

# Ethical Issues for Biostatisticians

## Background on lead exposure



## Outline

- Low-dose lead exposure
  - Background: Exposure and effects
  - Older arguments (2001)
    1. Kaufman's critique
    2. Needleman's reply
  - More recent developments (2003-present)
    1. Canfield et al's results in *NEJM* 2003
    2. CDC's recommendations
    3. Gilbert & Weiss's response
- Precautionary principle



## Lead

- Lead (Pb) is a soft malleable heavy metal that is highly resistant to corrosion and has poor electrical conductivity
- Lead has no biological function in humans; known to be poisonous
  - Many believe that there is no safe level of exposure to lead
- Lead is readily absorbed, particularly by children and pregnant women
- The rate of uptake of lead decreases as the dose increases
- Lead distributes among three compartments: blood, soft tissue (kidney, bone marrow, liver, brain), and mineralizing tissue (bones, teeth)

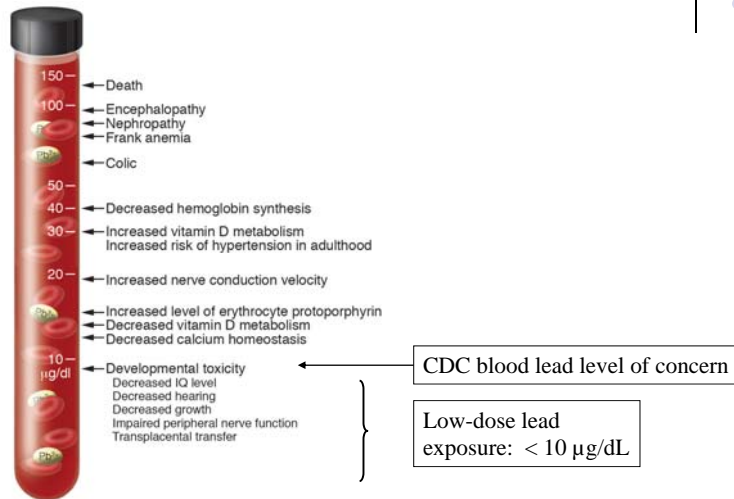


## Lead

- Primary lead exposure sources:
  - **Inhalation:** exhaust from **leaded fuel**, industry emissions, tobacco smoke, dust
  - **Ingestion:** **paint** (dust, chips), drinking water (pipes), soil (dust, food), ceramic dishes (food), **toys** (swallowing & mouthing charms, decorations, paint)
- Lead exposure causes acute effects (including death, at high enough doses) and chronic effects, including neurotoxicological effects (measured by lowered IQ, increased learning difficulties)
- “Prevention is the only plausible strategy” – treatment (chelation therapy) has not been shown to improve cognition, behavior, neuropsychological function (Rogan et al 2003)

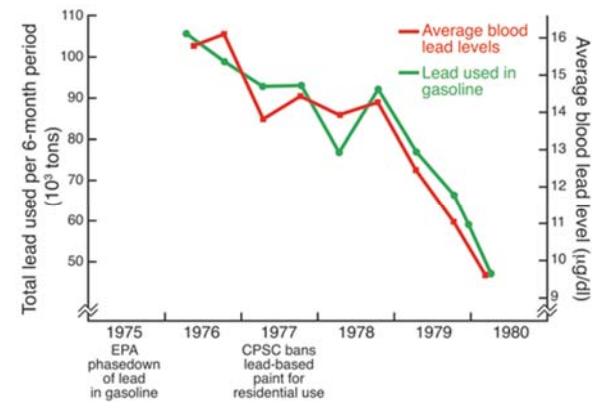


## Lead Health Effects (as a function of blood lead levels - BLL)



Source: Bellinger & Bellinger 2006

## Lead Exposure and Regulation – Policies Affect Public Health



Source: Bellinger & Bellinger 2006

## Kaufman's critique of low-dose lead effects on IQ loss

**Kaufman's message:** Studies are flawed by uncontrolled confounding, multiple comparisons, and errors in measurements. Results are overinterpreted.

- **Failure to control for important covariates (confounders)**
  - Omitted variables
  - Parental IQ is poorly measured
  - Lack of control for multiple comparisons
  - Comparisons use the highest vs. lowest exposure groups
  - Children's IQ measures have poor quality
- **Questionable interpretation of the IQ loss attributed to low lead levels**
  - No documented linear relationship
  - Scientific meaning of small changes in IQ
  - Societal consequences of lower IQs

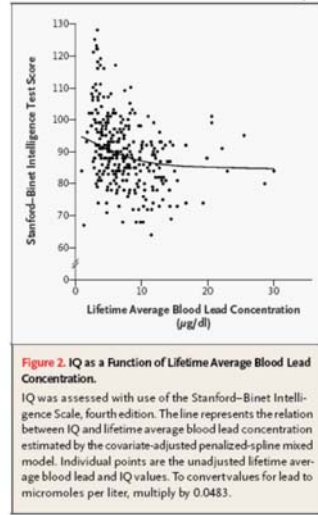
## Needleman & Bellinger's reply

- **Confounding**
  - IQ effect persists even with control for multiple different confounders and in studies designed to limit key confounders
  - Some variables are not confounders and don't warrant inclusion
  - Animal studies support the conclusions and aren't subject to confounding
- **Multiple comparisons**
  - Context is important and affects interpretation of findings
  - Rote application of the Bonferroni correction is inappropriate
- **Measurement error**
  - Nonsystematic and nondifferential measurement error tends to attenuate effects
  - Did not consider role in analysis: as confounder, exposure, outcome
- **Similar inference is supported by an array of additional endpoints**
  - Need to assess full investigations, not merely individual papers
- **Causal inference and epidemiology**
  - Evaluated the Hill criteria (temporality, experiment, gradient, plausibility and coherence, strength, consistency, specificity)
- **Precaution in the face of any residual uncertainty protects public health**

## Canfield et al (NEJM 2003) on intellectual impairment for low dose exposures



- Longitudinal assessment of BLL in 172 children; IQ tests at ages 3 and 5
- Inverse effect of lead on IQ; dose-response relationship was steepest at doses below 10  $\mu\text{g}/\text{dL}$
- Bellinger & Needleman 2003 reanalysis of the 48 lowest exposed children in another prospective cohort also showed a stronger effect if BLL on IQ loss than the estimate from the entire cohort



## CDC position – retain the blood lead level of concern at 10 $\mu\text{g}/\text{dL}$



### Why not change the blood lead level of concern at this time?

- “Recent studies suggest that adverse health effects exist in children at blood lead levels less than 10  $\mu\text{g}/\text{dL}$ . In the past the Centers for Disease Control and Prevention (CDC) has lowered the level considered elevated in response to similar reports.”
- Provides three reasons not to lower the level of concern
- “The recent studies support making primary prevention of childhood lead poisoning a high priority for health, housing, and environmental agencies at the state, local, and federal levels.”

## CDC position – retain the blood lead level of concern at 10 $\mu\text{g}/\text{dL}$



### CDC’s reasons not to lower the level of concern:

- No effective clinical interventions are known to lower the blood lead levels for children with levels less than 10  $\mu\text{g}/\text{dL}$  or to reduce the risk for adverse developmental effects.
- Children cannot be accurately classified as having blood lead levels above or below a value less than 10  $\mu\text{g}/\text{dL}$  because of the inaccuracy inherent in laboratory testing.
- Finally, there is no evidence of a threshold below which adverse effects are not experienced. Thus, any decision to establish a new level of concern would be arbitrary and provide uncertain benefits.

## Gilbert and Weiss’s Response



- No effective clinical interventions are known to lower the blood lead levels for children with levels less than 10  $\mu\text{g}/\text{dL}$  or to reduce the risk for adverse developmental effects.  
**Response:** CDC confuses medical with environmental interventions. The appropriate goal is to eliminate the need for medical intervention.
- Children cannot be accurately classified as having blood lead levels above or below a value less than 10  $\mu\text{g}/\text{dL}$  because of the inaccuracy inherent in laboratory testing.  
**Response:** Adequate laboratory procedures are available to detect BLL down to 2  $\mu\text{g}/\text{dL}$ .
- Finally, there is no evidence of a threshold below which adverse effects are not experienced. Thus, any decision to establish a new level of concern would be arbitrary and provide uncertain benefits.  
**Response:** While the statement that there is no evidence of a threshold is correct, the conclusion does not follow. The current action level of 10  $\mu\text{g}/\text{dL}$  gives false and inaccurate guidance to health professionals. Exposure prevention is needed for levels lower than the current action level. Any detectable blood lead level is unacceptable.

## Precautionary Principle



- Idea: “Action should be taken to prevent harm to the environment and human health, even if scientific evidence is inconclusive.” Meyers
- Key elements:
  - **Anticipatory action:** Duty to anticipate and prevent harm
  - **Right to know:** Community has the right to know about potential impacts. The burden to provide this information is with the proponent, not the public.
  - **Alternatives assessment:** Examine a full range of alternatives and select the one with least potential impact. Include the alternative of doing nothing.
  - **Full cost accounting:** Duty to consider all foreseeable costs, even if not included in the initial price.
  - **Participatory decision process:** Decisions are transparent, participatory, and informed by the best available information

## Precautionary Principle



- Goal: Reduce risk and harm to the environment and human health
- Working principle: Unnecessary risk that is not freely chosen is never acceptable
- Contrast: Tradition of risk assessment
  - In public health, combine the evidence that an agent is toxic (i.e. causes adverse health effects) with the distribution of exposure to that agent to estimate its effects on the population, i.e. the probability of an adverse effect
  - Approach is good for quantifying what we know and can estimate accurately (e.g. the weight a bridge will bear). Risk assessment is not good at assessing subtle and unknown risks, and incorporating uncertainty
  - Lack of proof of harm is often misinterpreted as proof of safety

## Precautionary Principle



- Precautionary approach: Principle that scientific uncertainty argues for precaution and alternatives, not freedom to pollute in the absence of proof of harm.
- Precaution is the operating principle for defining regulations in the European Union and San Francisco, but not for the U.S. government

## Precaution and Exposure



Distinguish perspectives:

- Environmental contaminants, e.g.
  - Lead
  - Air pollution
- Individual exposures to oneself and others in the immediate environment, including a fetus, e.g.
  - Smoking
  - Alcohol