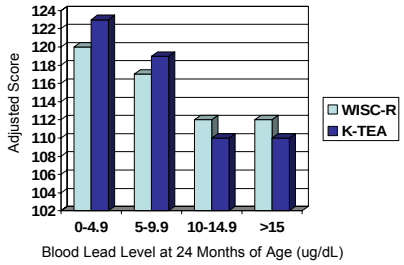
Periods of Enhanced Developmental Susceptibility to the Central Nervous System Effects of Environmental Lead: The Potential Importance of Later Blood Lead Concentrations

American Academy of Pediatrics Policy Statement of 2005

The policy on screening strongly recommends that all medicaid eligible children receive at least two screenings—at one and two years of age. However, it is also noted that a "low" blood lead concentration in a school-age child does not rule out earlier lead poisoning.

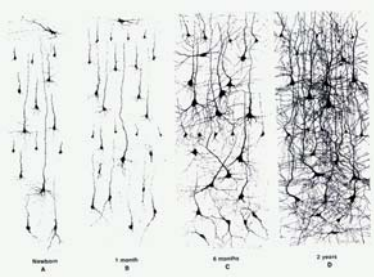
American Academy of Pediatrics (2005). Lead exposure in children: prevention, detection, and management. Pediatrics, 116, 1036-1046.

The Boston Prospective Study



Bellinger, et al. (1992), Pediatrics

Vulnerability after Birth: Special Case of the Human Brain



Golgi-stained sections of human cerebral cortex taken from equivalent areas of the anterior portion of the middle frontal gyrus at different ages. There is tremendous increase in the complexity of dentritic arborizations with increasing age with maximal density occurring between two and three years of age.

Beyond Infancy

The pruning and reorganization of cortical areas is a protracted process that lasts well into the second decade of life. Given the extended maturation of the brain it is not surprising that it is more susceptible to functional damage and resulting developmental dysfunction.

Seyffert & Silva, Current Pediatric Reviews, 2005

Beyond Two Year Blood Lead

- Blood lead is often considered merely a measure of recent exposure. However…..
- Late blood lead concentrations represent exposure from both exogenous and endogenous sources.
- At any given point in time (e.g., in the young school-age child), blood lead reflects an equilibrium between body burden and ongoing exposure to environmental sources.
- Blood lead measured concurrently with measures of neurodevelopmental outcomes may be better predictors of deficit.
- Blood lead measured concurrently with assessment of outcome may be a better indicator of biologic levels of exposure to the target organ (e.g., the CNS).
- Higher blood lead concentrations in later life may represent individual differences in absorption, retention and vulnerability.

Seeking Sensitive Periods

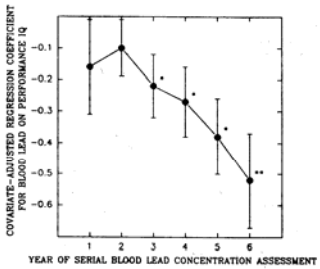


FIG. 1. Plot of covariate-adjusted regression coefficients (and SEs) for mean blood lead concentration by year of assessment and Performance IQ as measured by the Wechsler Intelligence Scale for Children-Revised. Data were previously presented in ref. 6. *$p < 0.05$; **$p < 0.001$.

Dietrich (1995) Neurotoxicol Teratol

The Evidence

It is not clear that only the period of peak blood lead concentration matters in terms of risks for neurodevelopmental vulnerability.

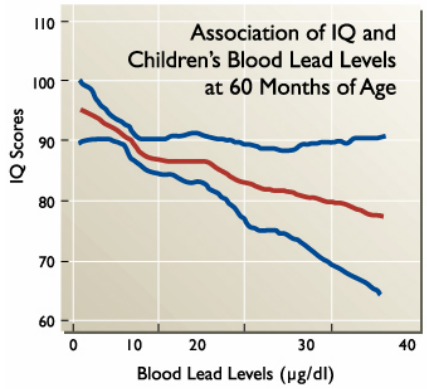
Rochester (Canfield, et al. 2003)
Cincinnati (Dietrich, et al. 1993; Ris, et al. 2004)
Kosovo (Wasserman, et al. 2000)
Port Pirie (Tong, et al. 1996)
TLC (Chen, et al. 2005)

Later Blood Lead Levels Predict School-Age Assessments of IQ: Port Pirie Cohort Study at 11-13 Years (Tong, et al 1996)

Table 5—*Estimated regression coefficients (SE) in IQ points per unit of log blood lead concentration from simple and multiple regression analyses**

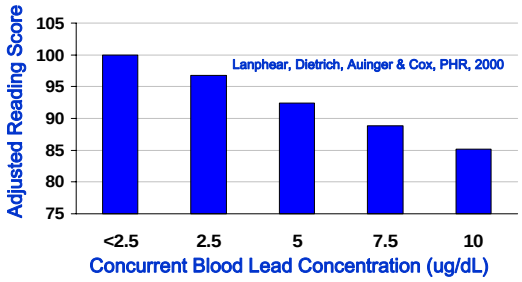
	Unadjusted			Adjusted†		
Time of blood sampling	Verbal IQ	Performance IQ	Full scale IQ	Verbal IQ	Performance IQ	Full scale IQ
Cord blood	−2.9 (1.3) (P=0.03)	−1.8 (1.6) (P=0.25)	−2.7 (1.4) (P=0.06)	1.0 (1.3) (P=0.43)	1.2 (1.8) (P=0.48)	1.2 (1.5) (P=0.41)
15 Months	−5.4 (1.3)	−5.2 (1.7)	−5.2 (1.5)	−2.8 (1.3) (P=0.03)	−0.6 (1.9) (P=0.76)	−1.8 (1.6) (P=0.24)
3 Years	−8.5 (1.5)	−9.4 (2.0)	−9.6 (1.7)	−2.6 (1.6) (P=0.11)	−4.2 (2.3) (P=0.07)	−3.8 (1.9) (P=0.05)
5 Years	−8.4 (1.3)	−7.2 (1.7)	−8.9 (1.5)	−3.7 (1.4) (P=0.01)	−3.7 (1.9) (P=0.06)	−4.0 (1.6) (P=0.02)
7 Years	−7.9 (1.3)	−8.6 (1.7)	−8.9 (1.5)	−2.8 (1.4) (P=0.05)	−3.6 (2.0) (P=0.06)	−3.4 (1.7) (P=0.04)
11-13 Years	−5.7 (1.3)	−6.2 (1.7)	−6.5 (1.4)	−2.4 (1.3) (P=0.06)	−2.0 (1.8) (P=0.12)	−3.1 (1.4) (P=0.04)
Lifetime average to age 3	−9.3 (1.8)	−7.8 (2.4)	−9.5 (2.1)	−4.6 (1.9) (P=0.03)	−3.2 (2.7) (P=0.23)	−4.3 (2.2) (P=0.06)
Lifetime average to age 5	−9.8 (1.9)	−8.6 (2.4)	−10.1 (2.1)	−5.0 (2.0) (P=0.02)	−4.4 (2.8) (P=0.10)	−5.1 (2.3) (P=0.03)
Lifetime average to age 7	−9.6 (1.9)	−8.7 (2.5)	−10.0 (2.2)	−4.3 (2.1) (P=0.03)	−4.3 (2.9) (P=0.14)	−4.6 (2.4) (P=0.06)
Lifetime average to age 11-13	−10.8 (1.8)	−10.8 (2.2)	−11.6 (1.9)	−3.9 (1.8) (P=0.03)	−4.7 (2.8) (P=0.07)	−4.3 (2.1)‡ (P=0.04)

*All simple regression coefficients except for cord blood lead concentration were significant (P<0.001); P values shown in parentheses are for multiple regression analyses.
†Adjusted for covariates described in the text.
‡Analyses were based on the unit of natural log blood lead concentration in µg/dl; this means that the expected deficit in full scale IQ associated with a doubling of lifetime average blood lead concentration—for example, from 0.48 to 0.97 mmol/l (10 to 20 µg/dl) is 3.0 points: 4.3×(ln[20]−ln[10])=3.0.



Canfield R, et al. NEJM 2003;348:1517-1526.

Blood Lead Concentration and Reading Scores: NHANES-III (6-16 Years)



Low-level Environmental Lead Exposure and Children's Intellectual Function

An International Pooled Analysis of Prospective Studies

Lanphear, B.P. et al. (2005), Environmental Health Perspectives, 113, 894-899.

Objectives

- To examine the relationship between IQ and blood lead concentration in children followed prospectively, from infancy through 5 to 10 years of age.
- To test for evidence of lead-associated decrements in IQ scores at blood lead levels below 10 μg/dL.
- To test whether the lead-associated IQ deficit was greater for a given change in exposure for children with lower peak blood lead concentrations.

IQ – Outcome Variable

Site	Type IQ Test	Age at IQ Test
Boston	WISC-R	10
Cincinnati	WISC-R	7
Cleveland	WPPSI	5
Mexico City	WISC-R	7
Port Pirie	WISC-R	7
Rochester	WPPSI-R	6
Yugoslavia	WISC-R	7

Blood Lead Variable Definition

Peak Blood Lead
Maximum blood lead of blood lead tests taken at 6 months, 1 year (or 15 month), 2, 3, 4, 5, 6, 7 year values

Early Childhood Blood Lead
Mean blood lead from 6 to 24 months

Mean Lifetime Average
Mean blood lead level from 6 month to concurrent value

Concurrent Blood Lead
Blood lead value at age concurrent with IQ testing or otherwise closest to IQ testing for each site.

Covariates

- Child's sex
- Birth order
- Birth weight
- Maternal IQ
- Maternal education
- Maternal age at delivery
- Marital status
- Prenatal smoking
- Prenatal alcohol use
- HOME Score

The Relationship of IQ vs Selected Blood Lead Indices Adjusted for All Available Covariates

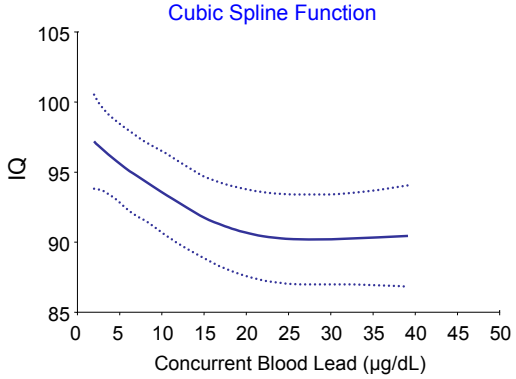
Variable	Concurrent (R^2=0.630)		Peak R^2=0.628)		Early Childhood (R^2=0.631)		Lifetime Average (R^2=0.629)	
	β	p value	β	p value	β	p value	β	p value
log blood Pb	-2.58	<.001	-2.79	<.001	-2.09	0.001	-2.97	<.001
HOME Score (z-score)	4.23	<.001	4.30	<.001	4.32	<.001	4.28	<.001
Maternal IQ	4.77	<.001	4.88	<.001	4.98	<.001	4.88	<.001
Maternal education	1.12	0.016	1.14	0.014	1.17	0.012	1.11	0.017
Birth weight (per 100 g)	1.53	<.001	1.53	<.001	1.48	<.001	1.51	<.001
Birth order	-0.44	0.275	-0.44	0.275	-0.46	0.252	-0.44	0.275
Child's Sex	0.46	0.486	0.46	0.489	0.44	0.511	0.46	0.493
Marital status	1.15	0.259	1.00	0.328	1.10	0.437	0.99	0.333
Maternal age	0.13	0.768	0.18	0.675	0.21	0.761	0.17	0.701
Smoking (Y/N)	-0.08	0.915	-0.06	.938	0.03	0.974	-0.05	0.947
Alcohol (Y/N)	0.74	0.401	0.40	0.707	1.08	0.227	0.81	0.361

Adjusted Log-linear Model of Full Scale IQ vs Selected Blood Lead Indices *

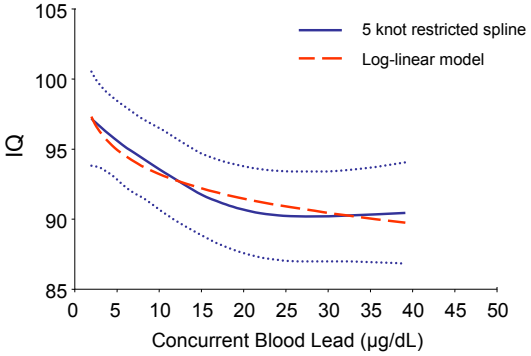
	Concurrent (R^2=0.631)	Peak (R^2=0.624)	Early Childhood (R^2=0.626)	Lifetime Average (R^2=0.624)
	β	β	β	β
Unadjusted Blood Lead	-4.66	-4.85	-3.57	-5.36
Adjusted Blood Lead	-2.70	-2.85	-2.04	-3.04

* All p values < 0.001

Relationship of Concurrent Blood Lead Concentration with Children's Intellectual Function using a Restricted Cubic Spline Function



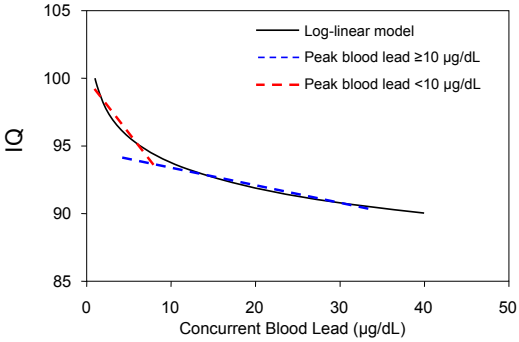
Relationship of Concurrent Blood Lead Concentration with Children's Intellectual Function



Estimated Lead-associated IQ Deficits by Concurrent Blood Lead Concentration

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

Relationship of Concurrent Blood Lead Concentration with Children's Intellectual Function at Blood Lead Levels Above and Below 10 µg/dL



Conclusions

- Lead-associated intellectual deficits occur at concurrent blood lead levels below 10 µg/dL
- No evidence of a threshold for lead-associated intellectual deficits
- Sufficient evidence to mount an aggressive campaign to eliminate childhood lead exposure

Overall Conclusions

- **The results of pediatric lead studies do not point to any particularly critical period of vulnerability.**
- **The current focus of screening for elevated blood lead concentrations in children only through two years of age may be insufficient.**