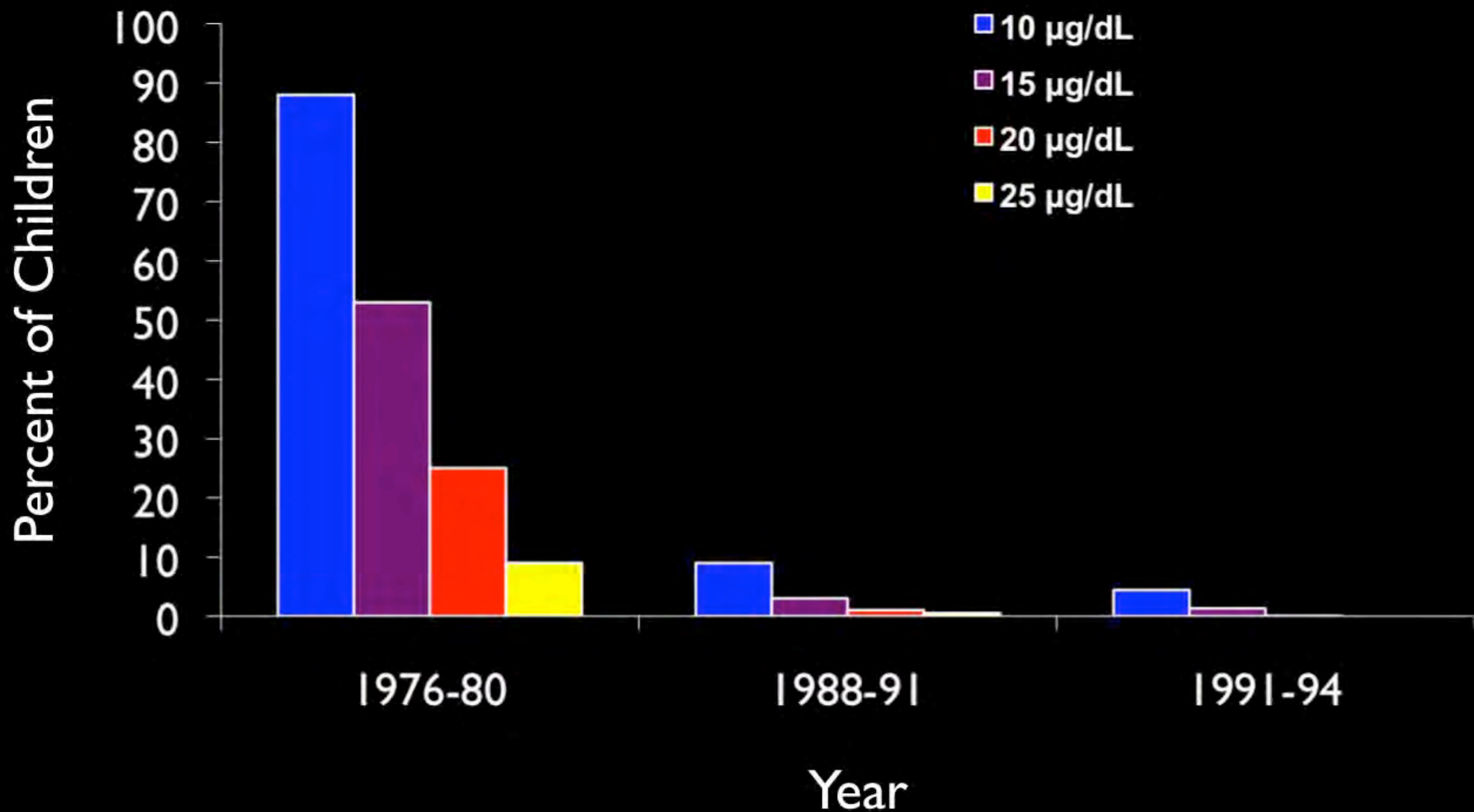


Blood Lead Concentrations Considered to Be Elevated by the Centers for Disease Control and Prevention.

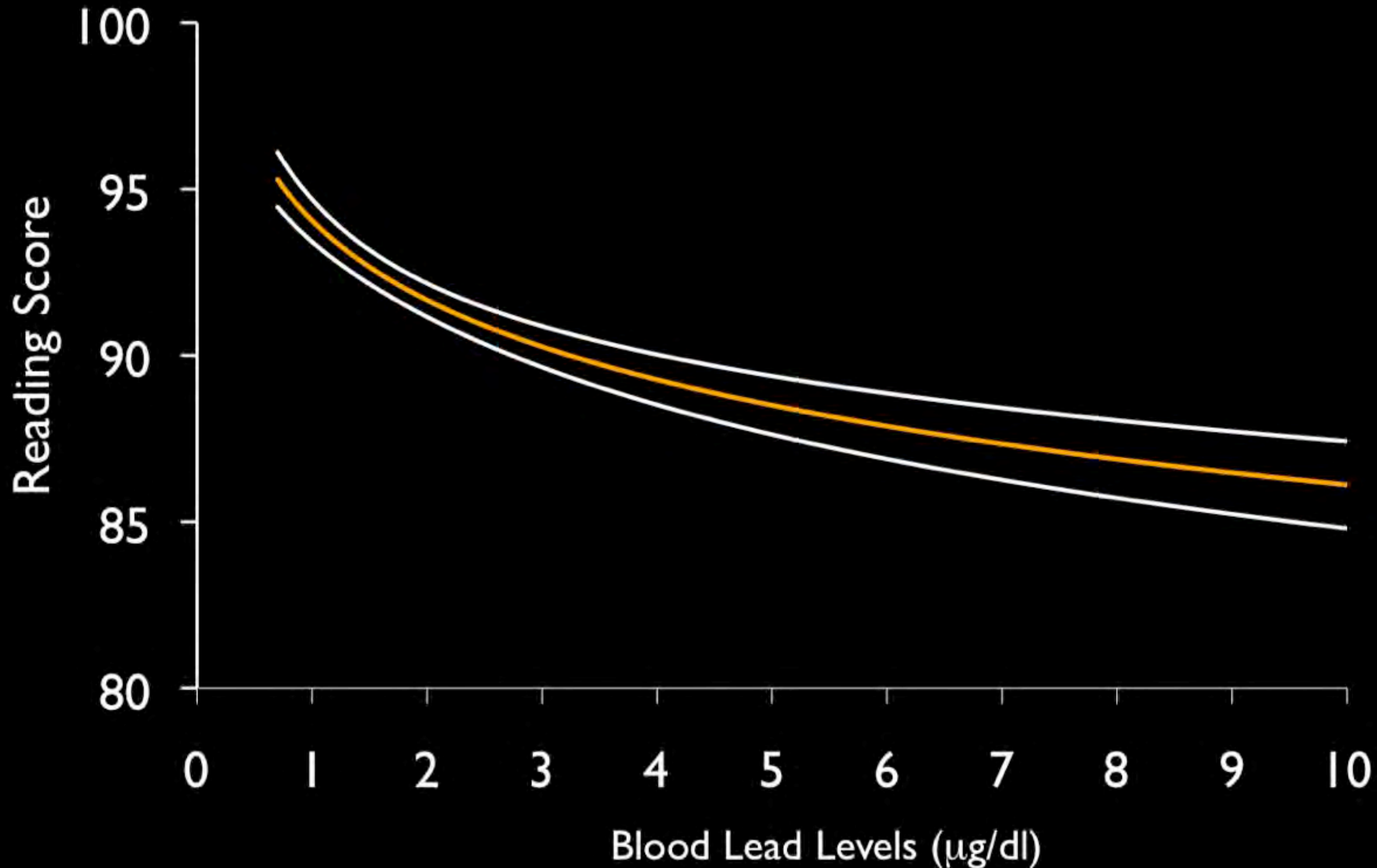
To convert the values for blood lead concentrations to micromoles per liter, multiply by 0.0483. Data are from the Centers for Disease Control and Prevention, 1991.¹

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

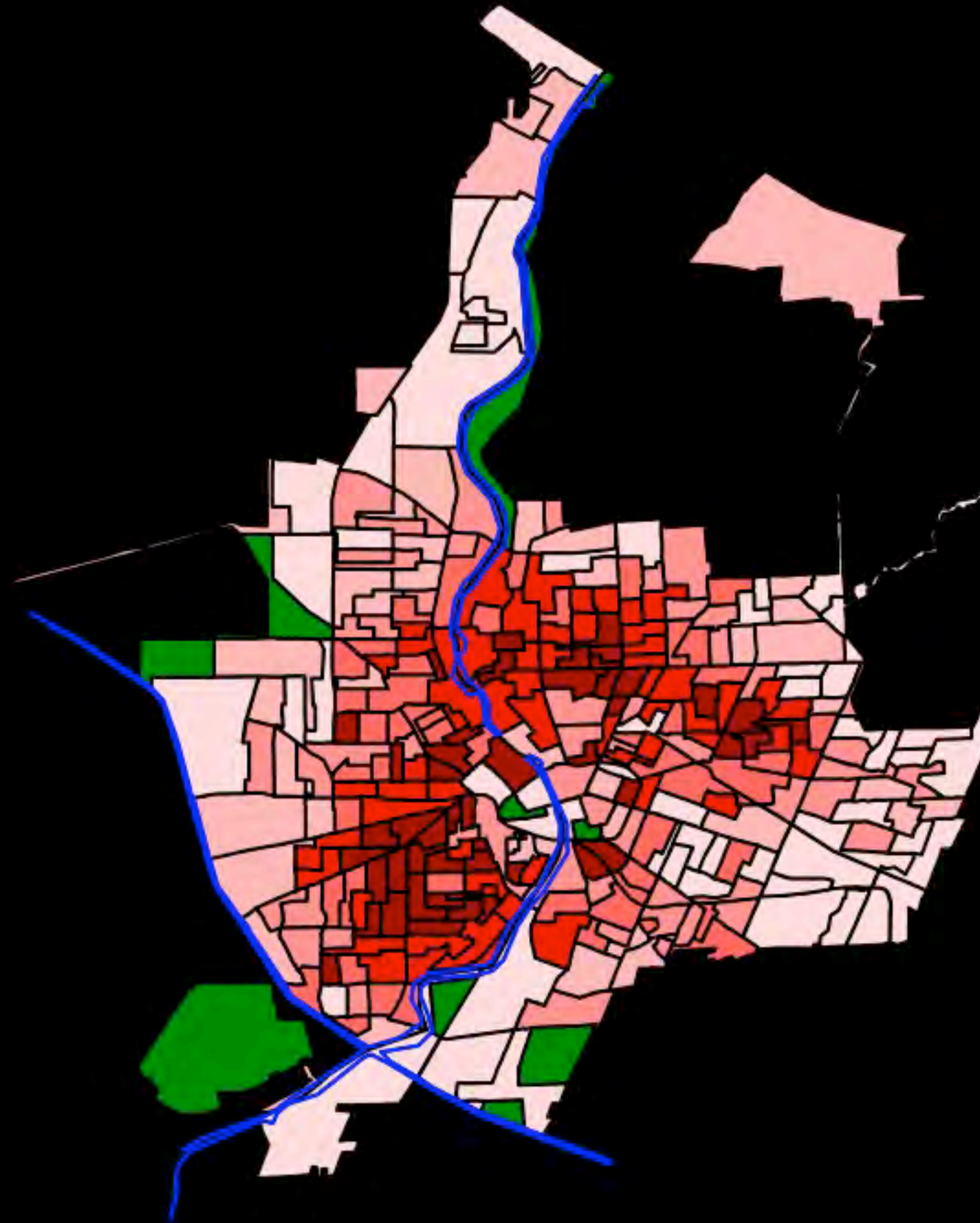
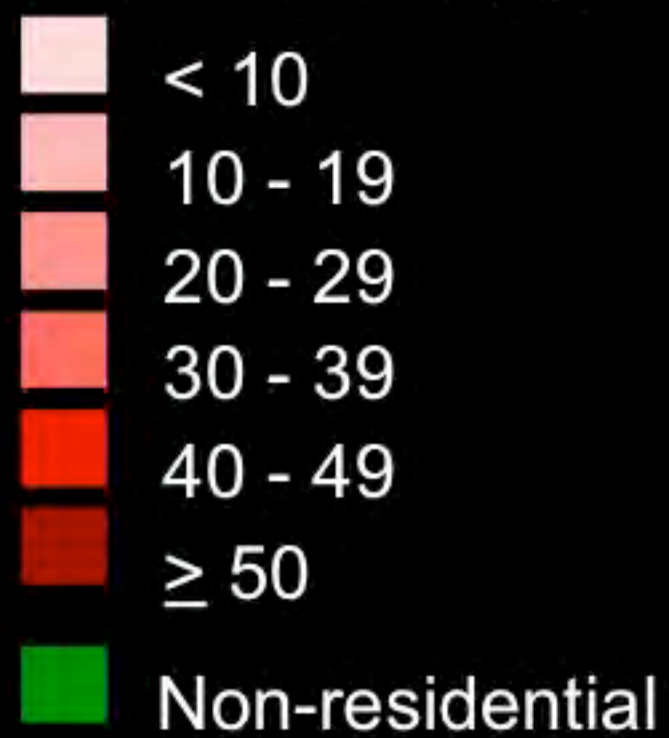


Reading Scores by Blood Lead Levels in US Children, NHANES III, 1998-1994

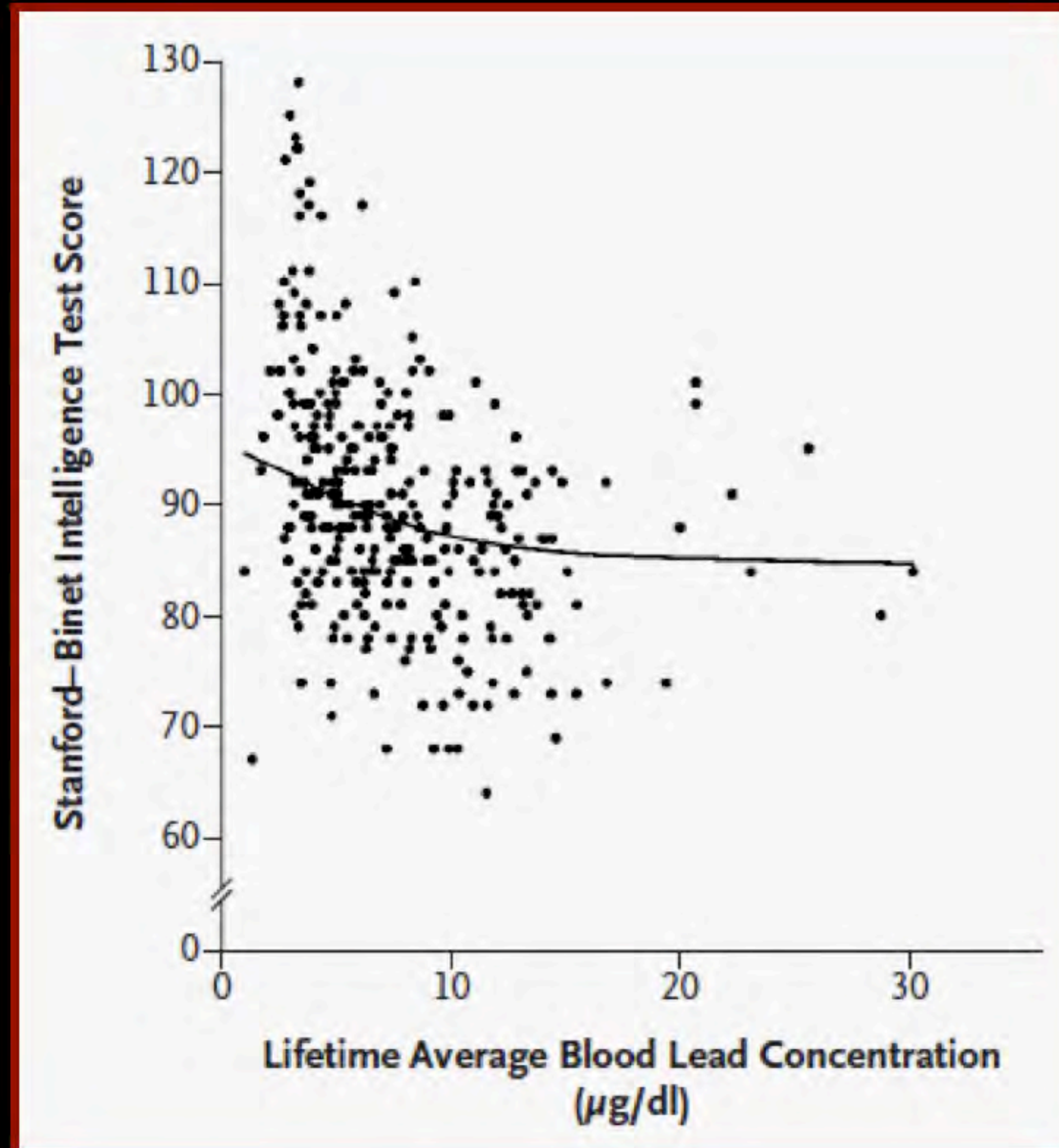


Blood Lead Levels $\geq 10 \mu\text{g/dL}$ among Children in Rochester, 1995

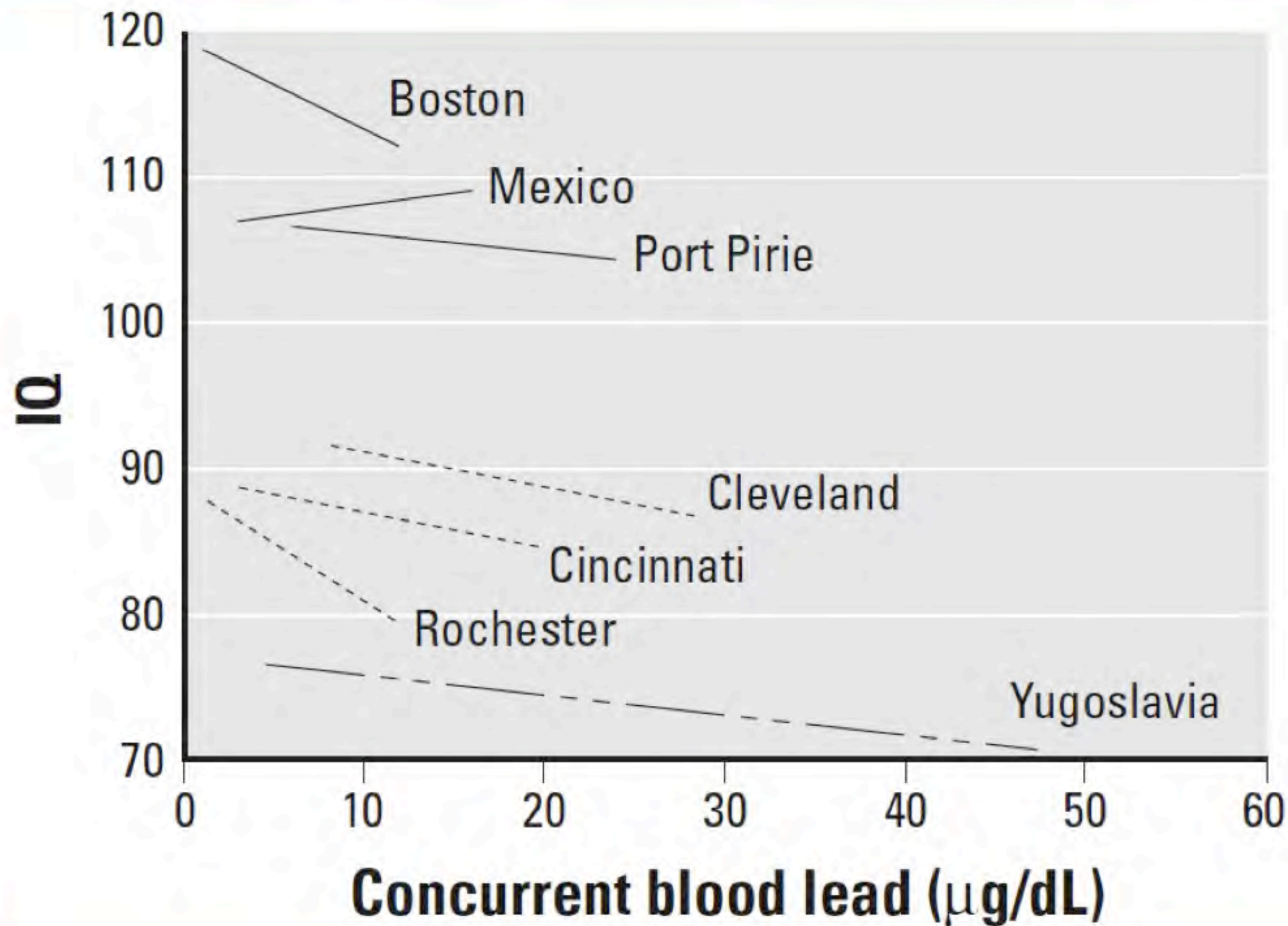
Percent $\geq 10 \mu\text{g/dL}$



Lead Toxicity at Blood Lead Levels $<10 \mu\text{g/dl}$



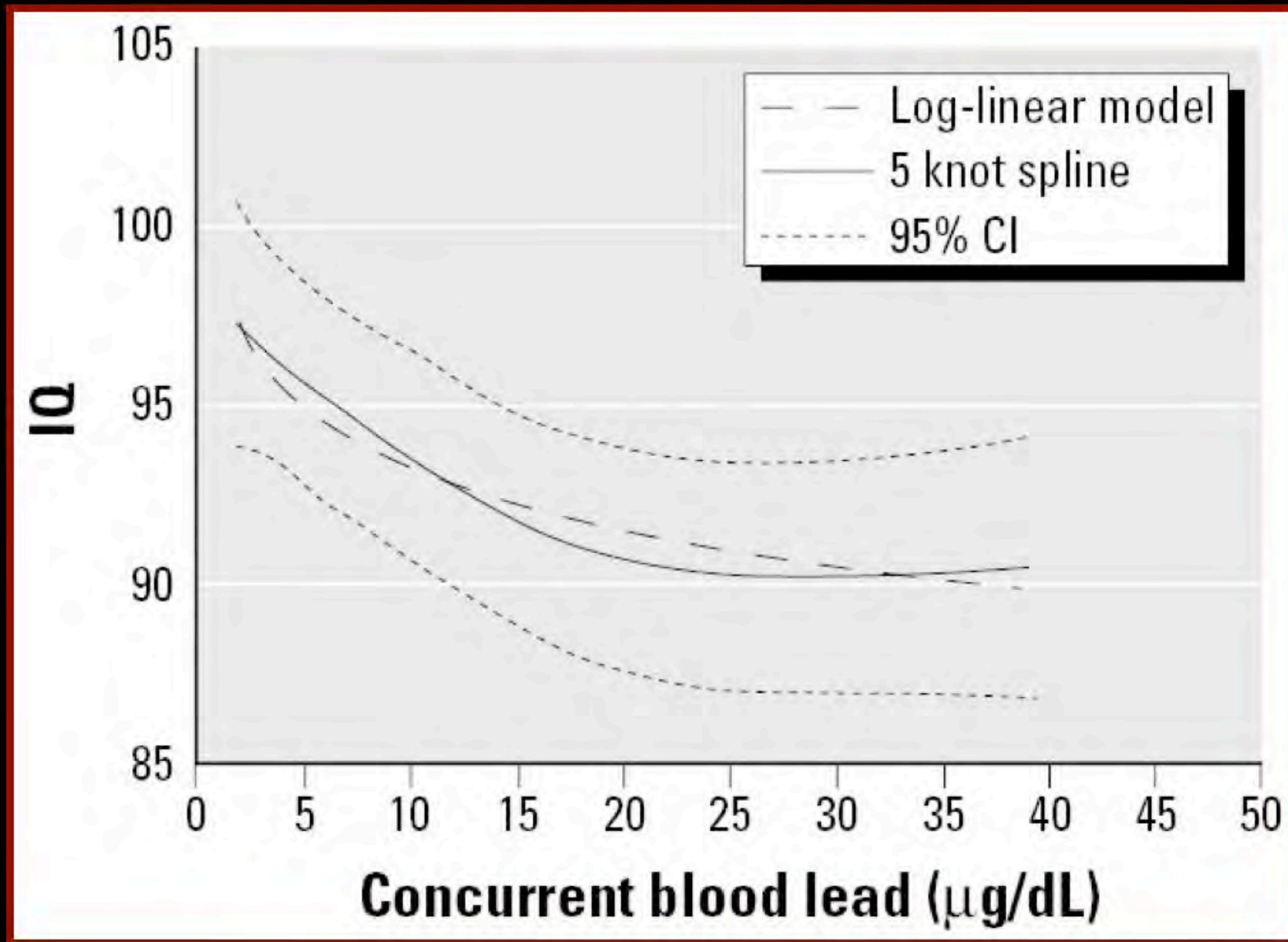
Relationship of Lead-IQ Scores among Children for Seven Prospective, Lead-Exposed Cohorts



Tests of Linearity

- Individual cohort analyses generally used linear models to describe the IQ vs blood lead relationship
- To assess whether a linear model provided a good fit to the pooled data, quadratic and cubic terms were added to the model
- Results indicated a significant departure from linearity:
 $Pb^2 \quad \beta=0.038, p<.001$
 $Pb^3 \quad \beta=-0.0003, p=0.003$
- Log of blood lead provided a good fit to the data

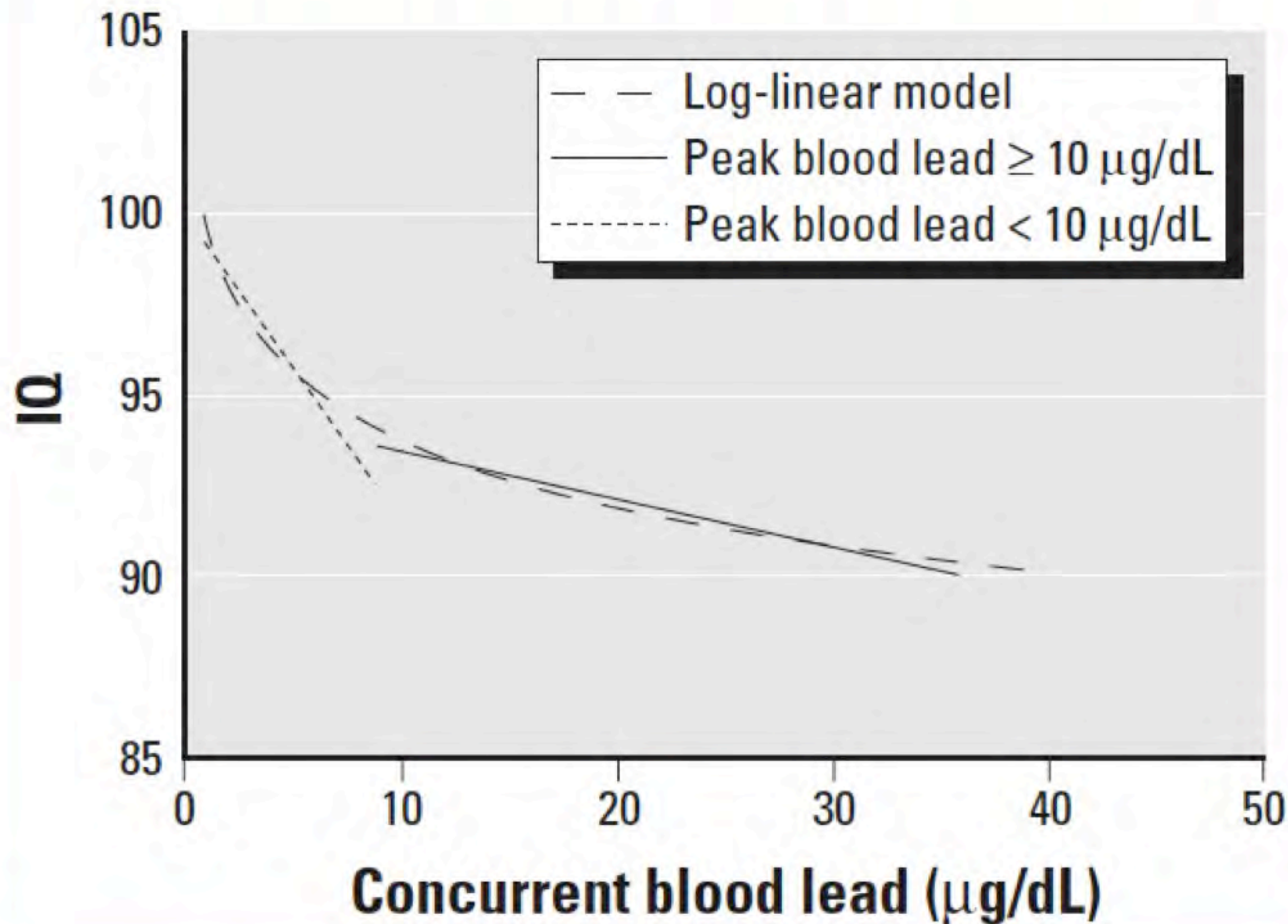
The Ongoing Search for a Threshold of Low-Level Lead Toxicity



Estimated Lead-associated IQ Deficits by Concurrent Blood Lead Concentration

Range of Blood Lead	Estimated IQ Deficit (95% CI)	
< 1 to 30 $\mu\text{g/dL}$	9.2	(5.7, 13.1)
< 1 to 10 $\mu\text{g/dL}$	6.2	(3.8, 8.6)
10 to 20 $\mu\text{g/dL}$	1.9	(1.2, 2.6)
20 to 30 $\mu\text{g/dL}$	1.1	(0.7, 1.5)

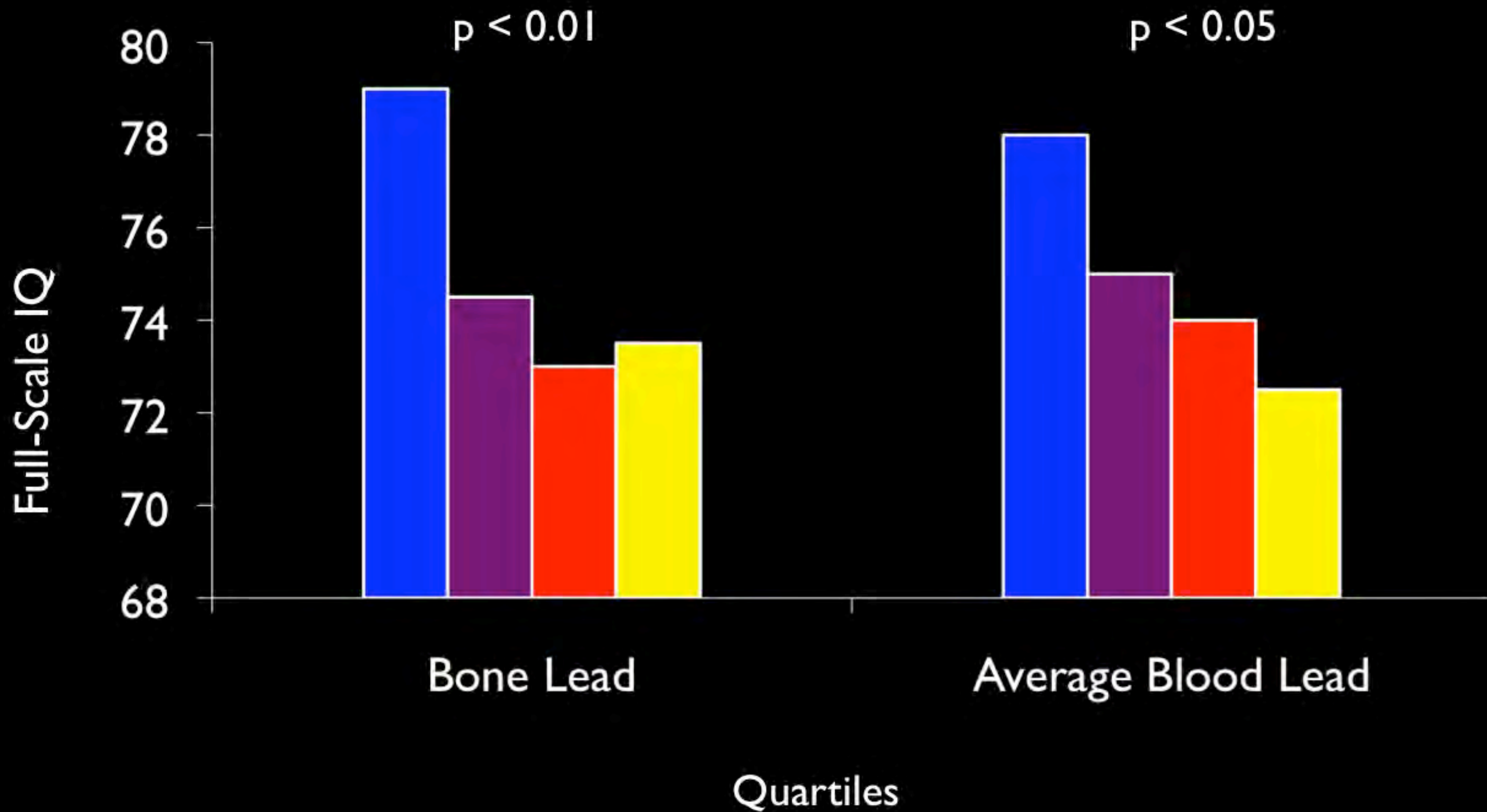
Log-linear and Linear Relationships of Concurrent Blood Lead Levels and IQ



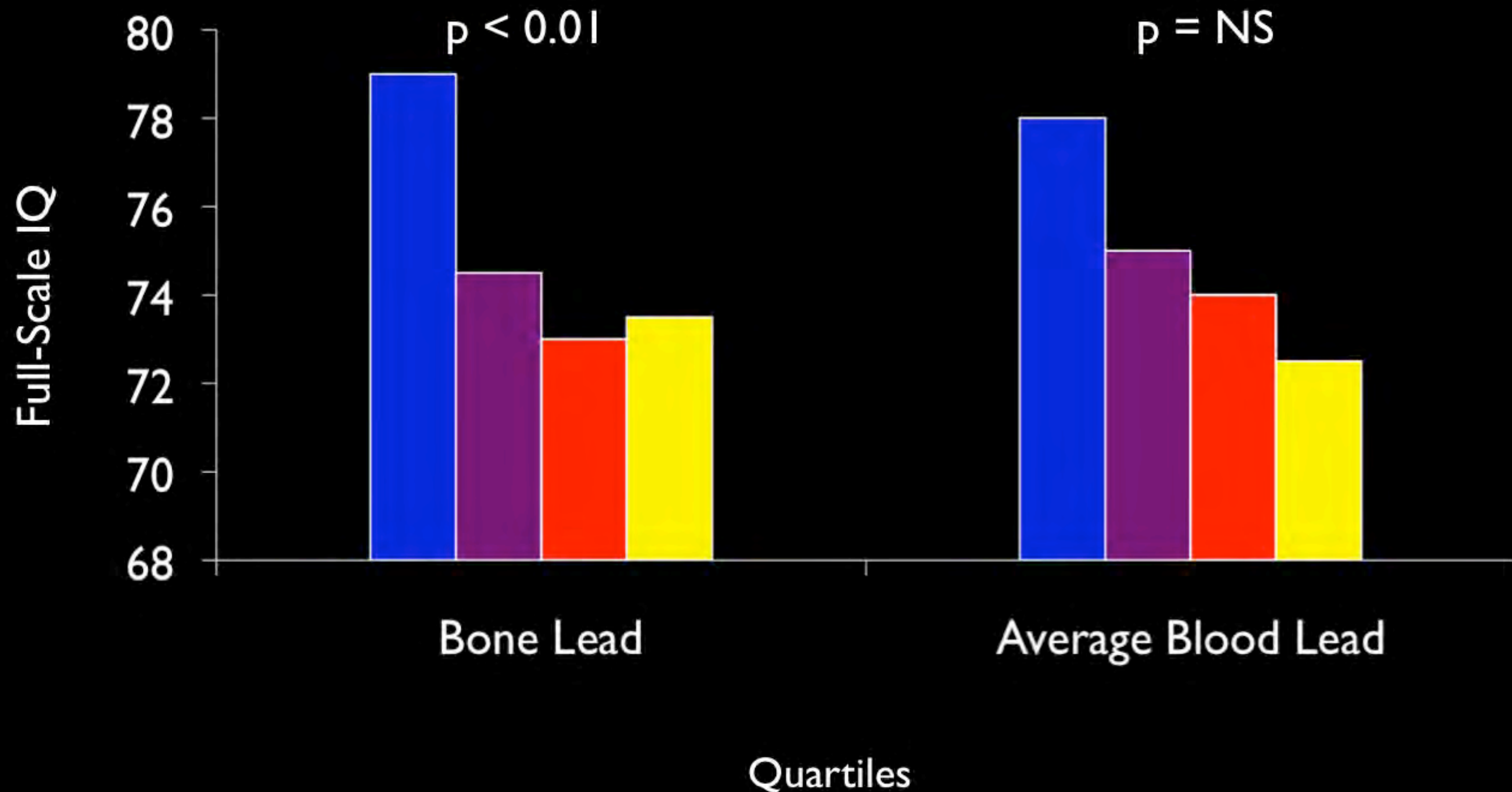
Concurrent Blood Lead Grouped by Peak Blood Lead Levels Above and Below 10 and 7.5 $\mu\text{g/dL}$

Peak Blood Lead	n	Linear β	p value
< 10 $\mu\text{g/dL}$	244	-0.80	.103
$\geq$ 10 $\mu\text{g/dL}$	1089	-0.13	
< 7.5 $\mu\text{g/dL}$	103	-2.94	.015
$\geq$ 7.5 $\mu\text{g/dL}$	1230	-0.16	

Mean Adjusted Full-Scale IQ Scores by Quartiles for Tibial Bone Lead and Mean Lifetime Blood Lead Levels



Mean Adjusted Full-Scale IQ Scores by Quartiles for Tibial Bone Lead and Average Lifetime Blood Lead Levels – Combined Analysis



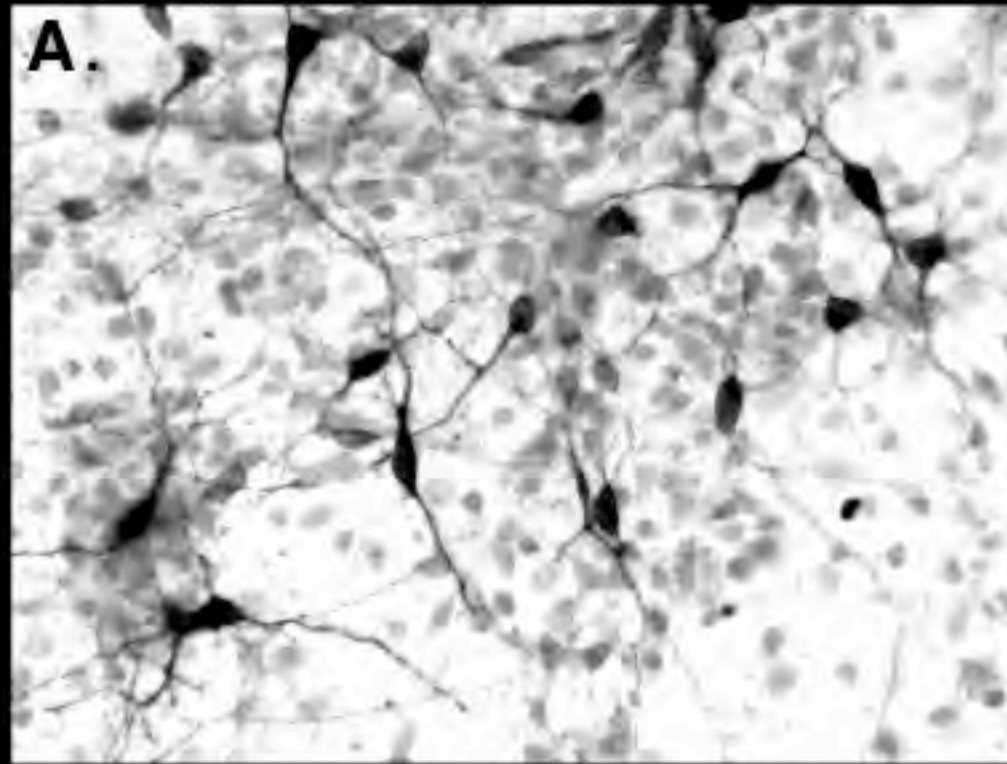


“Canfield et al. (2003) suggested a 7.4-point IQ effect (roughly one half standard deviation) as lifetime average BLL went from 1 to 10 $\mu\text{g}/\text{dL}$ —more than twice as strong a relationship as shown by most estimates at higher exposures. It may reasonably be asked whether such a strong relationship 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.”

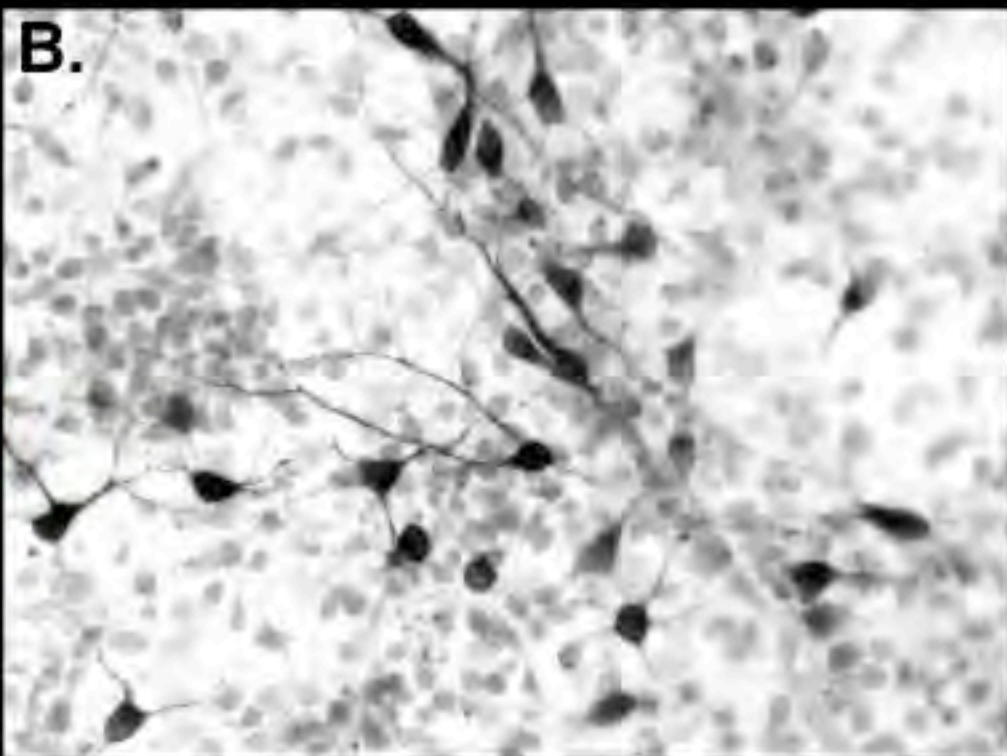
Research Supporting Adverse Cognitive Effects at Blood Lead Levels < 10 µg/dL

- 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.

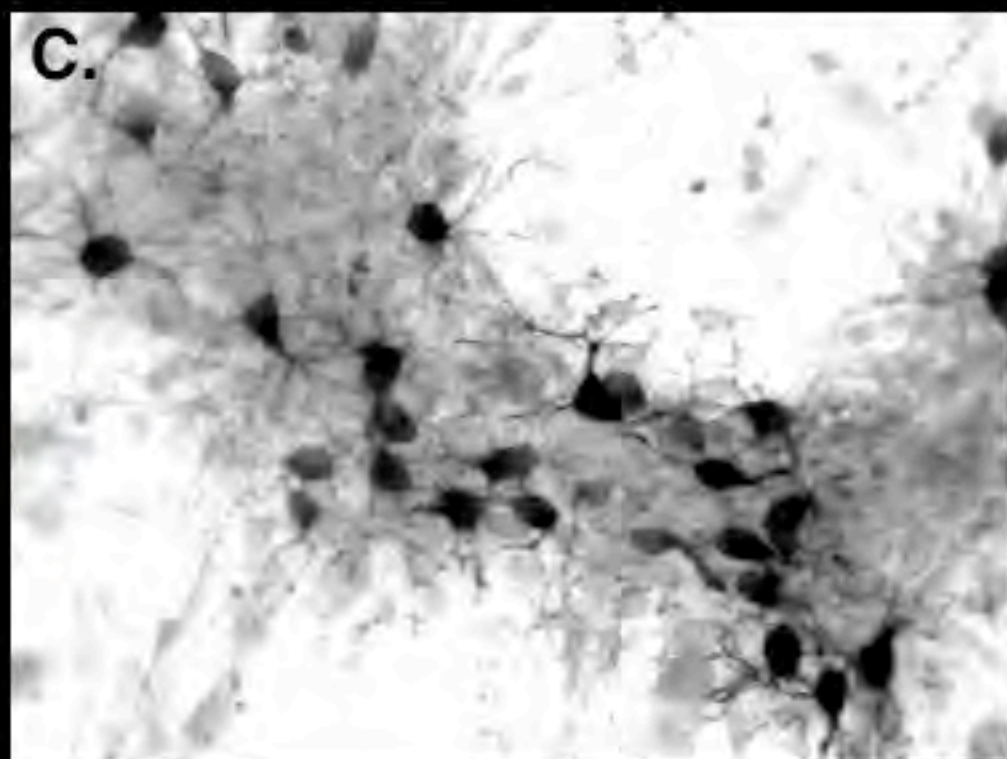
No Lead



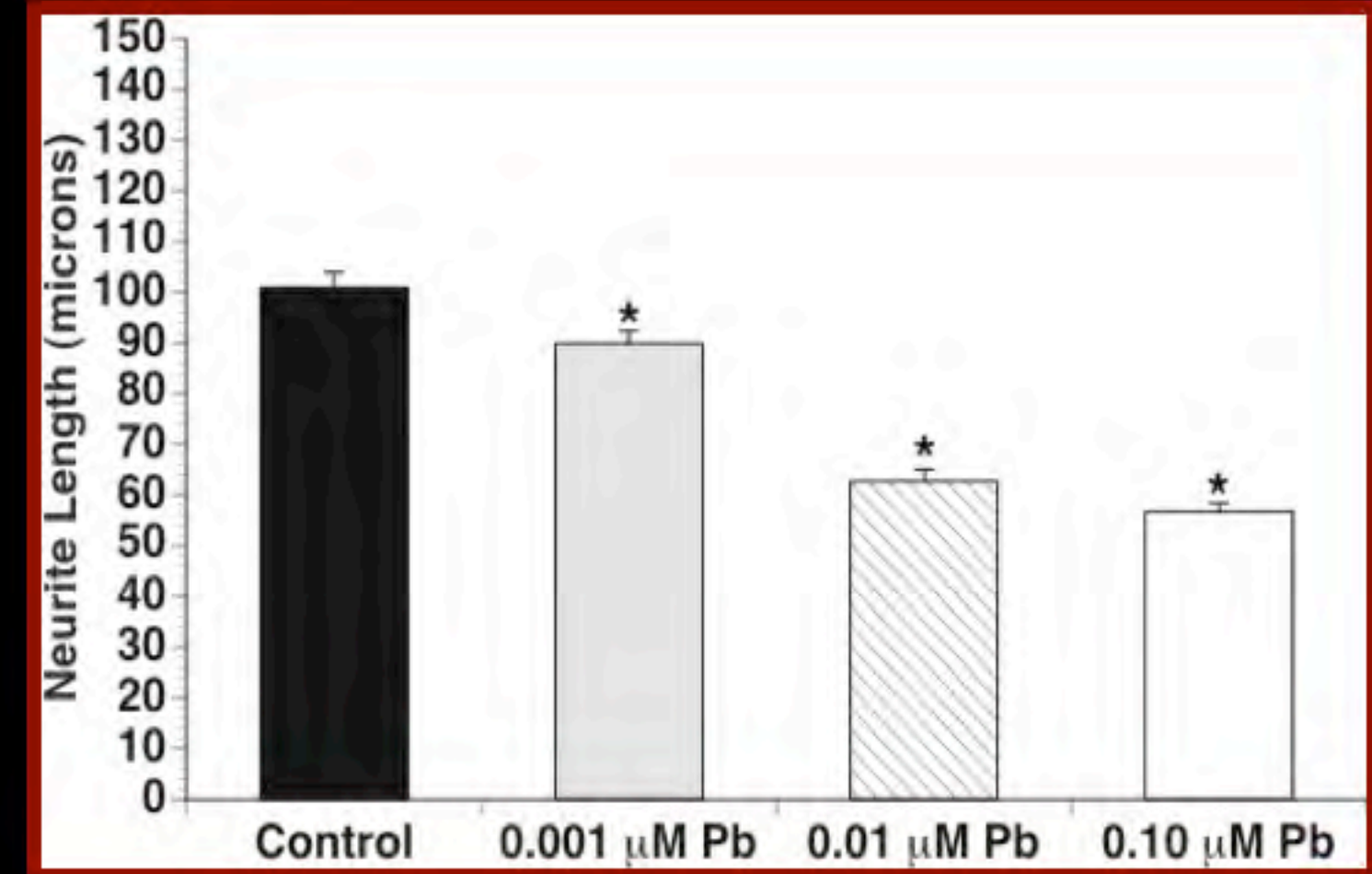
0.001 μM
0.024 $\mu\text{g/dl}$



0.01 μM
0.24 $\mu\text{g/dl}$



Lead Reduces Neurite Length in Dopaminergic Neurons after 48 Hr Exposure to Lead Acetate



The lowest concentration of lead acetate used (0.001 μM) caused a significant decrease in neurite length that was exacerbated by incubation in higher concentrations of lead (0.01 and 0.10 μM).

Mean IQ Change per 1 $\mu\text{g}/\text{dl}$ at 5 years for Children with Peak Blood Lead < 10 $\mu\text{g}/\text{dl}$ (n=101)

	Original Results	p value
Lifetime Average	-1.37 + 0.60	.026
Concurrent	-1.58 + 0.46	.001

Adjusted for maternal IQ, maternal education, prenatal tobacco exposure, household income, race, HOME Inventory, child's sex, birth weight, preterm birth and iron status.

Mean IQ Change per 1 $\mu\text{g}/\text{dl}$ at 5 years for Children with Peak Blood Lead < 10 $\mu\text{g}/\text{dl}$ (n=101)

	Original Results	p value	Adjusted for Breastfeeding and Mouthing Behaviors	p value
Lifetime Average	-1.37 + 0.60	.026	-1.45 + 0.61	.021
Concurrent	-1.58 + 0.46	.001	-1.61 + 0.47	.001

Adjusted for maternal IQ, maternal education, prenatal tobacco exposure, household income, race, HOME Inventory, child's sex, birth weight, preterm birth, iron status, breastfeeding, and mouthing behaviors (soil ingestion and paint chip ingestion).

Body Burdens of Lead in Ancient Peoples, Typical American and Overt Lead Poisoning

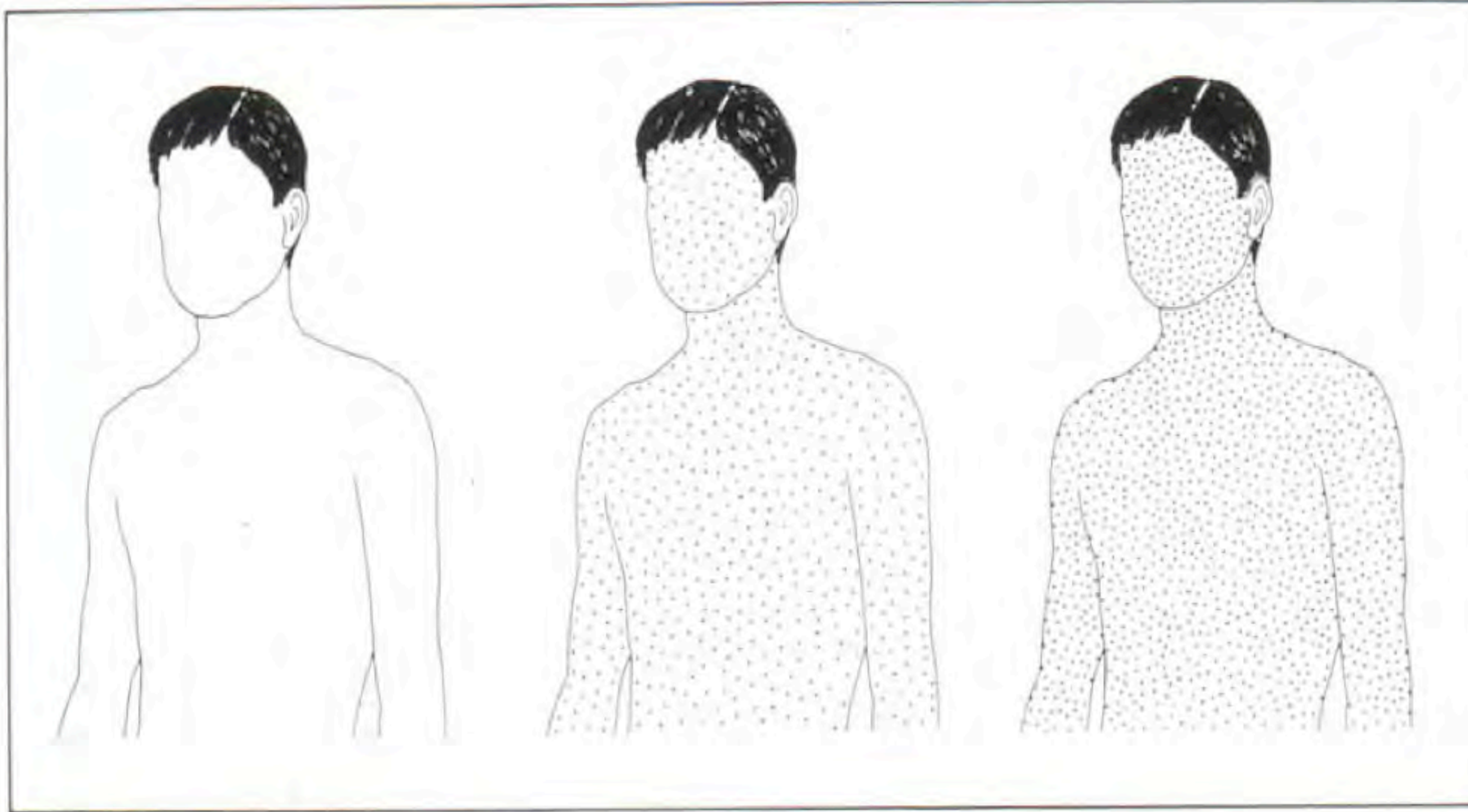


FIGURE 1-1 Body burdens of lead in ancient people uncontaminated by industrial lead (left); typical Americans (middle); people with overt clinical lead poisoning (right). Each dot represents $40\mu\text{g}$ of lead. Source: Patterson et al., 1991; adapted from NRC, 1980.

Supralinear Dose-Response

A Statistical Artifact?

- Inverse relationship between a normally distributed dependent variable and a lognormal independent variable is inherently nonlinear (Beck & Bowers)
- Due to unmeasured confounding by pesticides (Gulson)
- A statistical artifact introduced by failure to adjust for a strong, nonlinear confounder (Banner & Kahn)

Hornung RW, et al. The supralinear dose – response for environmental toxicants: A statistical artifact? Clinical Toxicology 2014.

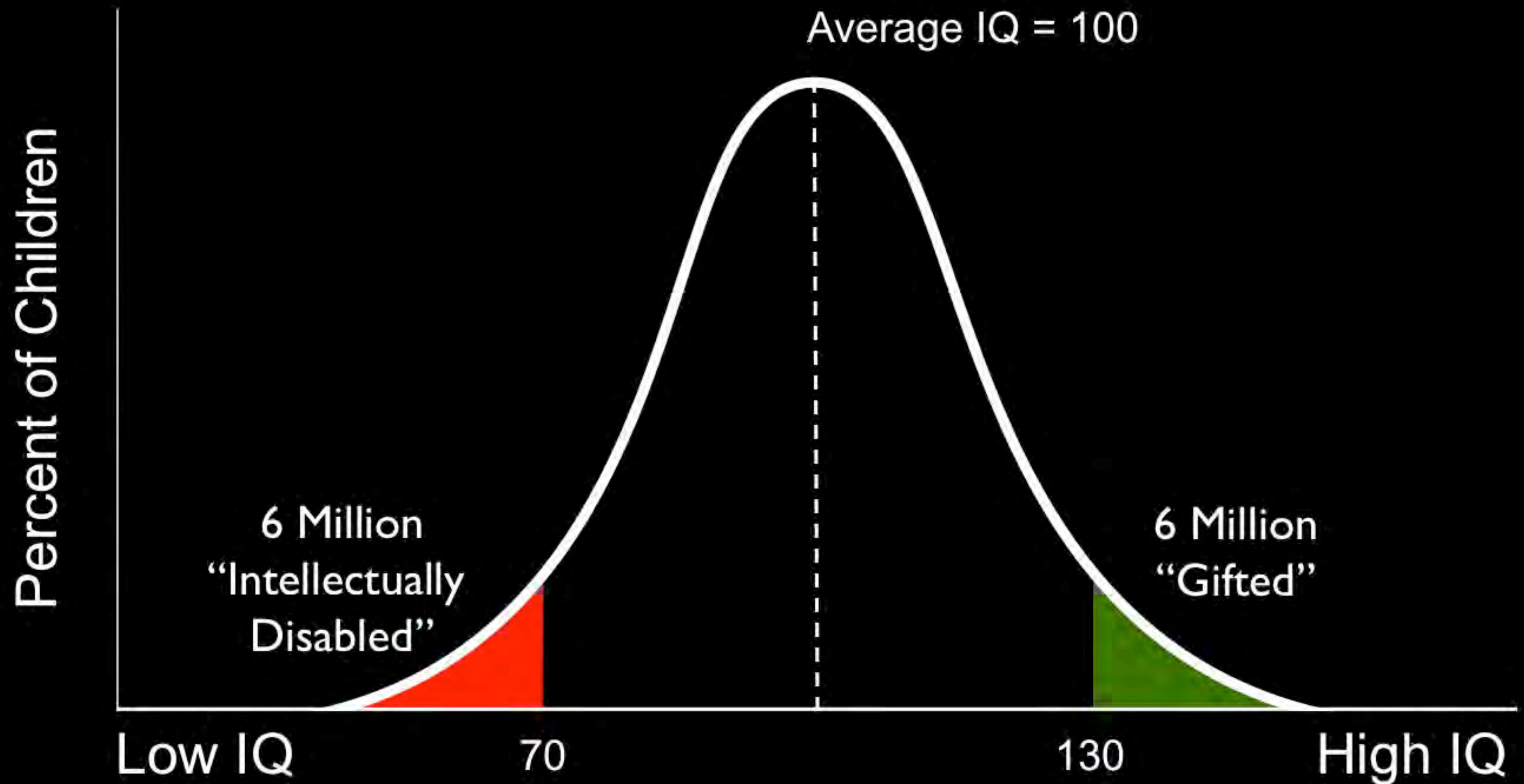
A statistical reevaluation of the data used in the Lanphear et al. (2005) pooled-analysis that related low levels of blood lead to intellectual deficits in children

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¹2220 South Vienna, Ruston, LA 71270, USA, ²Gradient, 20 University Rd., Cambridge, MA, USA, ³Program of Mathematics and Statistics, College of Engineering and Science, Louisiana Tech University, Ruston, LA, USA, ⁴65 Rogers Ave #1, Somerville, MA, USA, and ⁵ENVIRON International Corporation, Monroe, LA, USA

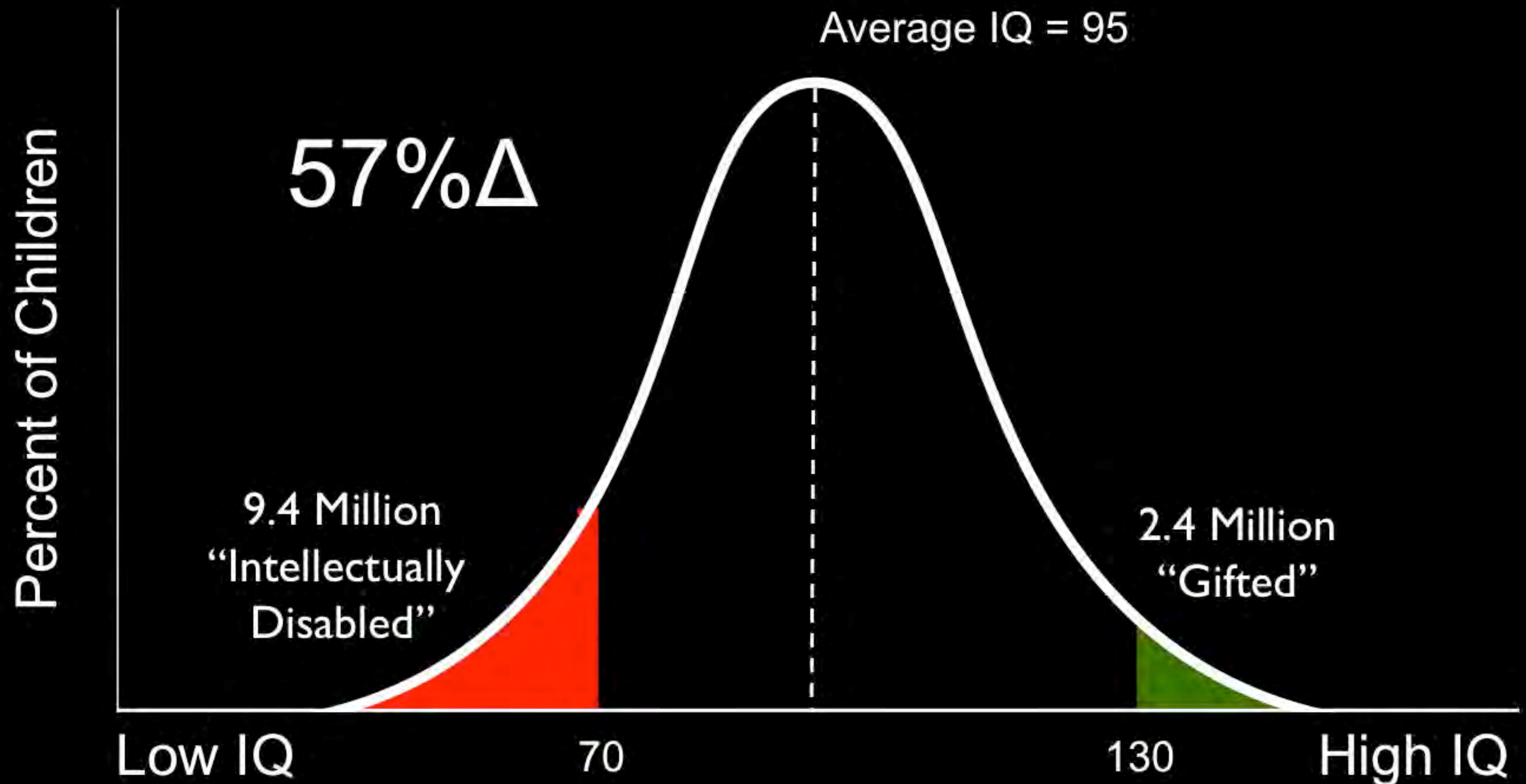
“Thus, even though our reanalysis of results in Lanphear et al. (2005) found some problems with their analyses, our independent analysis found results that mirrored the conclusions of Lanphear et al., namely, that the relationship between BPb and IQ was non-linear, that concurrent BPb provided the best statistical description of the exposure-response, and that there is statistical evidence for an association of BPb with IQ at peak BPb exposures below 7 mg/dL (and as low as concurrent BPb of 5 mg/dL).”

Little Shifts Matter



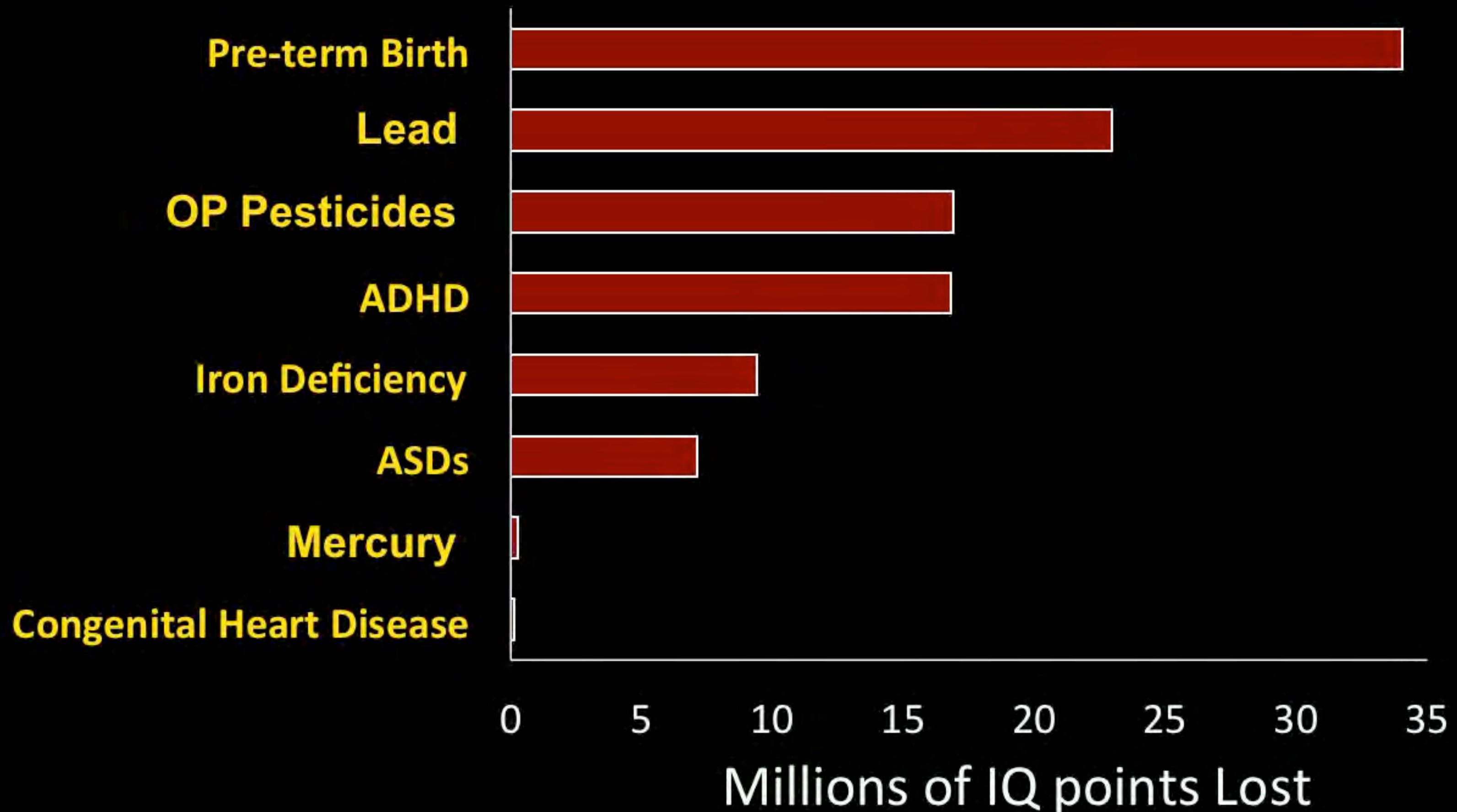
Adapted from Gilbert S, Weiss B. Neurotoxicology 2006;27:693-701

Little Shifts Matter

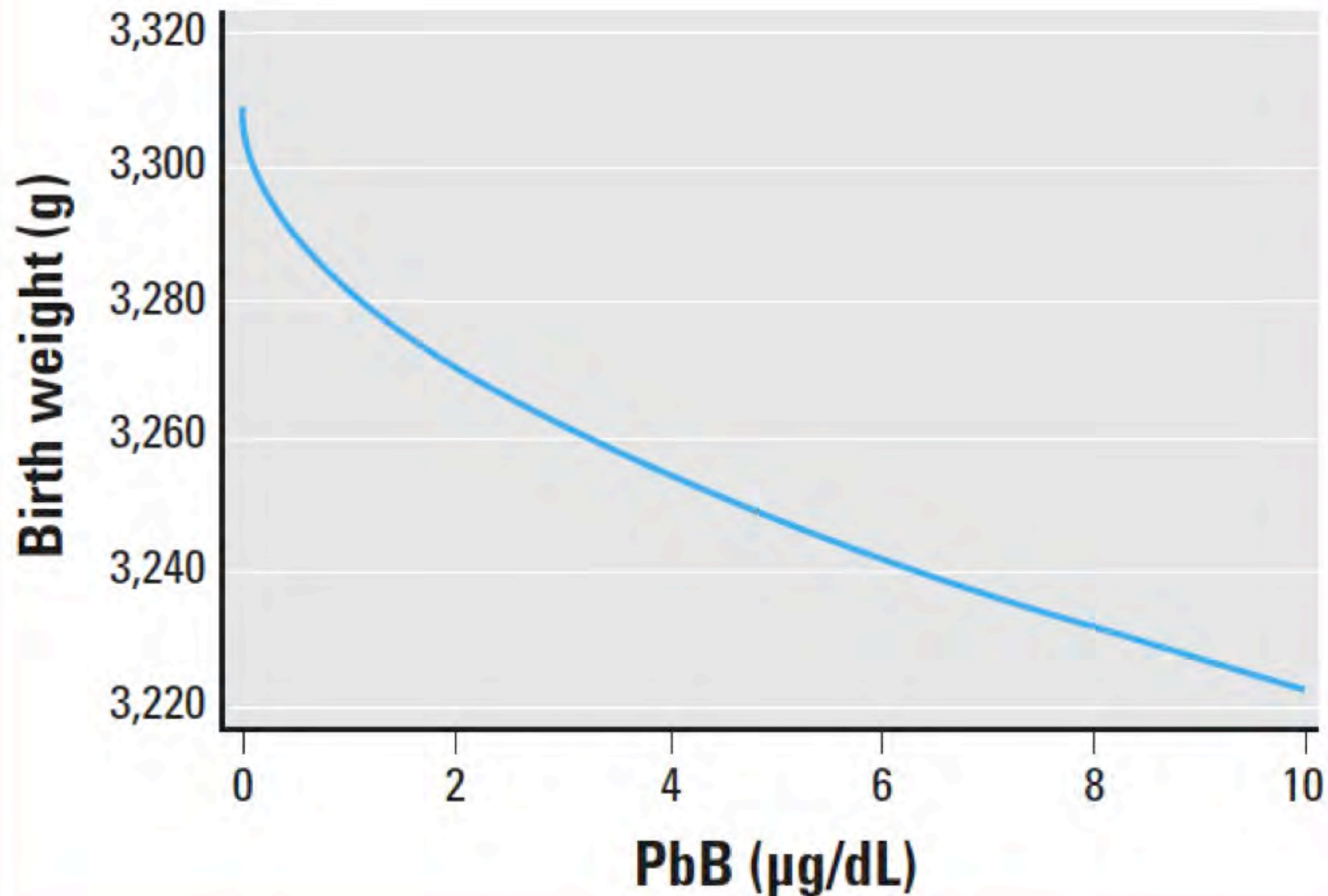


Adapted from Gilbert S, Weiss B. Neurotoxicology 2006;27:693-701

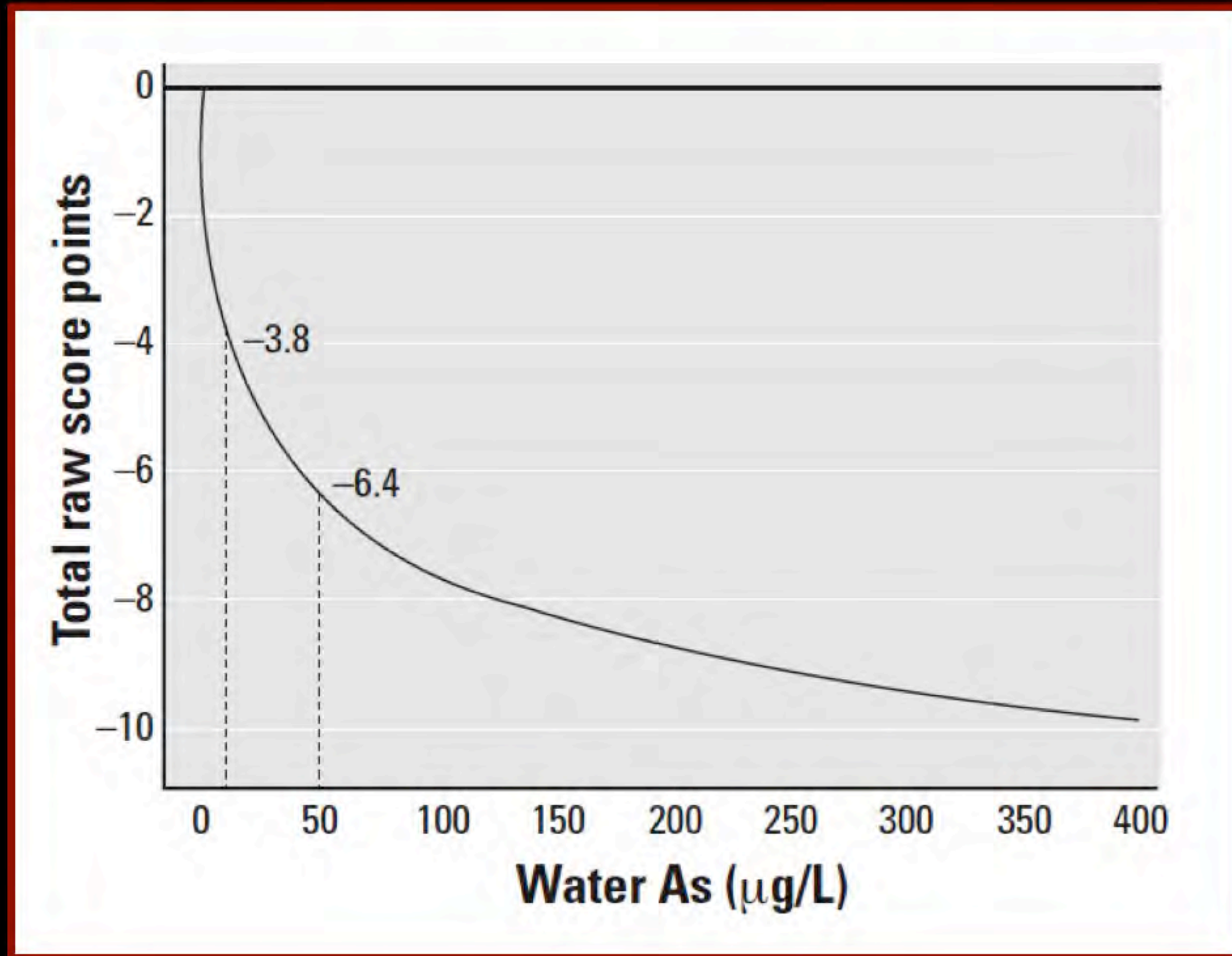
IQ Loss for Various Risk Factors



Dose Response Relationships of Maternal Blood Lead Levels and Birthweight

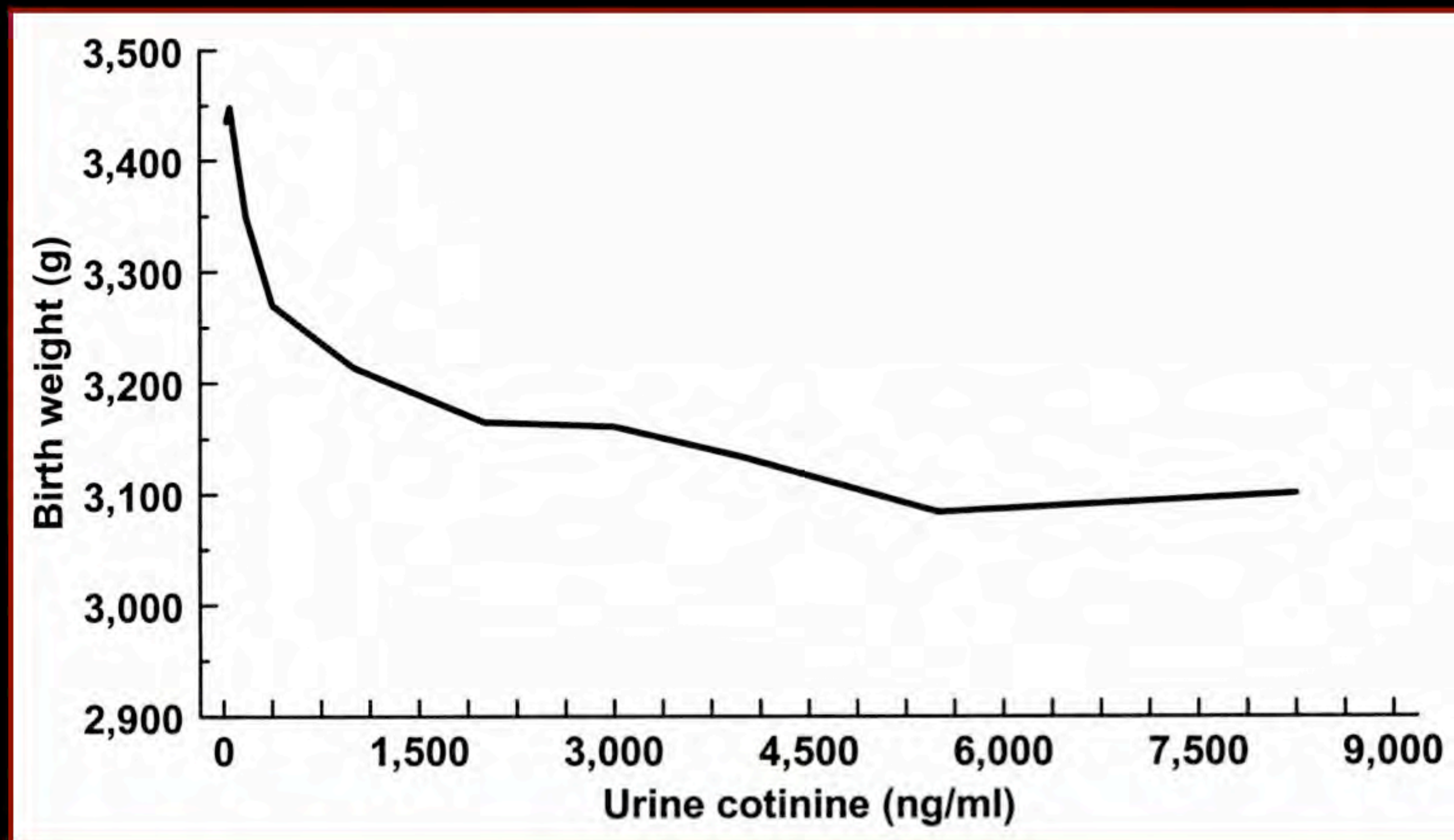


Relationship of Water Arsenic and Full-Scale IQ Scores in 10-year old Bangladesh Children



Wasserman G, et al. EHP 2004;112:1329-1333.

Mean adjusted birth weight by third-trimester urinary cotinine concentration (n = 2,481)



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

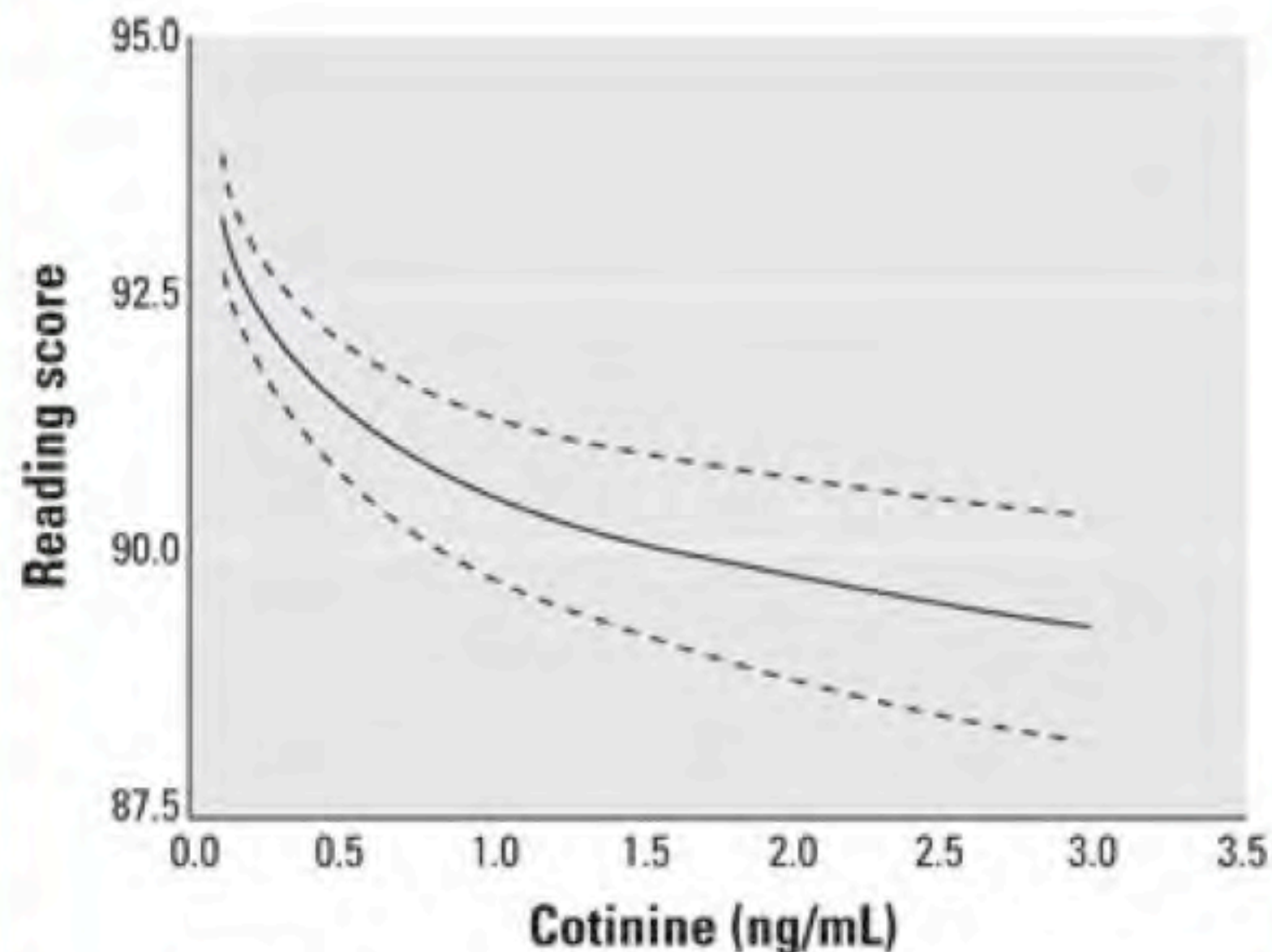


Figure 1. Log-linear regression line for reading scores by serum cotinine levels. Dashed lines indicate 95% confidence interval.

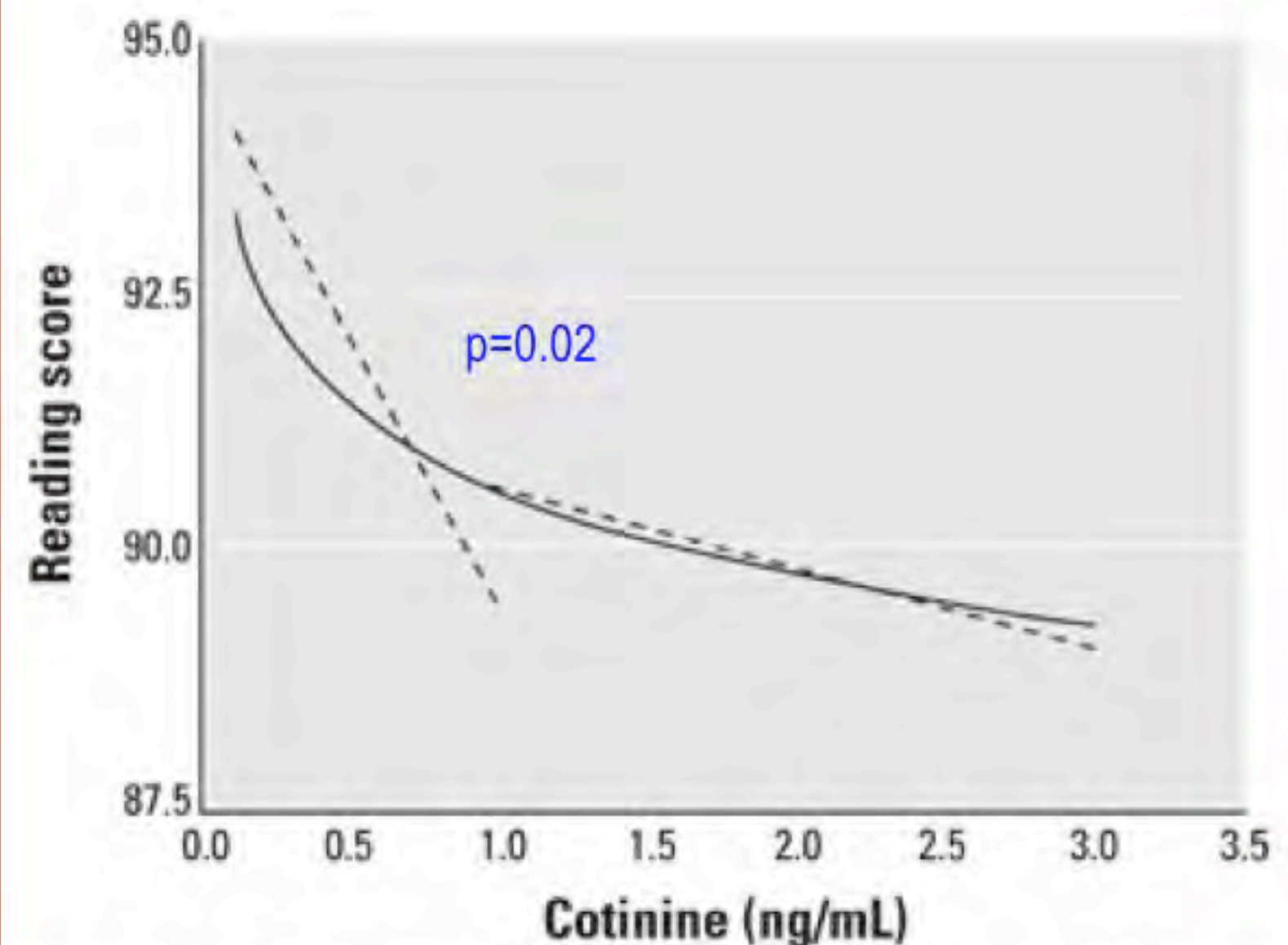
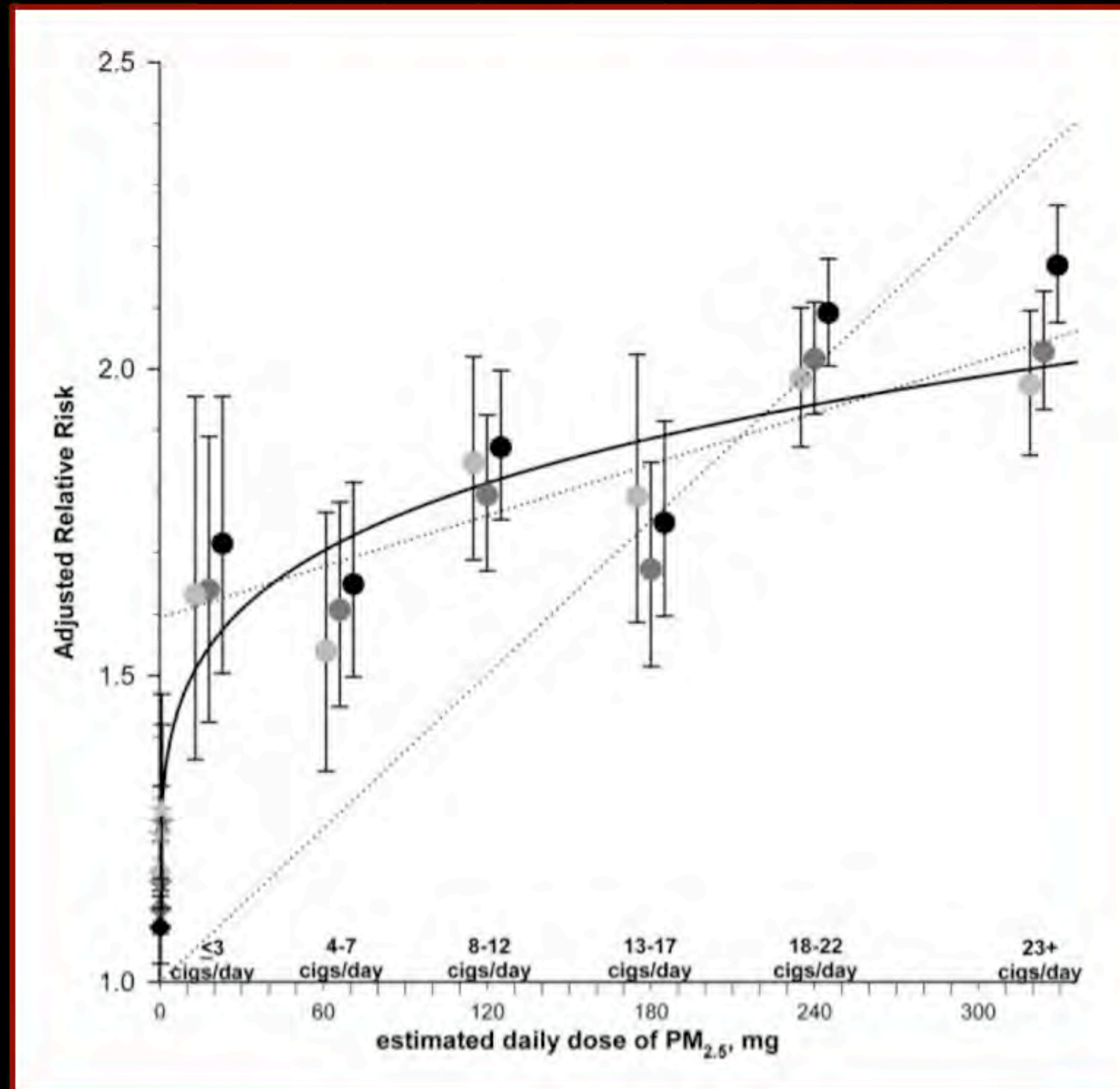
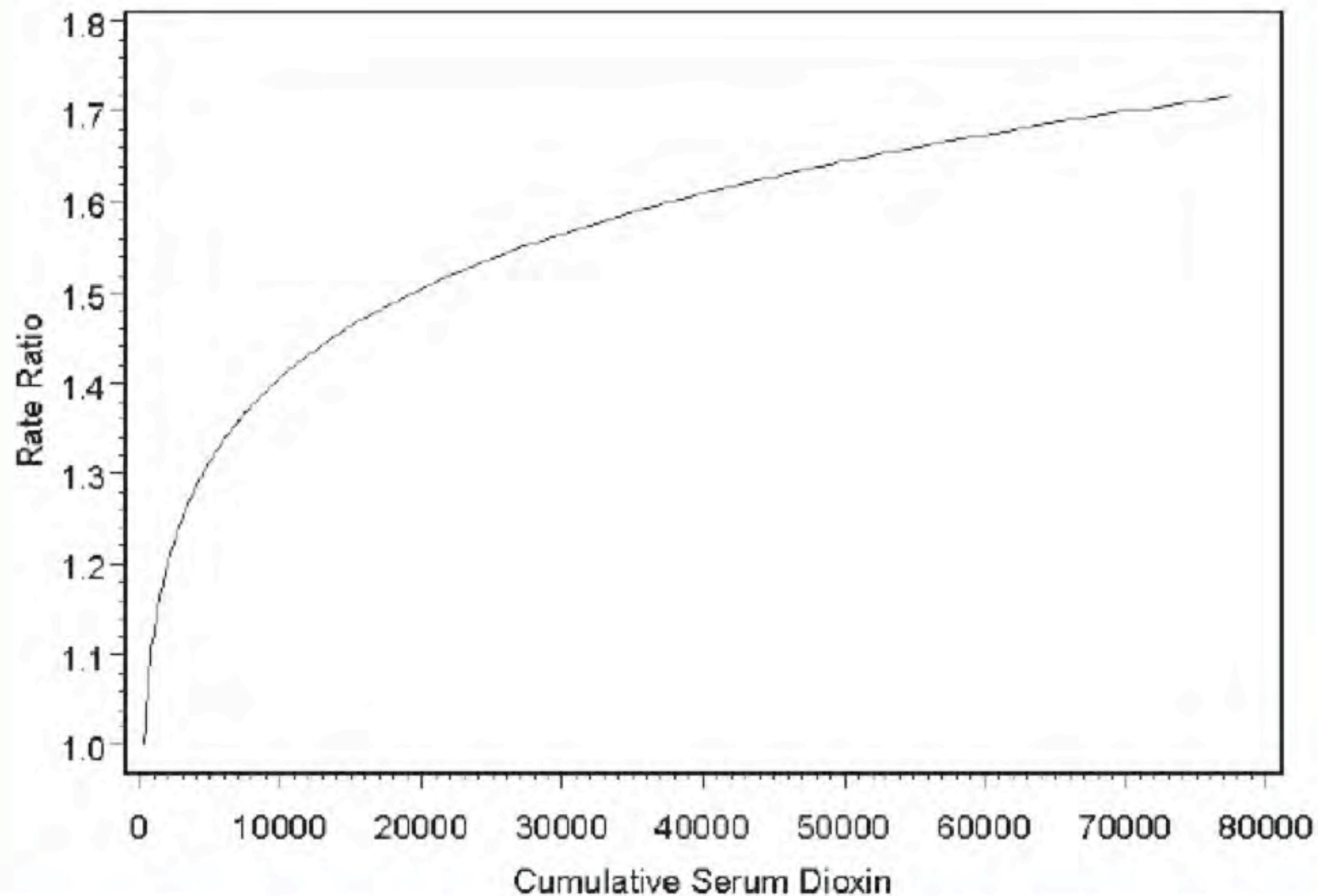


Figure 2. Log-linear model for cotinine (solid line) versus linear models for cotinine among children with cotinine above and below 1 ng/mL (dashed lines; ~ 80th percentile).

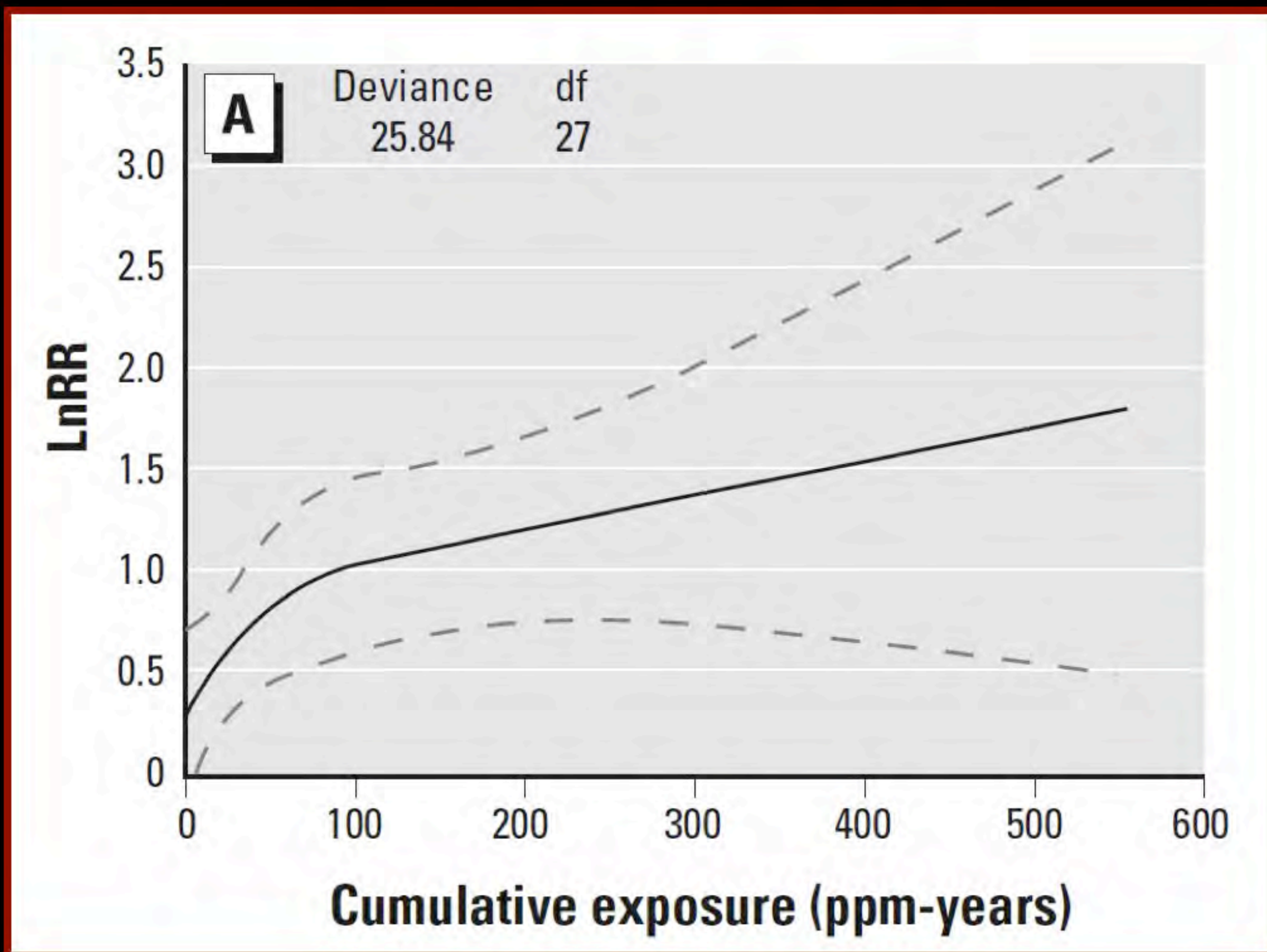
Risks of Ischemic Heart Disease, CVD and Cardiopulmonary Disease Mortality by Cigarette Smoke



Exposure Response Relationship for Cumulative Serum Dioxin and All-Cancer Mortality

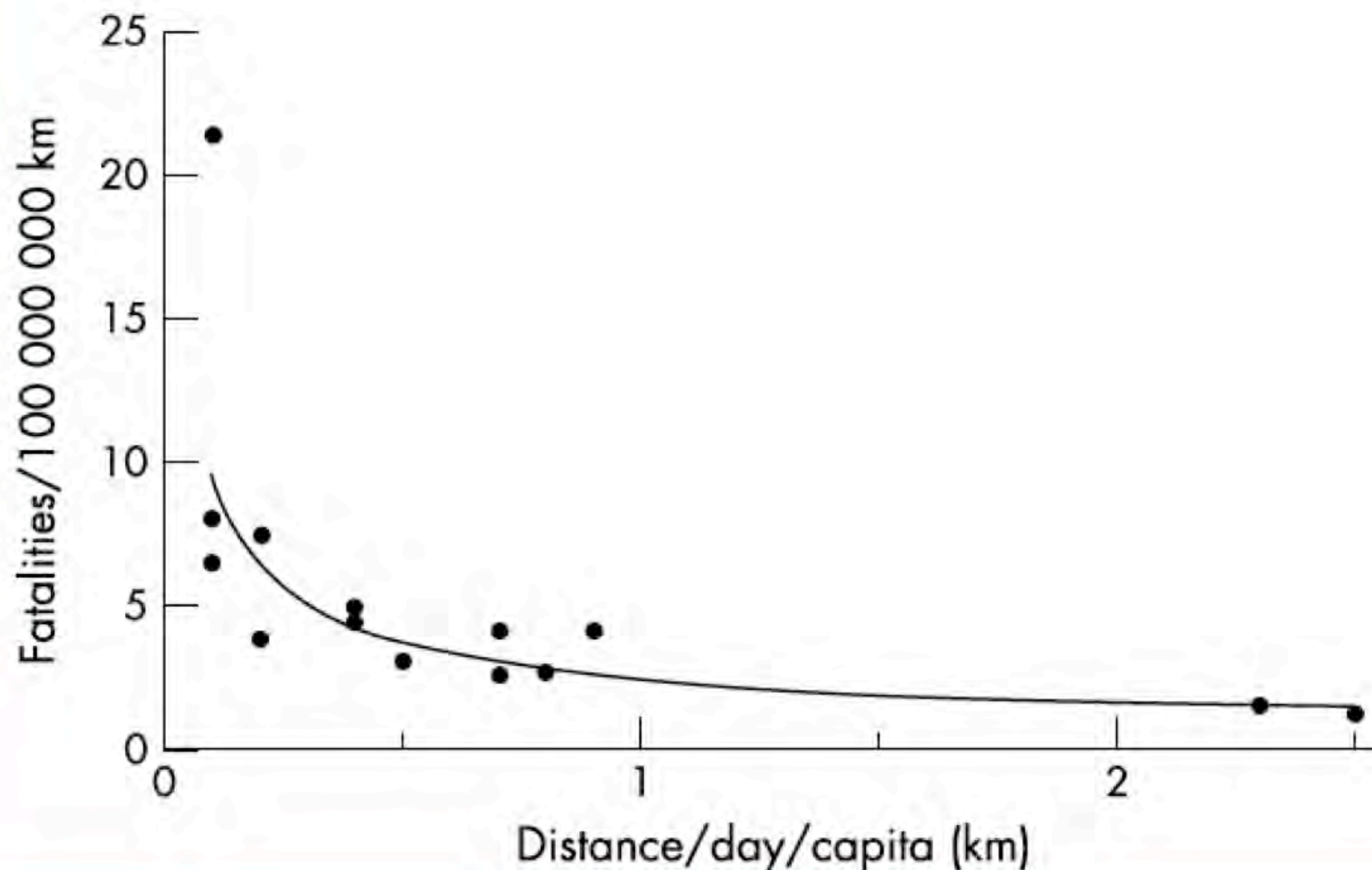


Exposure Response Relationship for Benzene and Leukemia: A Meta-analysis



Safety in Numbers

Bicycle Fatalities in 14 European Countries, 1998



Reasons Proposed for Observed Exposure-Response Relationship

- Saturation of effect (e.g., enzyme systems or platelet aggregation)
- Depletion of susceptible hosts
- Exposure misclassification
- Confounding or modification

Conclusions

- For a given exposure, environmental toxicants may be associated with steeper effects at lower levels
- Past studies often included “exposed” subjects in reference population, underestimating effect size
- Reinforce importance of population strategy versus high-risk strategy
- Steeper effects at low levels pose regulatory challenges and public health opportunities