

Historical perspective of lead toxicity and
new challenges

An Industry Physician's Perspective

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Goals

- I plan to provide some historical perspectives of lead exposure and toxicology.
- I will also try to provide some perspective on the complexity of issues in determining the scientific basis for establishing realistic target levels of exposure that will balance practicality and safety for lead workers.

Historical Trends

- Over history, lead exposure and toxicology have gone through four phases:
 1. Overt toxicity
 2. Subtle toxicity
 3. Biochemical toxicity
 4. “Statistical” toxicity

Overt toxicity

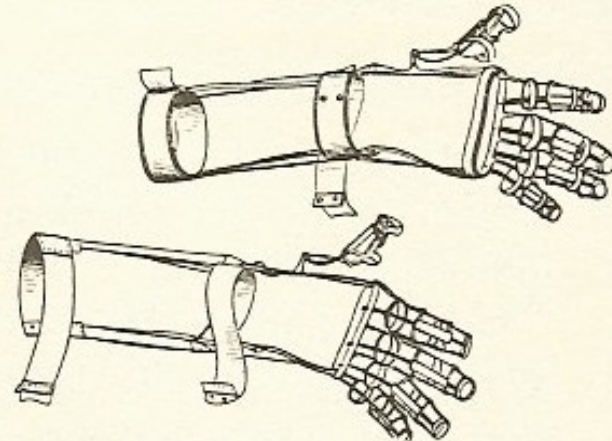
Overt toxicity results in objective signs and symptoms of lead poisoning

- The overt toxicity period extends from the dawn of mining and smelting of lead over 3000 years ago to the mid 1900s.
- It is still seen today in children with lead based paint exposure and occasionally in uncontrolled occupational or recreational exposures.

Wrist drop 1869



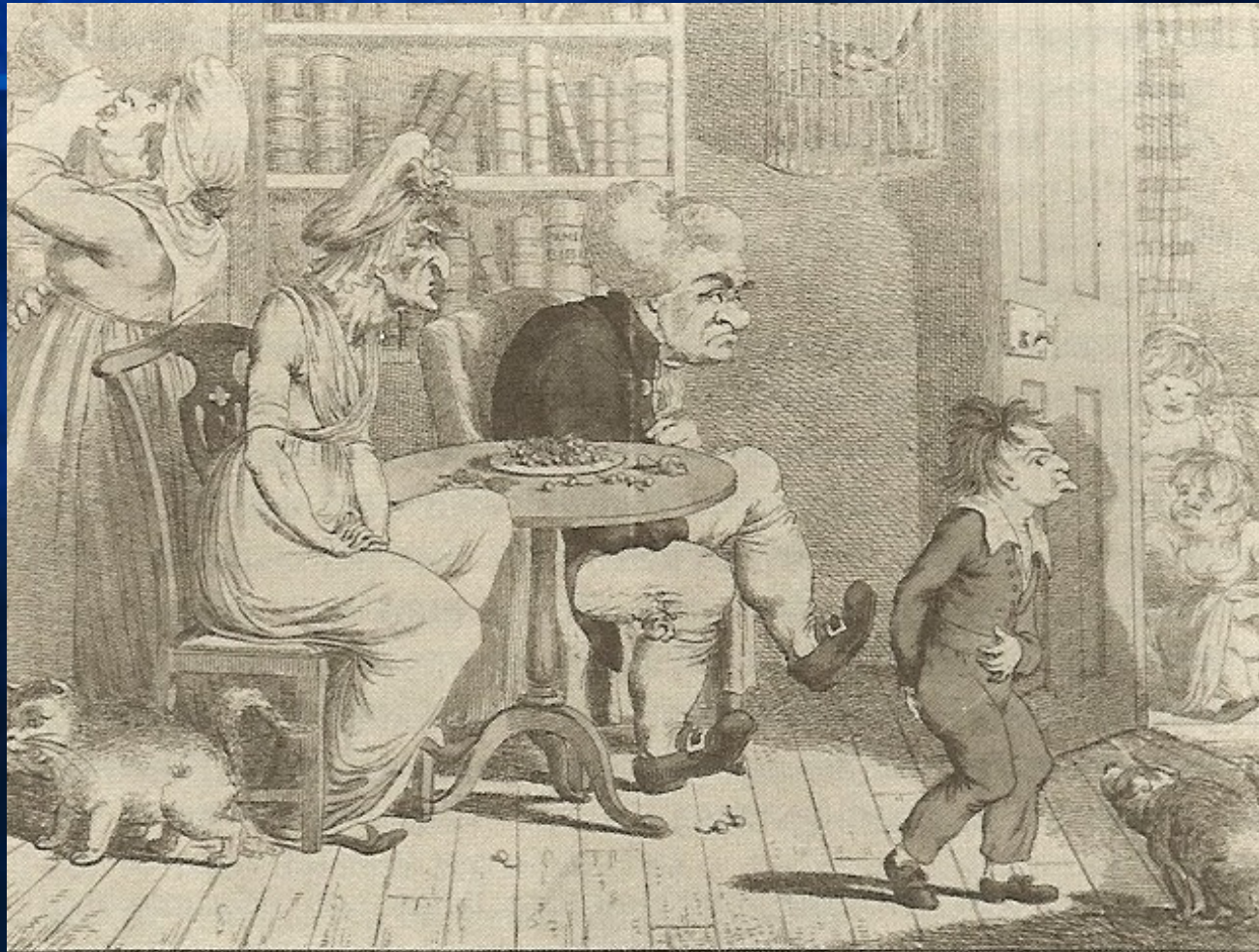
Lead palsy from use of "Laird's Bloom of Youth," from a photograph.



Dr. Hudson's extension apparatus for hands and fingers.

"Poison in the pot", Wedeen

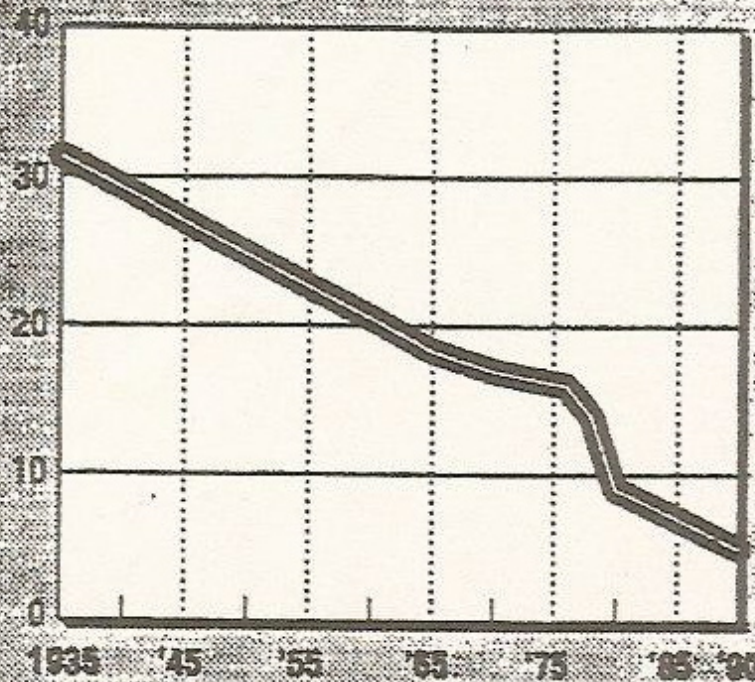
Leaded family portrait



THE DRY GRIPE'S or the Comforts of a HOT SUMMER.

U.S. Lead Levels Fall

In micrograms per deciliter of blood



Note: 1990 figure and those prior to 1976 are estimates based on various studies

A16 THE WALL STREET JOURNAL THURSDAY, SEPTEMBER 16, 1993

These median ranges were from reported US population studies of adults.

One can only imagine the lead levels of children during these years or before.

Despite the tendency to blame leaded gasoline, the major sources for lead were food, water, and paint

Sources of lead - Finland 1971

Source	Daily intake (μg)		Amount absorbed (μg)	
	Mean	Range	Mean	Range
Food	169	71—310	14	6—25
Beverages	35	4—116	3	trace —9
Air	20	11—33	7	4—12
Total	224	86—459	24	10—46

Estimated lead levels in today's diet is 1/10 the level in the 1960's and 1970's, < 35 ug total intake.

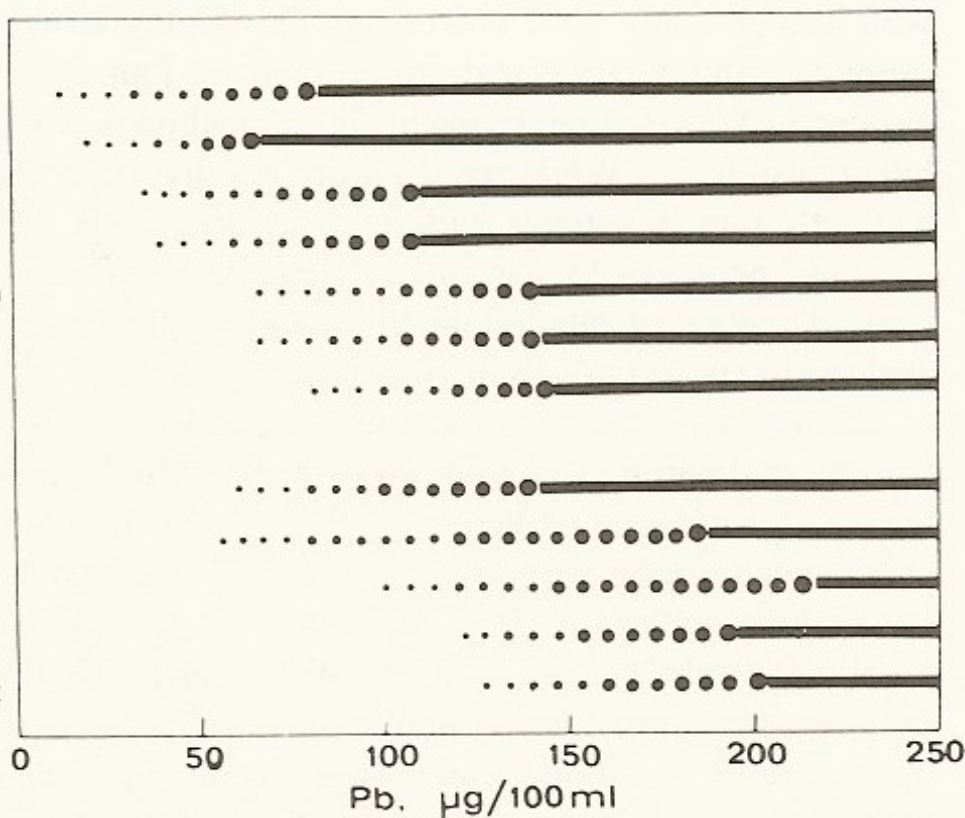
TABLE 1
Representation of the Relationship of Blood Lead Levels to the Clinical Manifestations of Lead Poisoning in 1976^a

HEMATOLOGICAL SYMPTOMS

- ALA-D inhibition in RBC
- PP elevation in RBC
- ALA excr. increased in urine
- CP excr. increased in urine
- Shortening of RBC life span
- Reticulocytosis
- Anemia

OTHER SYMPTOMS

- Subjective symptoms
- Peripheral neuropathy
- Encephalopathy
- Colic
- Kidney function impairment



^a Kidney function impairment was not suspected when the blood lead concentration was less than 125 µg/dl.

(From Hernberg, S., in *Effects and Dose-Response Relationships of Toxic Metals*, Nordberg, G. F., Ed., Elsevier, New York, 1976, chap. 815. With permission.)

Subtle toxicity

- Prior to 1978, the standards of care were limited to blood lead ranges below which overt symptoms of toxicity were either mild or negligible.
- OSHA removal levels were set at 80 ug/dl and minimal monitoring requirements were mandated. Long time workers often exhibited some residual lead effects; palor, mild anemia, fatigue, subtle cognitive dysfunction.

Biochemical toxicity

- In 1978, OSHA established a new Lead Standard bringing removal levels for workers down to 60 ug/dl or an average of 50 ug/dl over 6 months.
- Long term target levels were set at maintaining exposure below 40 ug/dl for a lifetime.
- Testing for blood leads, ZPP/EP, kidney function and urine were implemented to look for objective or “biochemical” markers of toxicity. At levels below 40 ug/dl symptoms are negligible and lead effects mostly identified statistically within the normal ranges of function.

Decline in workers lead levels

- In 1978 at the onset of the OSHA Lead Standard, it was not thought possible to meet removal levels or long term target level of <40 ug/dl.
- It became apparent that with higher attention to hygiene, workstation air controls, respirators, showers and protective uniforms that lead levels could be reduced dramatically.
- Average worker levels in 1978 were in the 60-80s; today the average worker levels in most operations are <20 ug/dl and over 90% are below 30 ug/dl, rarely over 40ug/dl.

Statistical toxicity

- During my participation on the national AOEC panel to reassess the latest medical literature it became apparent that emphasis was going to be placed on bone lead levels as a method of assessing “cumulative” exposure.
- Bone lead testing of both populations and lead workers were demonstrating effects that did not correlate with previous blood lead research

Statistical toxicity

- Areas that were noted were:
 1. Renal effects,
 2. Blood pressure effects
 3. Neuropsychological changes.
- Bone lead levels were extrapolated to equivalent “cumulative blood lead index”, or CBLI, an averaging of blood leads x years of exposure

AOEC expert panel

- Bone lead data is very complex and the relationship to adult exposure over time may be quite different than lifetime exposures which were elevated in childhood.
- Based on the extrapolations from some studies, some members of the panel wanted to limit lifetime averages to 10 ug/dl or less
- Others on the panel suggested MRP removal at 20 ug/dl until blood lead levels reduced to below 10 ug/dl and still others felt that all workers should maintain lead levels below 20 ug/dl with an absolute maximum of 40 ug/dl

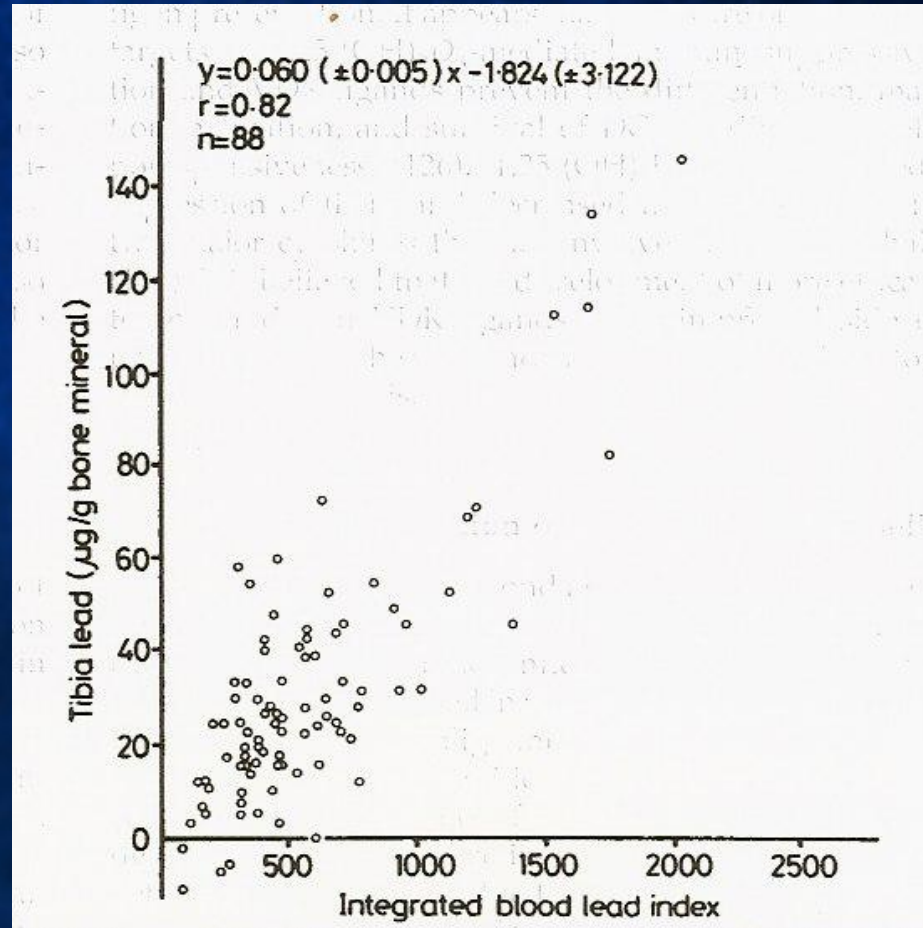
Problems with bone lead studies

- The most serious problem with interpreting and using data from older populations relates to the very high early life exposures that have residual effects in late adulthood
- Studies have shown that neuropsychologic, blood pressure and renal effects occur in childhood and early adulthood that may account for many of the current findings in epidemiologic studies

Problems with bone lead studies

- Workers entering the workplace with low body burden from remarkably lower early life exposure may have different accumulation and chronic effects than those found in occupational and population studies in the past
- Error rates increase as bone lead readings drop below the CBLI of 500mcg/year level
- Lack of standardization from different sites and research has resulted in inconsistent findings and reported effects

Bone lead vs CBLI



Problems with low lead studies

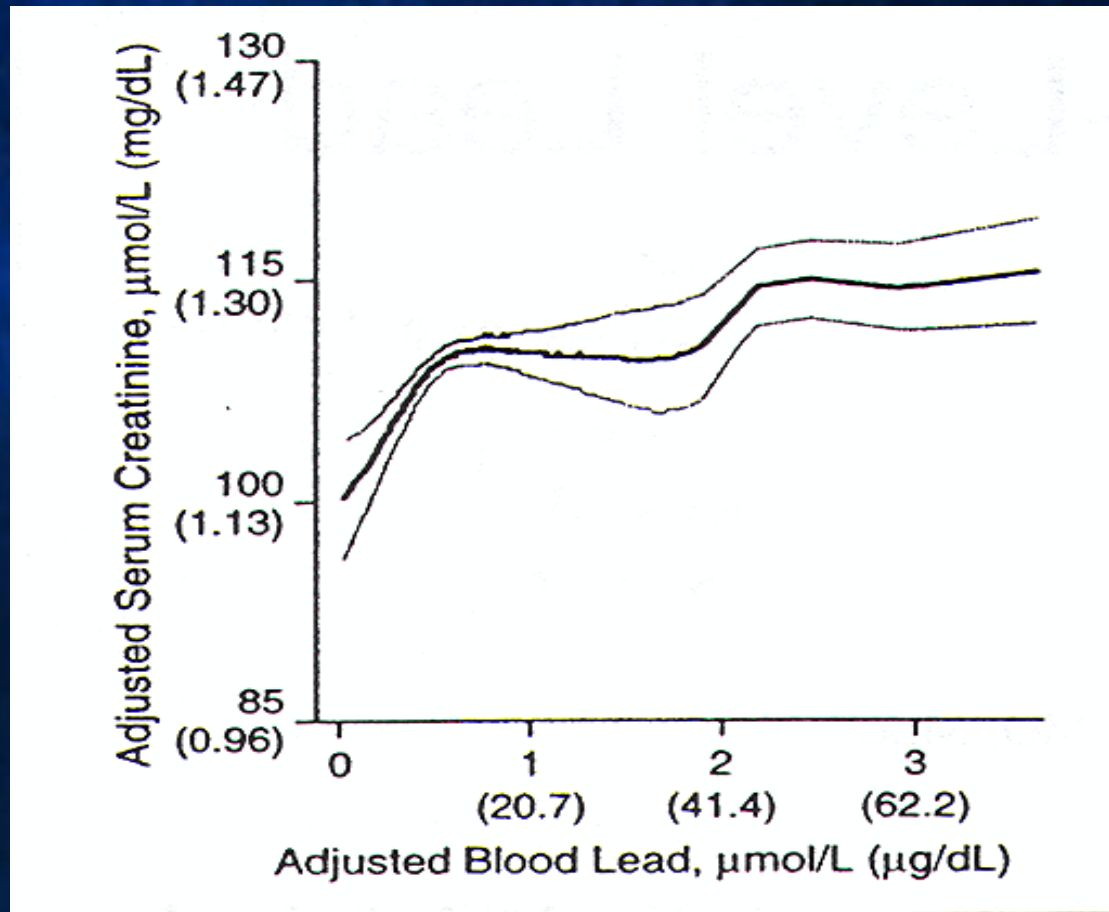
- At the lowest levels of exposure there are many factors that effect both the absorption, accumulation and toxicity of lead
- Nutritional status may greatly affect the studies of lead effects at lower levels
- Vitamin D, mineral intake (calcium, zinc, iron) and some B-vitamins alter all the above factors

Statistical toxicity - problems

- Statistical toxicity demonstrates a number of toxicologic aberrations
- The highest effects are found at the lowest levels and attenuate as lead levels increase, unlike traditional toxicity patterns in which there is a geometric increase in biomarkers of toxicity up to a maximum suppressive effect
- The standard model of toxicity is clearly shown in the heme metabolites, such as ALA, EP/ZPP

A longitudinal study of low level lead exposure and impaired renal function.

Kim, et al. 1996, JAMA vol 15



Inconsistencies in major areas

- Frequently effect size is small or the reported effects are inconsistent
- Effects of lead on blood pressure is a prime example of the inconsistencies between blood lead and bone lead studies and small effect size
- This projection of risk is not found in any of the occupational lead/BP studies to date

Inconsistencies in major areas

- Extrapolations from in the Hu/Cheng bone lead studies purport a 1.5-1.7 x increase in hypertension over a range of bone leads found in the Normative Aging Study
- There were no correlations between blood lead levels and PB variables in either study
- Hu's cross-sectional study showed correlation with tibia but not patella lead levels; Cheng's longitudinal study found patella, not tibia lead to reach levels of significance

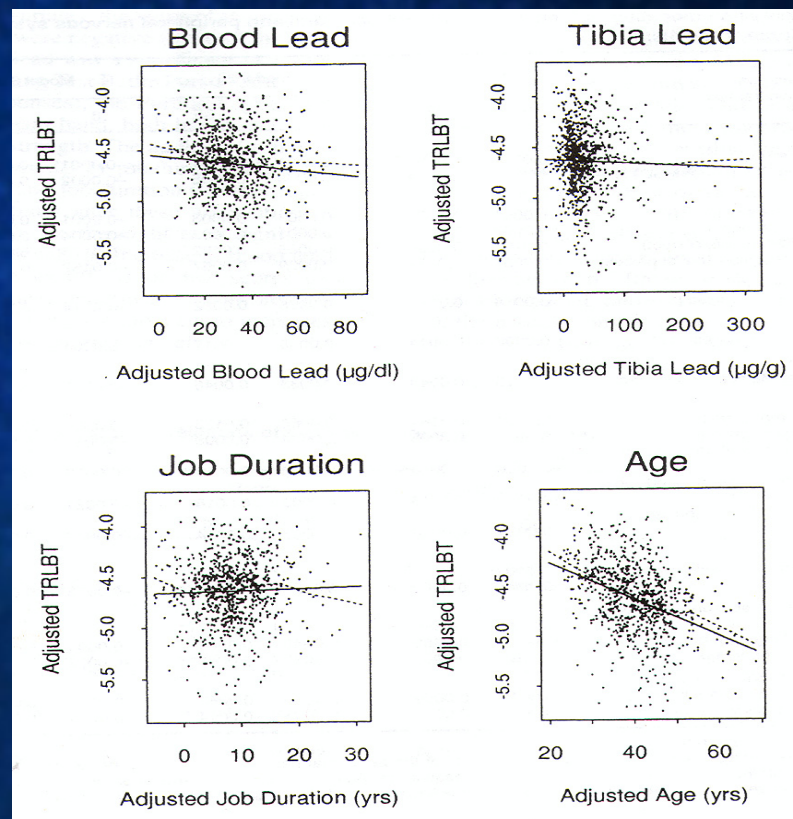
Blood pressure studies - blood lead, tibia lead, patella lead and CBLI VS BP/Hypertension

Study	# of Participants	PbB	Tibia Lead	Patella Lead	Mean (range) CBLI ug/yr	Comments
Hu et al. 1996	590	NS	+	NS	432 (160 - 780)	Normative Aging Study – NAS (population study)
Cheng et al. 2001	833	NS	NS	+	Similar to Hu et al	Normative Aging Study - NAS
Lee et al. 2001	798	NS*	+ systolic BP only	ND	262.4 (29 – 691gyrs)	Korean lead workers (relative to controls)*
Schwartz et al. 2000	543	+	NS	ND		Organolead workers
Korrick et al. 1999	*	NS	NS	+	n/a	Nurses Health Study
Parkinson et al. 1987	270	NS	ND	ND	TWA 48.6 ug/dl	lead workers - high PbB
Ehrlich et al. 1998	382	NS	ND	ND	579 (7-2681)	lead workers - high PbB

Neuropsychologic effects

- Neuropsychologic effects of lead are the most difficult to assess
- Inconsistencies are present throughout the ranges of bone and blood lead studies
- Meta-analyses and ongoing bone lead studies have done little to quantify safe levels of exposure for workers
- All bone lead population studies suffer from the same conflicting effects from very high early life exposures not present in today's workers

Graphics from the Schwarz study of Korean lead workers – Trail-Making Test B among 803 SK lead workers



Schwartz BS; Am J Epidem 2001

Current recommendations for lead workers

- Recently published recommendations by AOEC and in Environmental Health Perspectives suggest significant lowering of the exposure levels of all workers
- Industry has recognized that current research indicates that workers health may be affected at levels well below the current OSHA Standards and has been pro-active in achieving lower goals and exposure levels, a new and refreshing approach to past resistance to changing standards

Current recommendations for lead workers

- Recommendations by every major specialty now require assessment of the quality and strength of the research that supports specific aspects
- This assessment will require a thorough analysis of current and past literature for both the supportive and conflicting studies before firm guidelines are formulated
- Unfortunately, in the currently published “Guidelines”, this full assessment has been lacking making the specific recommendations less justifiable and reliable

Current recommendations for lead workers

- Recommendations should be a synthesis of practical, achievable goals that assess both risks and benefits of specific recommendations
- All occupations have risks inherent in the job
- The public health concerns for large populations may be far different than specific risks for an individual worker
- Longitudinal studies of today's workers with bone lead and CBLI assessment are needed to continually reassess the quality of future occupational standards