

Health Hazards of Low-level Lead Exposure to Adults

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Lead in whole blood: The most common clinical measurement for human biomonitoring

OSHA Construction Medical Removal Level for Adults (since 1977)	50 $\mu\text{g}/\text{dL}$
OSHA "return to work" level	40
U.S. population geom mean (mid -late 1970' s)	12.8
US Population Geometric Mean (2010)	1.1

*International standards for blood lead concentration
requiring temporary removal from workplace lead exposure*

Country	Blood lead concentration ($\mu\text{g/dL}$)
USA	60 (general industry); 50 (construction)
UK	60
Japan	60
Russia	50
Czech	40
Germany	40; 30 (women under 45 years of age)
France	40; 30 (all women)
Sweden	40; 25 (women under 50 years of age) [3 consecutive measurements]

Health effects of lead at low dose warrant a reappraisal of the levels of lead exposure that may be safely tolerated in the workplace.

- ***Chronic effects of cumulative dose***

- Hypertension / Cardiovascular disease*
 - Decrements in renal function*
 - Cognitive dysfunction*

- ***Acute effects of recent dose***

- adverse reproductive outcome*

Assessing the Relationship between Pb and Blood Pressure

- Animal exposure experiments
- In vitro and in vivo studies to assess mechanisms and biological plausibility
- Human epidemiological studies



Blood Pressure Elevation in Young Dogs during Low-Level Lead Poisoning

[Fine et al, Tox Appl Pharm 93:388-93; 1988]

- Six 3 month old female dogs and matched litter-mates
- Animals fed Pb acetate or placebo 1 mg/kg/d x 5 mo.
- BP measured regularly by Doppler in foreleg without anesthesia or trauma by blinded investigator
- **Blood lead at 15 weeks: 35.8 vs. 9.2 μ g/dl**
BP at 20 weeks **120 \pm 2.1 mm Hg vs 108 \pm 1.5**

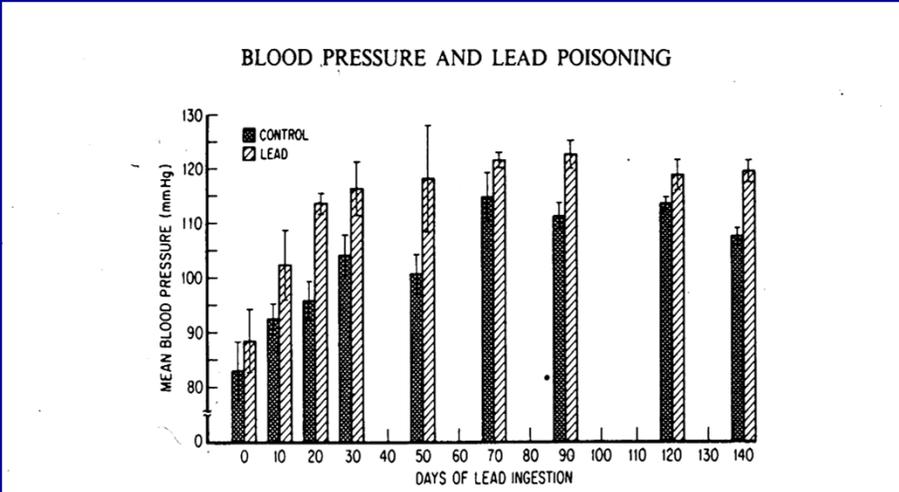


FIG. 1. Mean blood pressure levels during lead ingestion. The profile of the lead-exposed group was significantly higher than of the paired controls (repeated-measures ANOVA, $p = 0.0048$). The rise in the control group is normal for age. Measurements on Day 50 were obtained under pentobarbital anesthesia

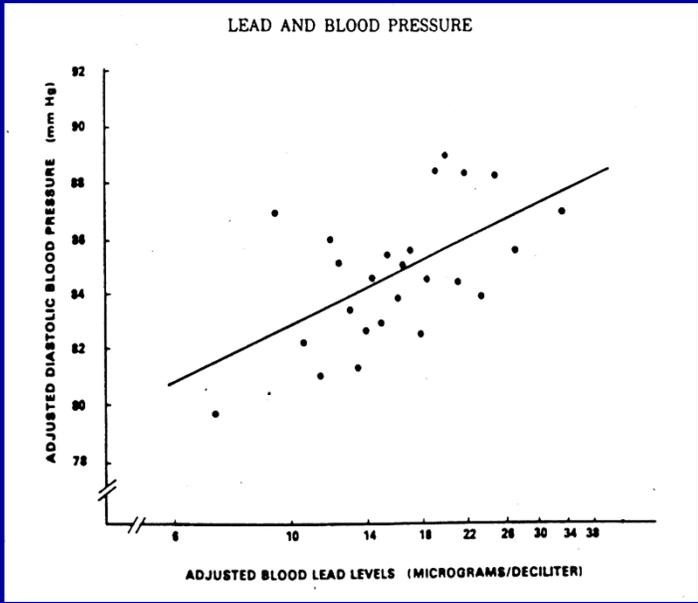
The Relationship Between Blood Lead and Blood Pressure in the NHANES II Survey

[Schwartz J Environ Health Persp 78:15-22; 1988]

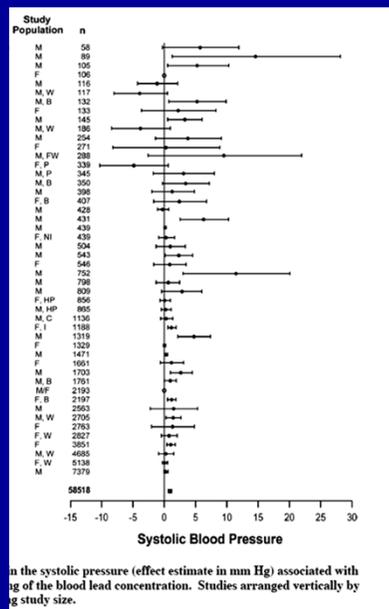
Representative cross-sectional survey of US Population 20,322 persons examined; PbB obtained on 9932

Mean blood lead in adults 13.1 $\mu\text{g}/\text{dl}$ (12.7 -13.7)

Blood lead significantly associated with systolic and diastolic blood pressure, after controlling for age, BMI, demographic, multiple nutritional factors



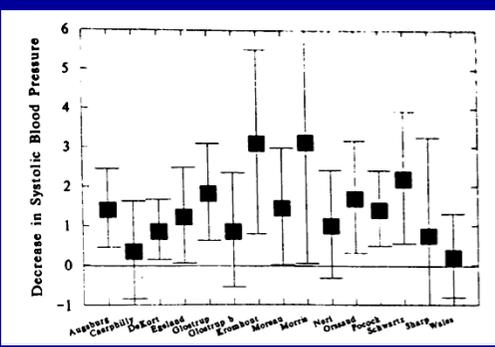
[Pirkle et al, 1985]



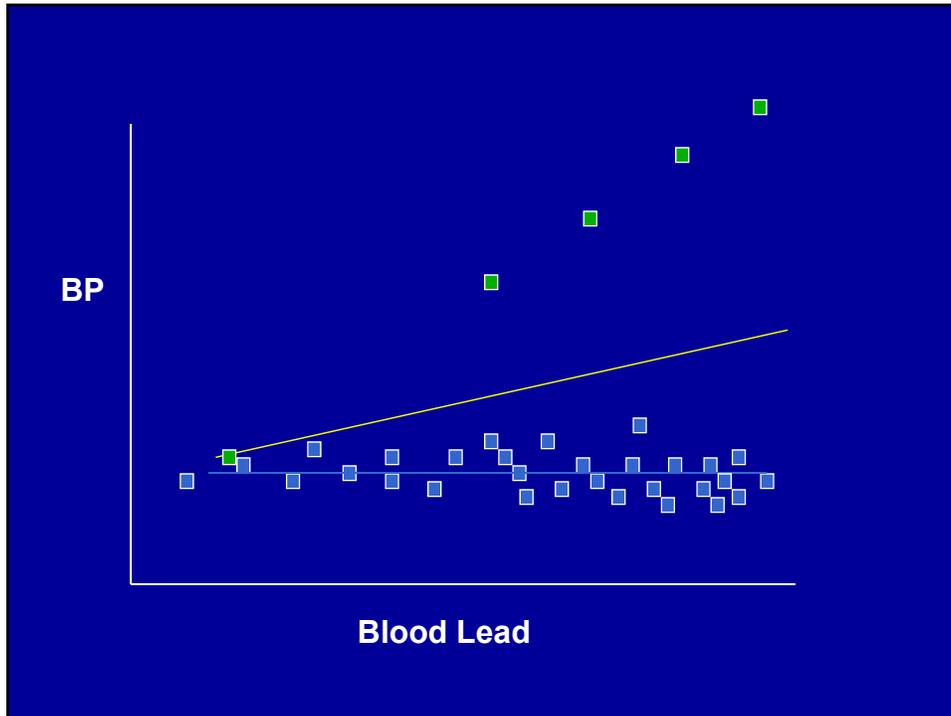
in the systolic pressure (effect estimate in mm Hg) associated with 10 μg of the blood lead concentration. Studies arranged vertically by increasing study size.

Nawrot et al, 2002

Schwartz, 1995



Meta-analyses:
 Δ PbB 5 → 10 μg/dL
 = Δ 1.0 or 1.25 mmHg
 in systolic blood pressure



Why measure lead in bone?

Greater than 90% of the body lead burden is found in the skeleton, where it remains with a half-life of years to decades.

Bone lead concentration is highly correlated ($r \approx 0.8$) with longterm, cumulative lead exposure (e.g. $\mu\text{g}/\text{dL} \cdot \text{years}$)



[photo source: Mt Sinai School of Medicine]

The Relationship of Bone and Blood Lead to Hypertension. The Normative Aging Study

[Hu H et al, JAMA 1996; 275:1171-1176]

Case control study: 146 hypertensive men; 444 controls selected from large, ongoing prospective study of aging. Mean age = 66.6 ± 7.2 y

Exposure reflects that of general population. (Mean PbB = 6.3 ug/dL)

Final logistic model (backward elimination) yielded 3 significant risk factors for hypertension:

Body mass index

Family history of hypertension

Tibia bone lead concentration

From the lowest quintile of bone lead to the highest quintile ($\Delta 29 \mu\text{g/g}$), the odds of being hypertensive increased by 50 % (O.R. = 1.5 (95% C.I. 1.1 - 1.8))

Lead and Hypertension in a Sample of Middle-Aged Women

Korrick AS et al, AJPH 1999; 89:330-335

Patella lead was associated with increased risk of hypertension in women with low level lead exposure

Case control study: 89 hypertensives and 195 controls

Boston subset of Nurses Health Study

Hypertensive = MD's diagnosis, or SBP ≥ 140 or DBP ≥ 90

Mean PbB = $3 \pm 2 \mu\text{g/dl}$

Logistic regression model: Δ 10th \Rightarrow 90th percentile bone Pb
 $6 \mu\text{g/g} \Rightarrow 31 \mu\text{g/g}$

yielded *odds ratio for Hypertension of 1.86 (1.09, 3.19)*

after adjustment for age, BMI, dietary Na, and family Hx of htn.

Compare the Δ tibia bone lead of 29 $\mu\text{g/g}$ associated with the O.R. = 1.5 for hypertension (Hu et al 1996) with cumulative lead exposure:

The linear slope between tibia bone lead ($\mu\text{g/g}$) and cumulative blood lead index ($\mu\text{g/dL} \cdot \text{years}$) is roughly 0.05

$$29 \div 0.05 = 580 \mu\text{g/dL} \cdot \text{years}$$

Considered in context of a 40 year working lifetime, a decrease in BLL from 25 $\mu\text{g/dL}$ to 10 $\mu\text{g/dL}$ would reduce the cumulative blood lead index by 600 $\mu\text{g/dL} \cdot \text{years}$

This might avert the 50 % increase in odds of developing hypertension observed by Hu et al (1996)

Blood Lead Levels and Cardiovascular Mortality: Results from NHANES III

(Schober et al, Environ Health Persp 114:1538-1541; 2006)

12 year longitudinal study of participants in the National Health and Nutrition Examination Survey.

Subjects ≥ 40 years of age (n = 9757)

<u>Blood Lead</u>	<u>RR of Cardiovascular Mortality</u>
< 5 $\mu\text{g/dL}$	1.0
5 - 9 $\mu\text{g/dL}$	1.20 (0.93 - 1.55)
$\geq 10 \mu\text{g/dL}^*$	1.55 (1.16 - 2.07)**

* Median = 11.8 $\mu\text{g/dL}$

** Test for trend ($P < 0.01$)

**Bone lead is a risk factor for cardiovascular mortality:
The Normative Aging Study** [Weisskopf et al, Circulation, 2009]

Prospective study of 860 Boston area men (67 ± 7.3 y.o.)
KXRF measurement of patella lead at baseline
241 deaths over avg. of 8.9 yrs of follow-up

	Tercile of Patella Lead			P trend
	< 22 µg/g	22 - 35 µg/g	> 35 µg/g	
CVD deaths (n)	33	41	63	
Hazard ratio I*	1.0 (ref)	1.39 (0.61 - 3.19)	2.45 (1.07- 5.60)	0.03
Hazard ratio II #	1.0 (ref)	1.63 (0.51 - 5.18)	5.63 (1.73 -18.3)	0.003

*Adjusted for age, smoking, education; # same model, excluding subjects with hx of heart disease or stroke at baseline

Factors independent of hypertension may contribute to the impact of lead on cardiovascular morbidity and mortality

Implicated modes of action of lead include oxidative stress, production of pro-inflammatory cytokines such as TNF-α, alteration in endothelial cell function, and others.

In epidemiological studies, including the NAS, lead biomarkers have been associated with alterations in cardiac conduction (e.g. QT and QRS) [Peters JL et al, 2012; Chen CC et al, 2013]

Blood Lead Below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) and Mortality Among US Adults

[Menke et al, Circulation 114:1388-1394; 2006]

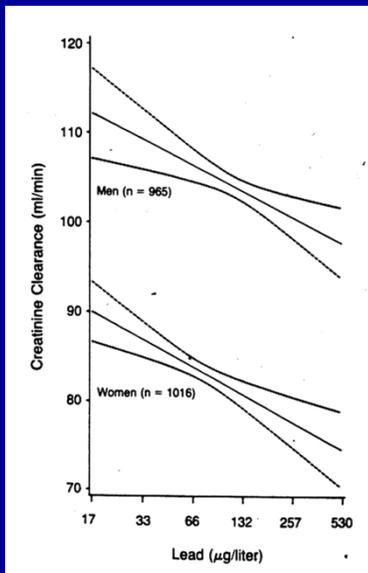
12 year longitudinal analysis of mortality among NHANES III participants (1988 - 1994) ≥ 17 yo (n = 13,946).

Hazard Ratios for Mortality, multivariate adjusted*

Cause	Tercile I BLL $\leq 1.93 \mu\text{g/dL}$		Tercile III BLL $\geq 3.63 \mu\text{g/dL}$	
	n	hazard ratio	n	hazard ratio
Myocardial infarction	50	1.0	234	1.89 (1.04 - 3.43)
Stroke	22	1.0	63	2.51 (1.20 - 5.26)
Cancer	67	1.0	238	1.10 (0.82 - 1.47)

*Age, race-ethnicity, sex, diabetes, BMI, current/former smoking, alcohol, physical activity, income, CRP, cholesterol, education, urban, menopause, hypertension, renal function

Impairment of renal function with increasing blood lead concentration in the general population



Staessen JA et al. NEJM 327:151-6; 1992

- Random population sample of 965 men and 1016 women (age 20 to 88)
- Blood lead range 1.7 - 72.5 $\mu\text{g/dL}$; geometric mean $\approx 10 \mu\text{g/dL}$
- Significant correlation between age-adjusted creatinine clearance and blood lead
- Relationship persisted after excluding subjects with occupational Pb exposure, or those with highest tercile of PbB (geom. mean 18.4 $\mu\text{g/dL}$)
- "Reverse Causation" remains unresolved question

Association of Cumulative Lead and Neurocognitive Function in an Occupational Cohort

[Khalil et al, Neuropsych 209:10-19; 2009]



Lead workers and controls previously assessed in 1982 underwent re-testing of neuropsych status, plus bone lead measurement, in 2004.

Mean BLL of workers in 1982 = 40 µg/dL; in 2004 = 12 µg/dL (n=83)
Control BLL (1982) = 7.2; (2004) = 3 (n=51)

Mean age of workers in 2004 = 54 ± 9 years; last worked with lead a mean of 6 years prior (interquartile range 0.02 - 16 y).

Tibia bone lead of exposed subjects	57 µg/g (20, 86)
of unexposed subjects	12 µg/g (-8, 32)

Regression Coefficients for Δ Cognition by Bone Pb

Peak tibia Pb (µg/g)	Total Cognitive Score	Spatial	Executive Function
Exposed	- 0.352*	- 0.338*	- 0.342*
Nonexposed	- 0.049	0.079	0.166

* $P < 0.01$; Adjusted for age, education, income, BP, yrs employed, yrs since last worked, smoking, etoh, and baseline score

In models, blood lead was not associated with cognitive function

The lead exposed workers experienced 17% greater loss in total cognitive score as compared with nonexposed controls.

[Khalil et al, 2009]

Bone lead concentration predicts decrements in cognitive function in older adults

Normative Aging Study (Weisskopf et al, Epidemiology. 18:59; 2007)

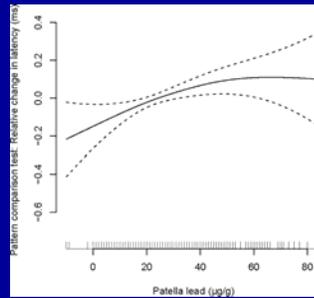
N = 1089 older, mainly white men, mean age 68.7 ± 7.4 yrs.

Repeat neuropsych testing over ≈ 3.5 yr interval

Median PbB = $5 \mu\text{g/dL}$ (IQR 3 - 6)

Bone lead: longitudinal \downarrow visuospatial performance (N = 761)

Response
latency on
pattern
recognition test

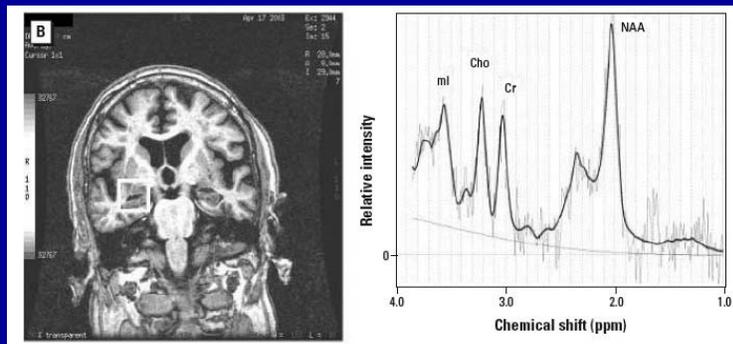


Patella Pb

Proton Magnetic Resonance Spectroscopic Evidence of Glial Effects of Cumulative Lead Exposure in the Adult Hippocampus

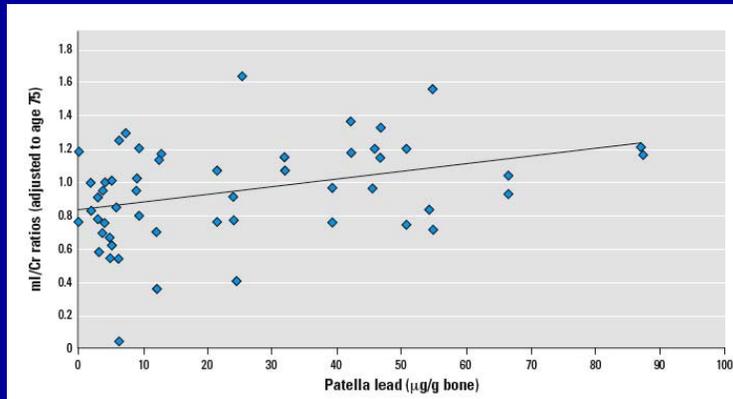
[Weisskopf M et al, EHP. 115:519-523; 2007]

A subset of the Normative Aging Study, (n =31 older men, mean age 77), underwent XRF bone lead measurements, and noninvasive PMR scanning to measure specific brain tissue metabolites in the hippocampus.



Cumulative Lead Exposure was associated with Age-adjusted Myoinositol to Creatinine Ratio

Myoinositol, a component of glial cells (astrocytes), may be a biomarker of glial proliferation and plaque formation present in preclinical Alzheimer's Disease.



[Weisskopf et al, 2007]

Environmental lead exposure and cognitive function in community-dwelling older adults. [

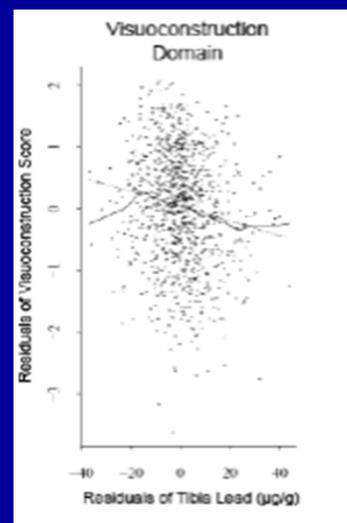
Shih et al. Neurology 14:1556-1562; 2006]

N = 991 randomly selected, sociodemographically diverse community dwelling adults, aged 50 to 70 yrs

Mean PbB = 3.5 ± 2.2 µg/dL

Tibia lead: ↓visuoconstruction on neuropsych testing

Δ 13 ppm equivalent impact of 4.8 years of age



Blood Lead Levels Measured Prospectively and Risk of Spontaneous Abortion [Borja-Aburto et al, 1999]

- 562 of 668 women followed through week 20; (16% loss to follow-up)
- Average blood lead at enrollment: 11 ug/dL
- Cases (n=35) PbB = 12 ug/dL Controls (n=60) PbB = 10 ug/dL

<u>PbB level (ug/dL)</u>	<u>Odds Ratio</u>
< 5 [referent]	1.0
5-9	2.3
10-14	5.4
≥ 15	12.2

test for trend $p = 0.021$

for Δ PbB of 5 $\mu\text{g/dL}$, O.R. = 1.8 (C.I. 1.1, 3.1)

Decrease in Birth Weight in Relation to Maternal Bone-Lead Burden [Gonzalez-Cossio T et al. Pediatrics 100:856-862; 1997]

Study of 272 full-term, parturient women in Mexico City and birth weight of their infants

Maternal blood lead $8.9 \pm 4.1 \mu\text{g/dL}$

Maternal tibia bone lead $9.8 \pm 8.9 \mu\text{g/g}$ (range 12 – 38 $\mu\text{g/g}$)

In a multivariable regression model, every increase of 10 $\mu\text{g/g}$ in maternal tibia bone lead was associated with a 73 gram (95% CI, 25 -121) decrease in birth weight.

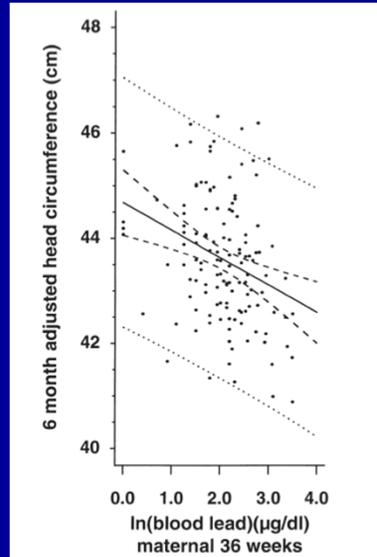
The relationship was nonlinear and most pronounced in highest quartile of bone lead (> 15 – 38 $\mu\text{g/g}$), where birth wt decrement relative to first quartile was 156 g.

“Because lead remains in bone for years to decades, mobilization of bone lead during pregnancy may pose a significant fetal exposure with health consequences, long after maternal external lead exposure has declined.”

Prenatal (maternal) BLL at 36 weeks gestation predicts child head circumference at 6 months of age

Subjects were part of a prospective longitudinal study of effect of lead on development, beginning with pregnancy (Mexico City Prospective Lead Study)

Median Maternal BLL @36 weeks = 8 $\mu\text{g}/\text{dL}$ (IQR 5.5 - 12)



Rothenberg et al, Neurotox Teratol 21:1; 1999

Prenatal Lead Exposure is Associated with Postnatal Changes in IQ

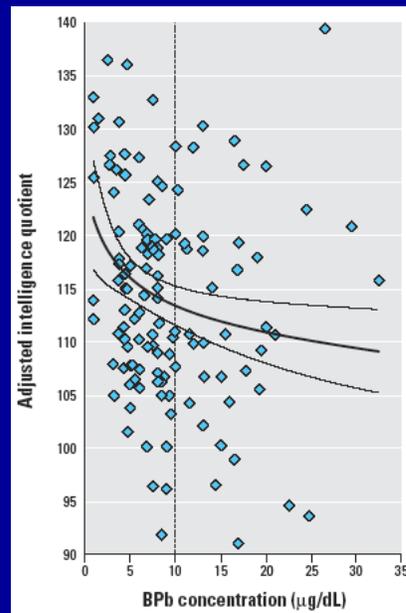
Mexico City Prospective Lead Study

(Schnaas et al 2006)

3rd Trimester PbB = 7.8 $\mu\text{g}/\text{dL}$

Every doubling of PbB associated with IQ \downarrow 2.7 pts at 6 - 10 yrs of age

N = 150



Recommendations for Medical Management of Adult Lead Exposure

Michael J. Kosnett,¹ Richard P. Wedeen,² Stephen J. Rothenberg,^{3,4} Karen L. Hipkins,⁵ Barbara L. Materna,⁶ Brian S. Schwartz,^{7,8} Howard Hu,⁹ and Alan Woolf¹⁰

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BLL (µg/dL)	Management
< 5	None indicated
5 - 9	Discuss health risks Reduce Pb exposure for women who are or may become pregnant
10 - 19	Decrease lead exposure. Increase biological monitoring. Consider removal from exposure to avoid long term risks if exposure control over an extended period does not decrease BLL < 10, or if medical condition present that increases risk with continued exposure
20 - 29	Remove from exposure if repeat BLL measured in 4 weeks remains ≥ 20

BLL (µg/dL)	Management
30 - 39	Remove from lead exposure
40 - 79	Remove from lead exposure Refer for prompt medical evaluation Consider chelation for BLL >50 with significant symptoms or signs
≥ 80	Remove from lead exposure Refer for immediate/urgent medical evaluation Probable chelation therapy

Summary of Key Points

Occupational health standards that tolerate blood lead concentrations > 20 µg/dL are insufficiently protective and are outdated.

Low to moderate levels of lead exposure in adults – blood lead levels in the range of 10 to 20 - are associated with a risk of hypertension and cardiovascular disease, cognitive dysfunction later in life, adverse reproductive outcomes, and a possible decrement in renal function,

The goal is to keep long-term BLL < 10 µg/dL (< 5 µg/dL in women of reproductive age); a single level over 30, or two consecutive BLL over 20 µg/dL merit medical removal protection (MRP)



“...You will see by it, that the Opinion of this mischievous Effect from Lead, is at least above Sixty Years old; and you will observe with Concern how long a useful Truth may be known, and exist, before it is generally received and practiced on.”

Benjamin Franklin

July 31, 1786