



Lead: health effects of exposures in pregnancy and early childhood

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Objectives

- Discuss the absorption and distribution of lead in the body
- Provide some historical perspective of our understanding of lead toxicity
- Use cases to illustrate toxic health effects of lead in children
- Discuss treatment, including chelation



Your work makes a difference!

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Lead is a toxic (poisonous) metal.

Lead is a toxic (poisonous) metal

- Lead exposure: When a person comes in contact with lead by **swallowing** or **breathing in** lead or lead dust.
- Even low levels of lead can adversely affect the health of children.



No safe blood lead level (BLL) has been identified.

The amount of lead in blood is the blood lead level (BLL), measured in micrograms of lead per deciliter of blood ($\mu\text{g}/\text{dL}$).

CDC uses a blood lead reference value (BLRV) to identify children who should be referred for follow up.

The BLRV is based on the U.S. population of children ages 1-5 years who are in the highest 2.5% of children when tested for lead in their blood in the National Health and Nutrition Environmental Survey (NHANES).

<https://www.cdc.gov/nceh/lead/data/blood-lead-reference-value.htm>



What is a “high” blood lead level?

Year	Blood lead level ($\mu\text{g}/\text{dL}$)	Interpretation*
1960	60	NA
1970	40	Undue or increased lead absorption
1975	30	Undue or increased lead absorption
1978	30	Elevated blood lead level
1985	25	Elevated blood lead level
1991	10	Level of concern
2012	5	Reference value
2021	3.5	Reference value

Abbreviation: NA = not available.

* <https://stacks.cdc.gov/view/cdc/61820>

Blood lead levels in U.S. children have declined.

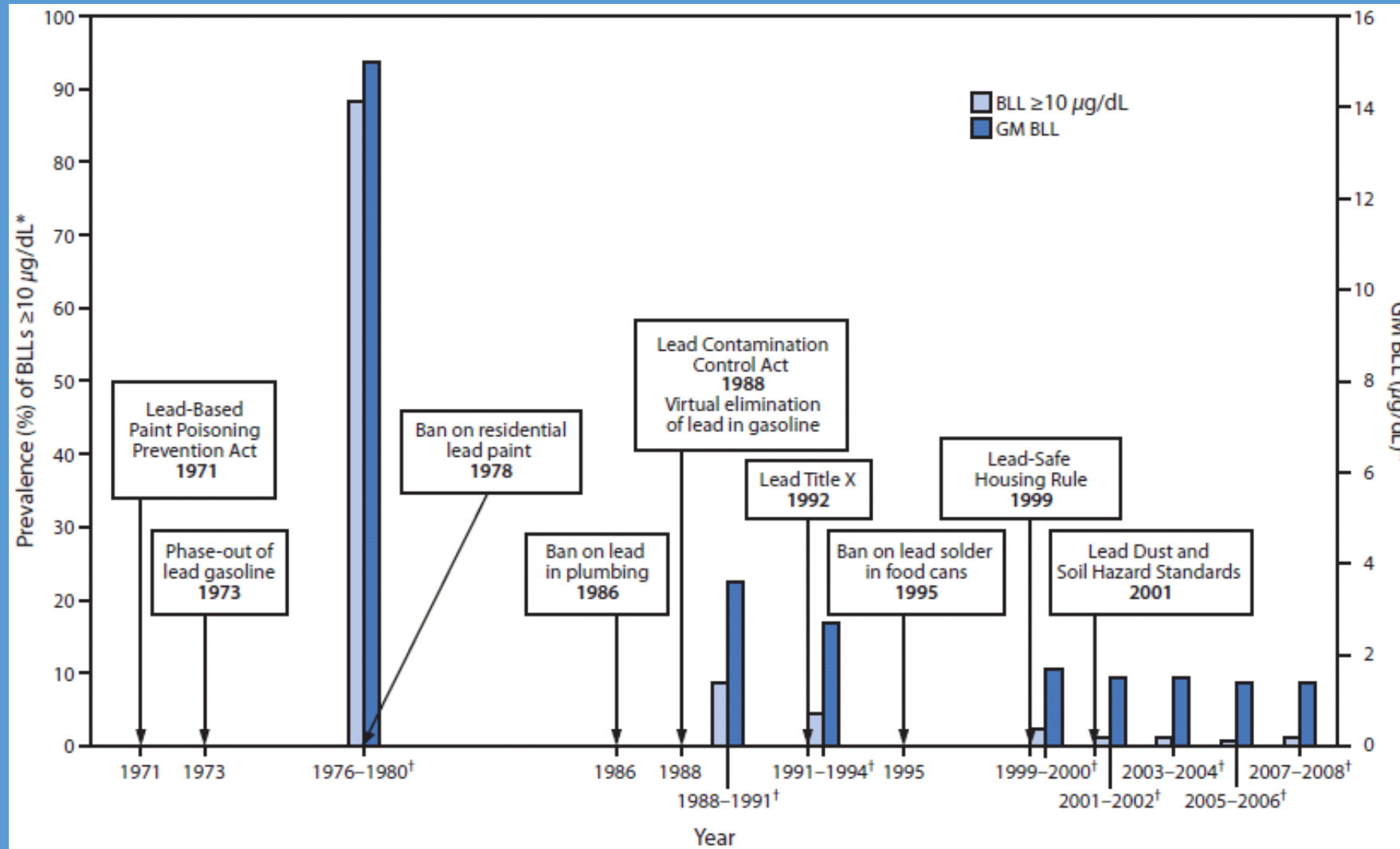


Image from https://www.cdc.gov/mmwr/preview/mmwrhtml/su6104a1.htm?s_cid=su6104a1_x

Current lead levels in children

- 1/2 million children have blood lead levels > blood lead reference value of 3.5 ug/dl (the level where action should be initiated)
- Healthy People 2030 goal: reduce BLL in children 1 to 5 years old; target 1.18 ug/dl

<https://www.cdc.gov/nceh/lead/overview.html>

Children can be exposed to lead by swallowing or inhaling it*:

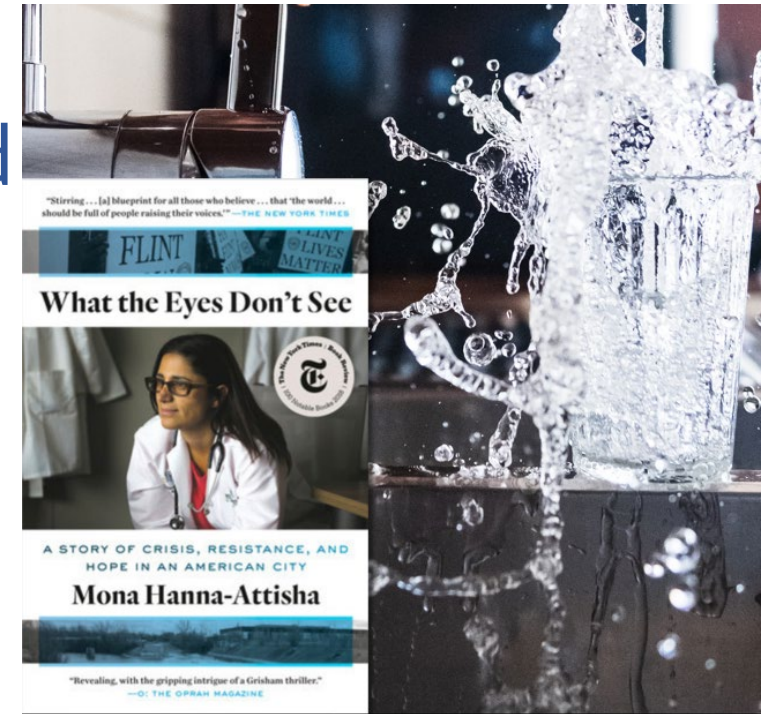
Lead-based paint in homes and buildings built before 1978 (currently 2.6 million households in the US where young children exposed to lead)

Contaminated **soil** from exterior lead-based paint, car exhaust, and factories using lead

Contaminated **drinking water** delivered lead plumbing materials

*absorption through the skin is not a significant exposure route for inorganic lead

Source: <https://www.cdc.gov/nceh/lead/prevention/sources.htm>



Lead Poisoning: many sources

Epidemiologic Notes and Reports

Lead Intoxication Associated with Chewing Plastic Wire Coating — Ohio

Recreation

Pool Cue Chalk: A Source of Environmental Lead

Food

Vol. 47 / No. 48

MMWR

Lead Poisoning Associated with Imported Candy and Powdered Food Coloring — California and Michigan

Sources from hobbies

Epidemiologic Notes and Reports

Lead Ingestion Associated with Ceramic Glaze — Alaska, 1992

FIGURE. Heart-shaped charm bracelet that is the subject of the voluntary recall announced March 23, 2006, by Reebok International Ltd. and the Consumer Product Safety Commission



Photo/Consumer Product Safety Commission

Adult Lead Exposure Sources

Occupational exposure:

- *abatement/cleanup, building demolition*
 - *renovation, remodeling, painting*
- *Manufacturing lead-containing products*
 - *Work with firearms/ at a firing range*
 - *Welding*
 - *Recycling*

Non-occupational exposure:

- *recreational activities/hobbies*
 - *Sometimes food and drink*
- *Take-home residues from work*

<https://www.cdc.gov/nceh/lead/prevention/sources/jobs-hobbies-activities.htm>

TABLE 1

Jobs and Industries with Potential Lead Exposure

<i>General Industry</i>	
Lead production or smelting	Battery manufacturing or recycling
Brass, bronze, copper, or lead foundries	Automotive radiator repair
Ammunition/explosives production	Lead soldering
Scrap metal handling	Ceramic manufacturing
Firing ranges	Cable/wire stripping, splicing or production
Machining or grinding lead alloys	Rubber manufacturing
Manufacture of radiation shielding	Plastics manufacturing
Repair/replacement of refractory material in furnaces	Leaded glass manufacturing
Ship building/repairing/breaking	Paint/pigment manufacturing
Mining	

Non-occupational and Environmental Sources of Lead Exposure

Remodeling or painting pre-1978 housing	Lead solder in stained-glass artwork
Peeling paint	Lead-soldered cans
Ethnic medicines or folk remedies (e.g., azarcon, greta, pay-loo-ah, kandu, some Ayurvedics)	Lead-contaminated candies
Pica (ingestion of lead-containing nonfood items, e.g., soil or ceramics, plaster, or paint chips)	Backyard scrap metal recycling
Retained lead bullet or fragments	Moonshine (liquor from a homemade still)
Melting lead for fishing weights, bullets, or toys	Antique pewter plates, mugs, utensils, toys
Imported vinyl miniblinds	Imported brass or bronze kettles, cookware
Recreational target shooting	Lead-glazed tableware or cooking vessels
Lead-contaminated drinking water supply	Leaded crystal tableware
Using lead glazes for ceramics	Mine tailings
Painting/stripping cars, boats, bicycles	Beauty products such as kohl eye make-up, certain hair dyes

Why are young children more susceptible to lead poisoning?

- Hand to mouth behavior
- Sensitivity of developing organs
- Incomplete development of blood-brain barrier up to 36 months of age increases lead entry
- Take in more food and water per body mass
- Children have higher metabolic rates and deposit 2.7x more lead in lung tissue than adults
- Absorption 5-10x greater (Children absorb 40-50% of ingested lead vs 10-15% absorption for adults)
- Absorption increased with deficiency of iron, calcium and possibly zinc

Reference: Goldfrank's Toxicologic Emergencies , Ninth Ed. , 2011 McGraw-Hill

Hand to mouth behavior— An efficient method for lead absorption in young children!



Photo used with permission from the UNC Institute for the Environment

Distribution, Persistence and Excretion of Absorbed Lead

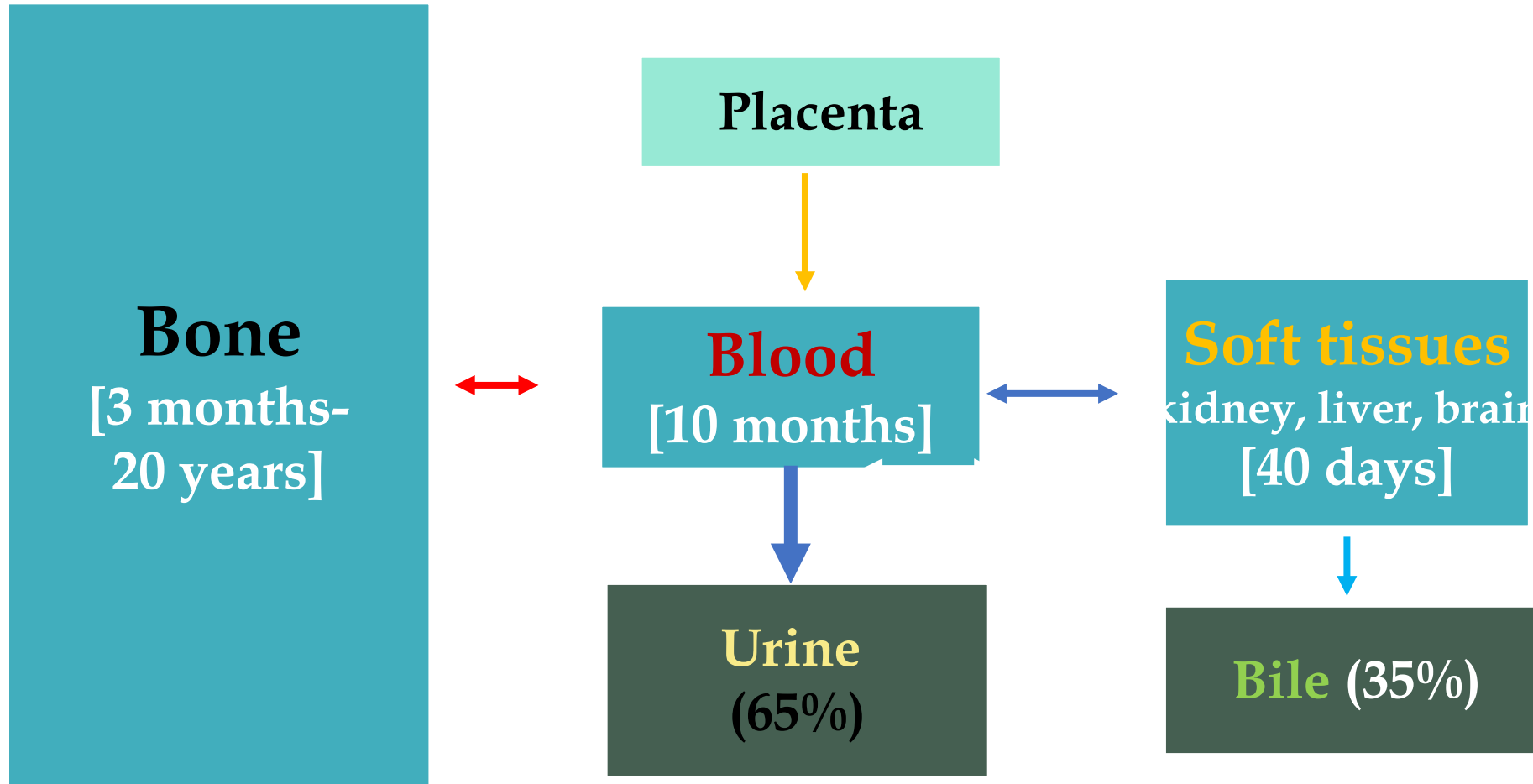




Figure 7. Long Bone Radiograph of Hands – “lead lines” shown as increased density on the metaphysis (growth plate) of the proximal segments of phalanges and distal segments of ulna and radius in a 5-year-old male with radiological growth retardation and BLL of 37.7 $\mu\text{g}/\text{dL}$ (Photo courtesy of Dr. Celsa López, Clinical Epidemiologic Research Unit, IMSS, Torreón, México).

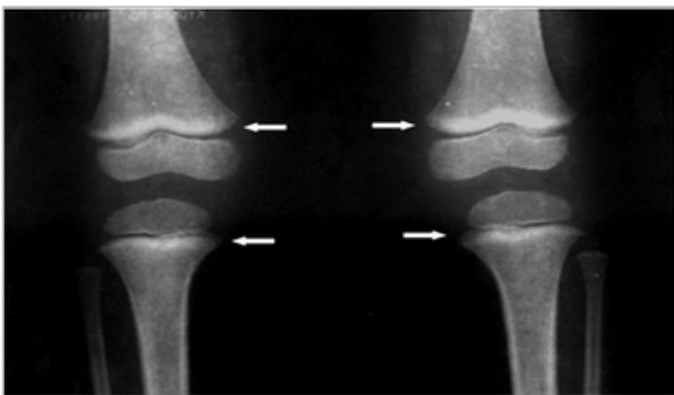


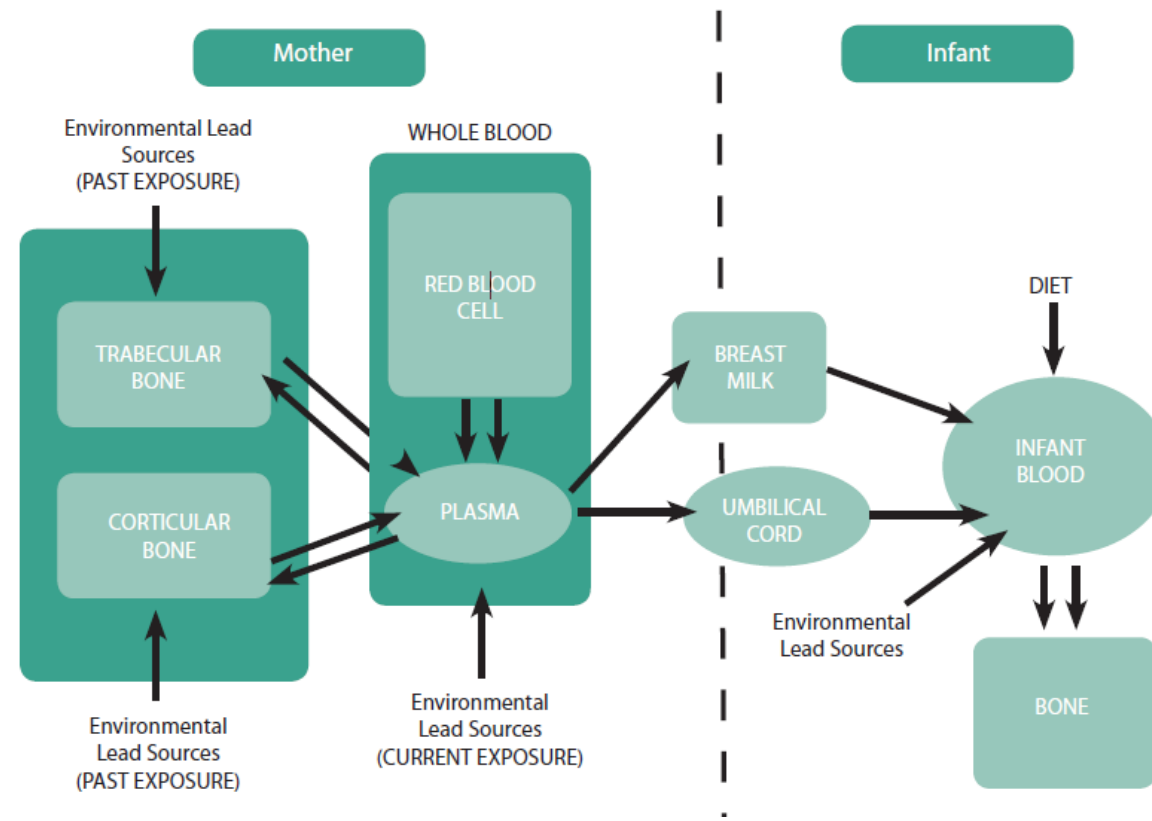
Figure 8. Long Bone Radiograph of Knees – “lead lines” in three-year old girl with BLL of 0.6 $\mu\text{g}/\text{dL}$. Notice the increased density on the metaphysis growth plate of the knee, especially in the femur (Photo courtesy of Dr. Celsa López, Clinical Epidemiologic Research Unit, IMSS, Torreón, México).

Bone-to-Blood Lead Transfer

- ✓ Bone lead maintains blood lead levels long after exposure occurs
- ✓ Increased transfer from bone to blood with **pregnancy**, lactation, menopause, physiologic stress, chronic disease, hyperthyroidism, kidney disease, broken bones, advanced age, and calcium deficiency

Lead and Reproductive Health

Figure 3-1. Major Lead Exposure Pathways from Mother to Infant



- Also associated with decreased sperm counts (BLL 30-40 $\mu\text{g}/\text{dL}$)

<https://www.cdc.gov/nceh/lead/docs/publications/leadandpregnancy2010.pdf> , ACOG, 2012

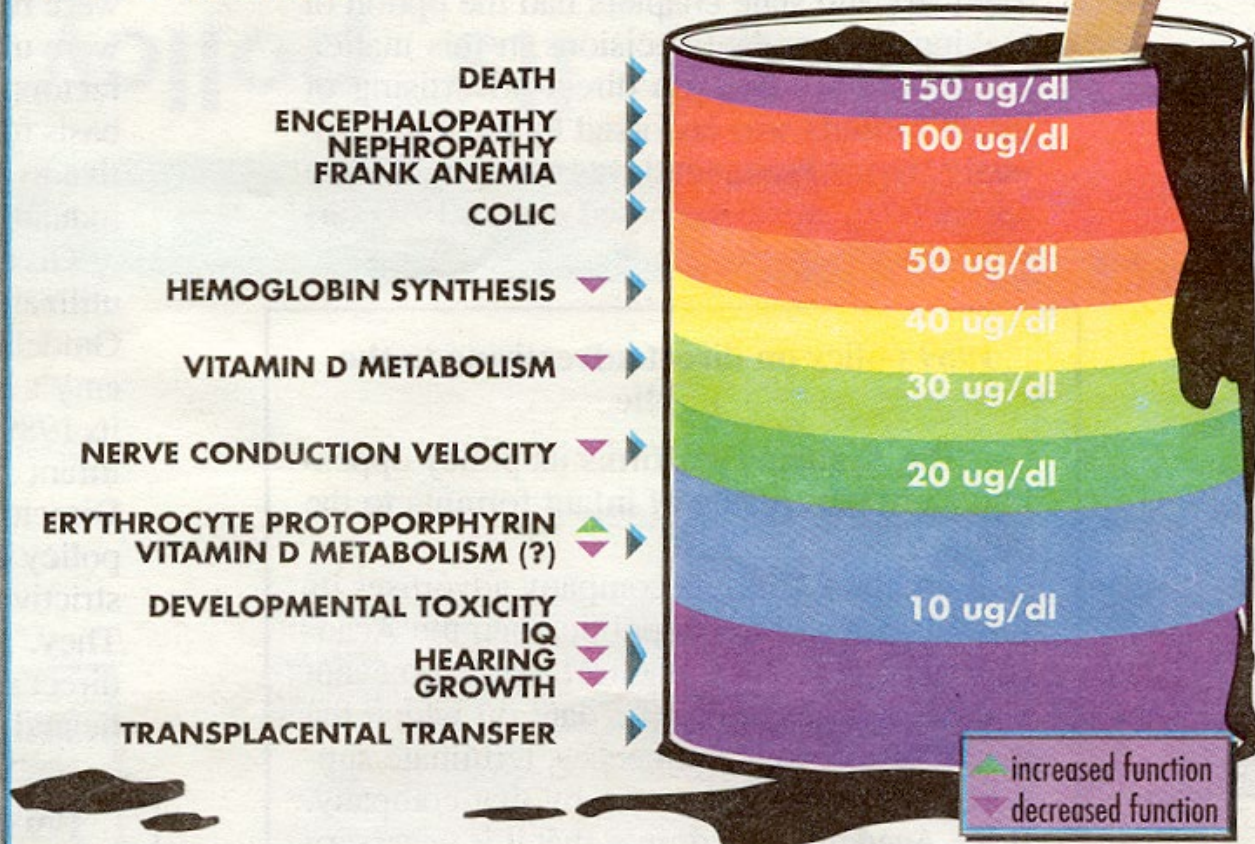
Risks of elevated blood levels during pregnancy

- Harm to baby's kidneys, brain and nervous system
- Learning or behavior problems in childhood
- Maternal hypertension
- miscarriage
- Premature birth
- Low birth weight

<https://www.cdc.gov/nceh/lead/prevention/pregnant.htm>

INORGANIC LEAD:

The Lowest Observed Effects in Children



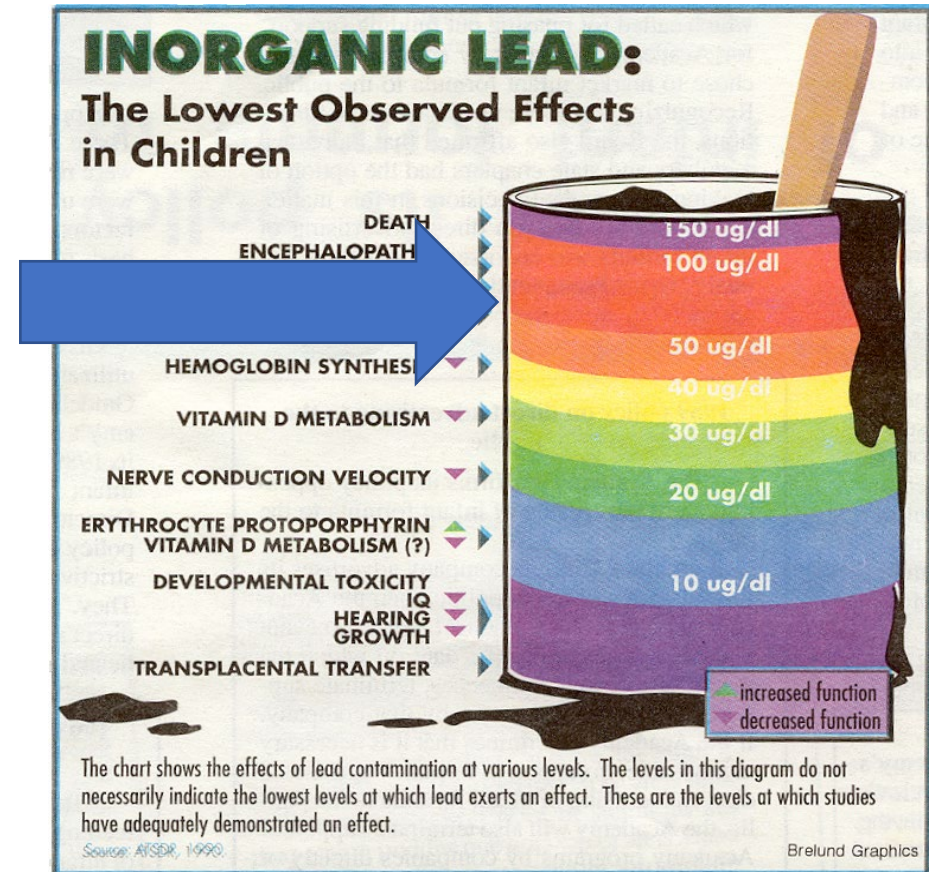
The chart shows the effects of lead contamination at various levels. The levels in this diagram do not necessarily indicate the lowest levels at which lead exerts an effect. These are the levels at which studies have adequately demonstrated an effect.

Source: ATSDR, 1990.

Brelund Graphics

Symptoms of Acute Lead Poisoning

- GI: Anorexia, constipation, abdominal pain, vomiting
- Neurologic: Irritability, overactivity, lethargy, ataxia
- Severe: Seizures, coma, hypertension, papilledema, cranial nerve paralysis
- Long-term: often with permanent brain damage (impaired cognitive and/or motor function), growth failure



Findings Associated with Chronic Lead Poisoning

- Malaise; fatigue
- Anemia
- Abdominal pain; anorexia, nausea, vomiting, constipation.
- Headache, ataxia, seizures, coma
- Increase in dental caries
- Delays in growth
- Delayed development, speech
- Altered behavior
- Psychoeducational problems (ADD)

Chronic lead poisoning even affects adults:

- Increase in hypertension, heart attacks, strokes
- 2 fold increase in CV death as adult if poisoned as child

Let's look at some real cases...

Case 1: North Carolina, 2017

- 13 month-old child with developmental delay
- A confirmed blood lead level was 22 $\mu\text{g}/\text{dL}$ (lead poisoning)
- The child's home was built after 1978 and no lead paint hazards were found
- Family of SE Asian/Indian origin

Balguti kesaria

- An Ayurvedic medicine, *Balguti kesaria*, that the parents had been giving the child was found to contain 220mg/kg lead
- NC reported to the FDA
→ August 2017 Safety Alert



<https://www.fda.gov/drugs/drugsafety/ucm570237.htm>

Safety Alerts for Human Medical Products

2018 Safety Alerts for Human Medical Products

2017 Safety Alerts for Human Medical Products

Balguti Kesaria Ayurvedic Medicine: FDA Warning - High Levels Of Lead

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[Posted 08/04/2017]

AUDIENCE: Consumer, Health Care Professional

ISSUE: The U.S. Food and Drug Administration is warning parents and caregivers not to use "Balguti Kesaria (or Kesaria Balguti) Ayurvedic Medicine" due to the risk of lead poisoning.

FDA has not reviewed this product for safety or effectiveness. Exposure to lead can cause serious damage to the central nervous system, the kidneys and the immune system. In children, chronic exposure to lead—even at low levels—is associated with impaired cognitive function, including reduced IQ, behavioral difficulties, and other problems.

BACKGROUND: This product is sold online and manufactured by multiple companies, including Kesari Ayurvedic Pharmacy in India. Individuals have also mailed or brought the product into the United States. "Balguti Kesaria Ayurvedic Medicine" is used with infants and children for a variety of conditions including rickets, cough and cold, worms and dentition (teething).

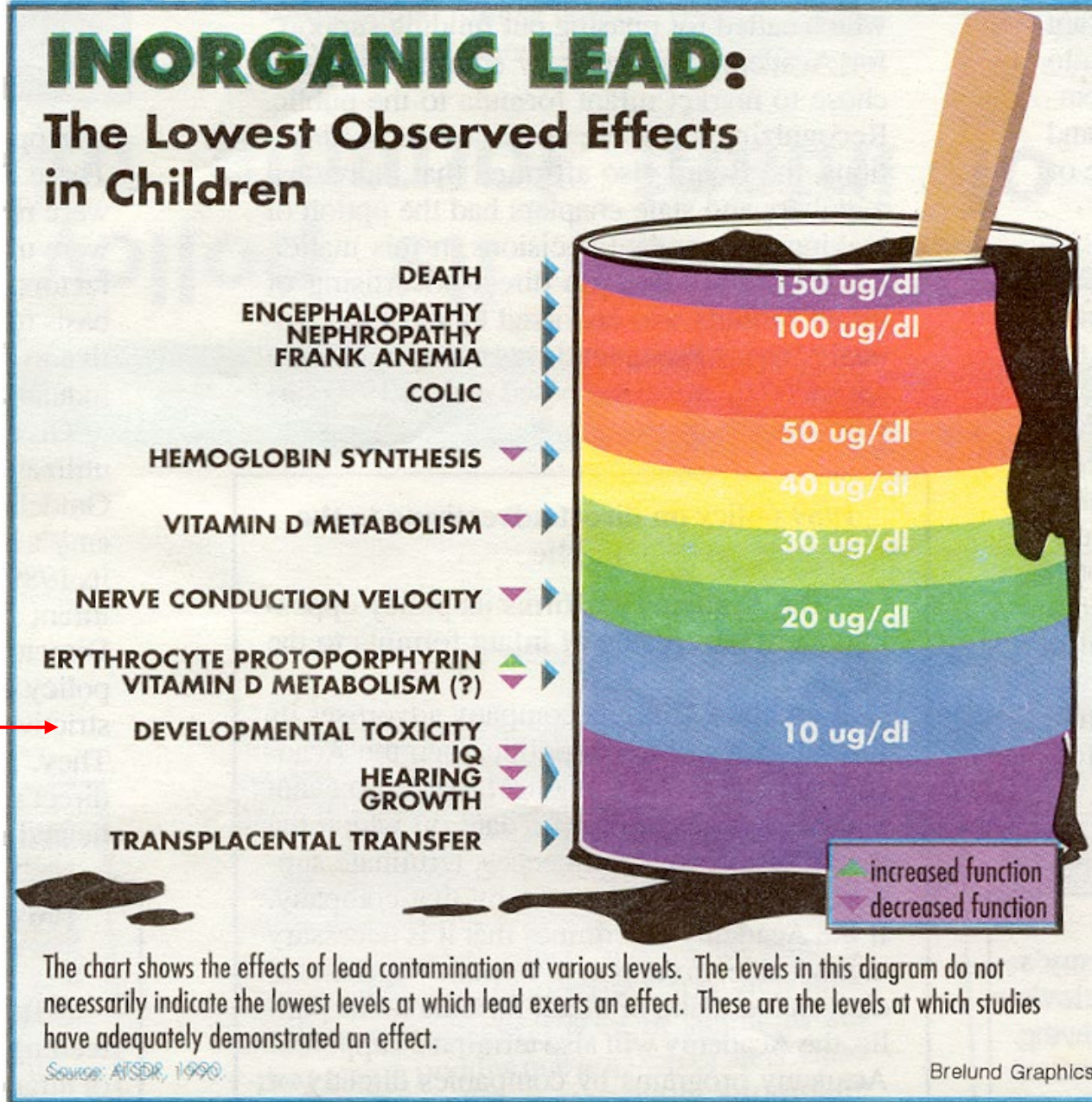
FDA initially learned of this risk from the North Carolina Division of Public Health after the product was tested and found to contain high levels of lead. FDA was also notified by the Michigan Department of Health and Human Services of high levels of lead in two children who were given this product. Michigan's testing also found high levels of lead in the product. To date, FDA has received one adverse event report of high levels of lead and developmental delays in a child who was given this product.

RECOMMENDATION: Anyone who is using this product or giving it to a child should stop immediately and consult a health care professional.

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Developmental



Health Effects at Low Levels of Exposure

“There is evidence that at low levels of lead exposure, biomarkers of cumulative lead exposure, such as lead in bone, may be associated with an adverse impact on neurocognitive function that is not reflected by measurement of lead in blood.”

(Shih et al., 2007; Bandeen-Roche et al., 2009; Weuve et al., 2009)

Blood Lead Level	Health Effects
Blood lead levels below 5µg/dL	<p>Children: Decreased academic achievement, decreased IQ, and decreases in specific cognitive measures, increased incidence of attention-related behaviors and problem behaviors</p> <p>Adults: Decreased kidney function, maternal blood lead associated with reduced fetal growth</p>
Blood lead levels below 10µg/dL	<p>Children: Delayed puberty, reduced postnatal growth, decreased IQ and decreased hearing</p> <p>Adults: Increased blood pressure, increased risk of hypertension, and increased incidence of essential tremor</p>

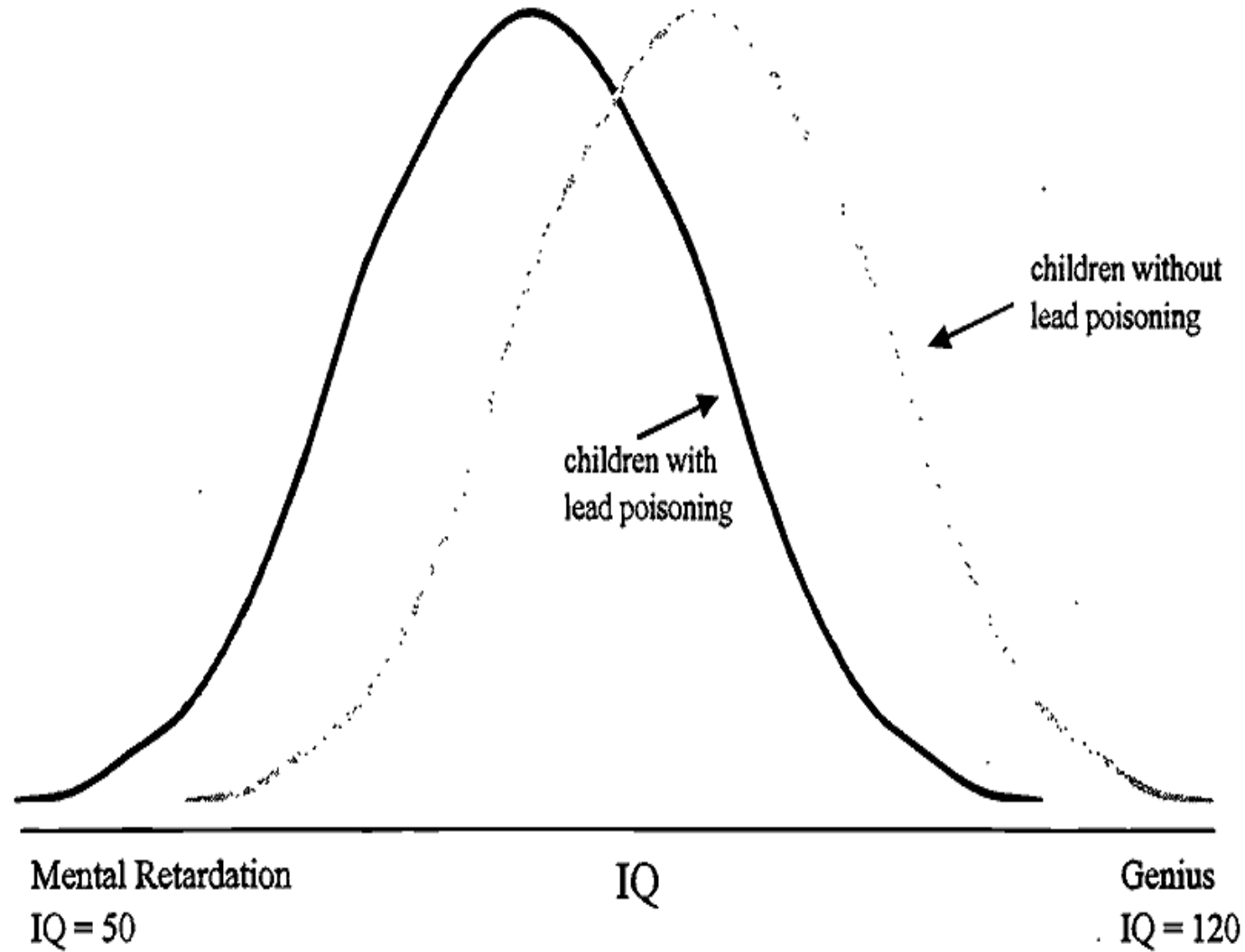
<https://www.niehs.nih.gov/health/topics/agents/lead/index.cfm>

Cognitive Effects at Low Lead Levels

Problems at Low Lead Levels

- Canfield et al. 2003 studied BLLs from children (n=172) at 6,12,18,24,36,48,60 months
- Stanford-Binet IQ test at age 3 and 5 years
- Each BLL increase of 10 $\mu\text{g}/\text{dL}$ associated with 4.6 decrease in IQ.
 - Relationship was non-linear decrease in IQ in those with BLL of 1-10 $\mu\text{g}/\text{dL}$

Canfield RL, Henderson CR, Jr, Cory-Slechta DA, et al. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med. 2003



Case 2: North Carolina

- 2 year old boy with a capillary BLL of 18
- Venous BLLs 12 → 13 → 12 → 12 → 7
- Symptoms: constipation, developmental delay, behavioral problems
- Risk assessment: child bites his nails, licks furniture and chews toys
- Father works in a plant that produces lead; BLL dropped to 7 after father changed jobs
- Sibling tested and had an elevated blood lead level

Case 3: North Carolina, 2018

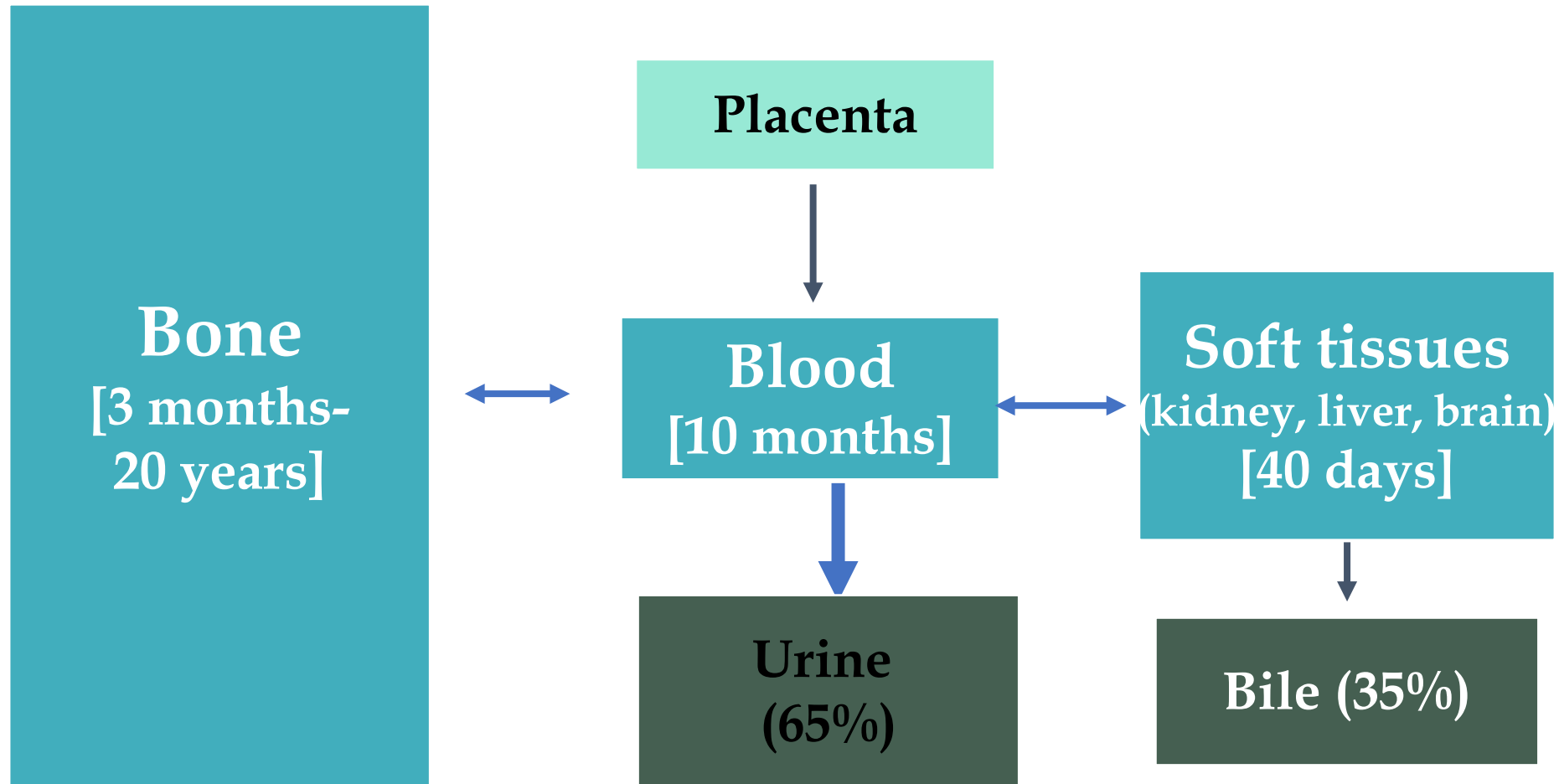
- 12 month-old girl taken for routine screening
- No symptoms of concern, but history of constipation
- Confirmed BLL of 65.9 $\mu\text{g}/\text{dL}$
- Referred for hospital admission
- Abdominal xray: no foreign body
- Labs: mildly decreased hemoglobin=anemia
- Admitted for chelation with DMSA (succimer)

Case 3 (continued): source of exposure

- History of spending increasing amounts of time in a shooting range owned by a family member
- Older sibling also confirmed to have lead poisoning
- Case patient BLLs: January = 66 → chelation
June = 47
August = 42

??? Why isn't the blood lead level dropping more quickly ???

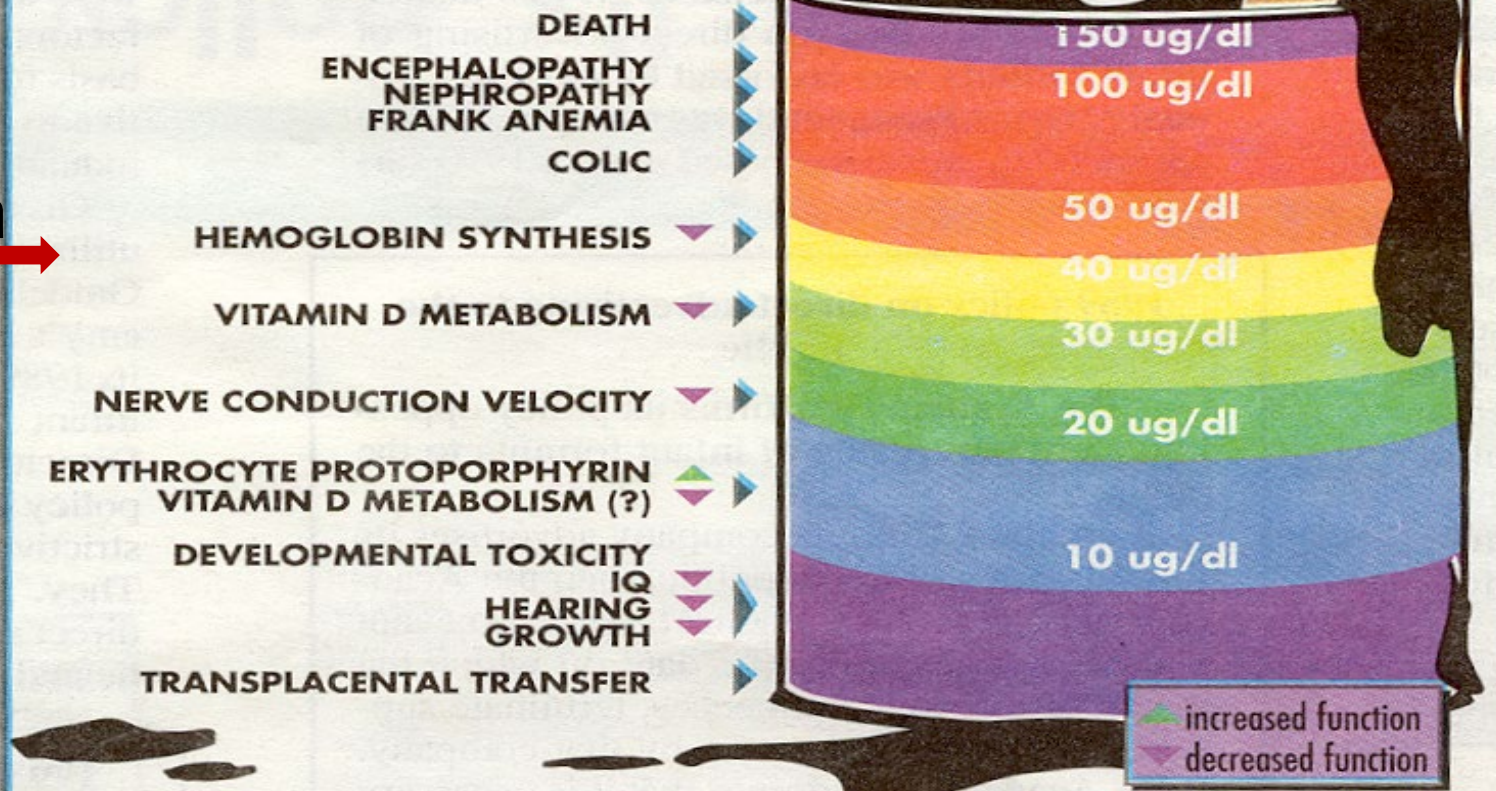
Most absorbed lead is stored in bone



INORGANIC LEAD:

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Anemia →



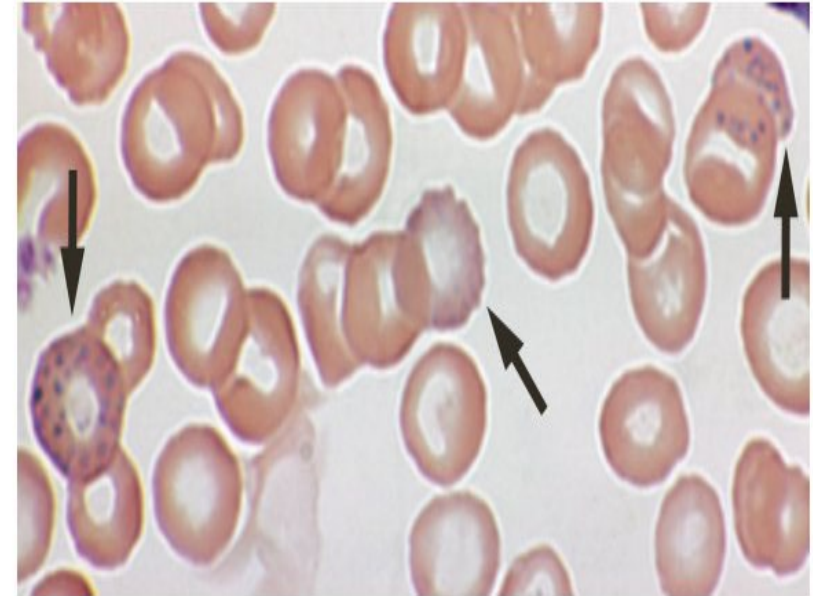
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Source: ATSDR, 1990.

Brelund Graphics

How lead causes anemia (low hemoglobin)

- Inhibits enzymes required for red blood cell (rbc) formation
- Decreases erythropoietin production in the kidney
- Decreases the life span of a rbc by making the cell membrane more fragile



Pale, small rbcs (“microcytosis, hypochromia”)

Case 4: New Hampshire, 2000

- 2 y.o. girl presented to a community hospital ED with c/o low grade fever and vomiting x 1 day
- Lab findings:
 - microcytic anemia – hemoglobin 7.6g/dL (normal >11.4)
 - Basophilic stippling of red blood cells
 - Throat swab rapid strep test – Positive
- Discharged home, rx'd antibiotic for strep throat and medication for nausea/vomiting

Case 4: New Hampshire, 2000

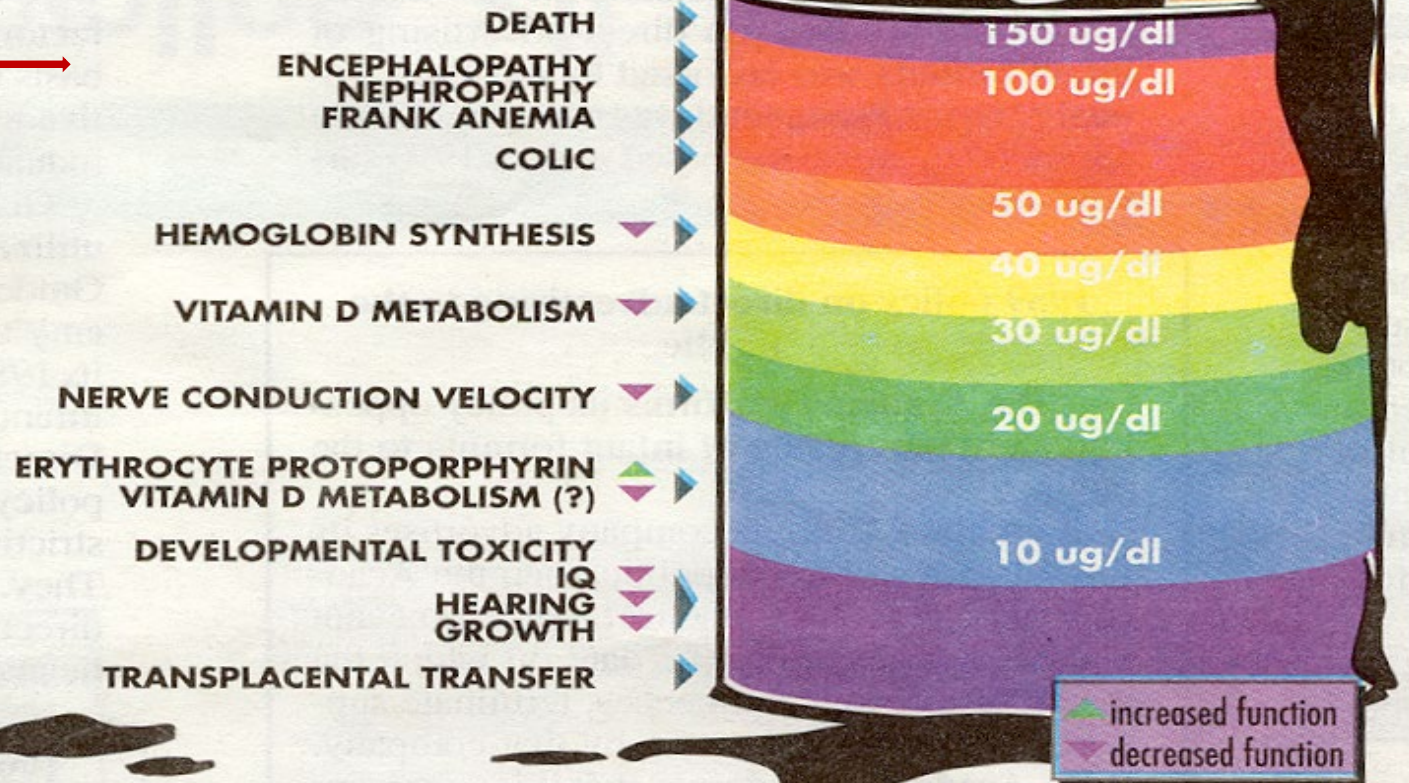
- 19 days later, admitted to same hospital for worsening vomiting
- Transferred the next day to a tertiary care hospital
- Later that day she developed hypotension, difficulty breathing and became unresponsive, so was intubated and started on mechanical ventilation
- CT scan showed diffuse cerebral edema (brain swelling)

Case 4: New Hampshire, 2000

- A BLL drawn 1 day earlier = 391 $\mu\text{g}/\text{dL}$
- Chelation therapy started with british antilewisite (BAL) and calcium ethylenediaminetetraacetic acid (CaN_2EDTA)>> BLL decreased to 72 $\mu\text{g}/\text{dL}$
- Surgical treatment of increased intracranial pressure
- However, coma persisted. Patient removed from life support 2 days after transfer

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Brelund Graphics

Demographic information

- Family Sudanese and had been living in Egypt 18 months
- Arrived in NH as refugees 3 weeks before illness onset
- Living in an apartment built prior to 1920
- The patient had been seen eating paint and plaster from holes in a wall

Environmental Investigation

- BLLs in the mother and 3 siblings (ages 5-15): 4-12 $\mu\text{g}/\text{dL}$
- Lead isotope composition from the porch paint (35% lead) and window well dust ($6732\mu\text{g}/\text{ft}^2$) most closely matched the patient's blood lead composition

Acute lead encephalopathy

- Typical BLL >70-100 µg/dL
- Nerve palsies (cranial nerves)
- Seizures
- Bizarre behavior
- Ataxia (imbalance)
- Loss of developmental skills
- Cerebral edema/increased intracranial pressure (persistent vomiting, headache)
- Coma

Lead Effects on the Brain

- Affects the function of neurotransmitters
- Increases permeability of blood vessels in the brain – bleeding and swelling may occur
- Increased intracranial pressure may cause death
- Early symptoms are non-specific: Irritability, poor attention span, developmental regression, lethargy and mood changes

Steps in treatment

#1. REMOVAL FROM FURTHER EXPOSURE

- Must be in a lead-free environment during chelation
- Admit to hospital if BLL >70 or if >45 with symptoms

#2. Optimize nutrition: iron, calcium, zinc

#3. Chelation: using a medication to remove lead from the body when BLLs are very high (>70, or consider if >45)

- Multiple treatments may be required
- Total body content of heavy metal decreased by 1-2%
- BLL decreased by ~75% after 48-72 hours of BAL/CaNa₂EDTA
- +/- GI decontamination e.g., whole bowel irrigation

Why not use chelation for all levels of lead poisoning?

Double-blinded RCT in 2001 of chelation, compared Succimer (up to three courses) vs. placebo. All received standard environmental investigation and attempts at remediation/prevention and ending exposure.

- 780 Children, ages 12-33 months, Initial BLL's 20-44 µg/dL
- Children followed over 36 months with serial BLL's and neurocognitive, psychological, behavioral testing
- BLL's decreased more quickly with succimer, but same in both groups after 1 year
- No improvement in any testing with succimer
- Authors recommended no chelation in children with BLL <45 µg/dL

Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med. 2001 May 10;344(19):1421-6.

Key points on health effects of lead

- Children can develop health effects *without* apparent symptoms
- Symptoms can be vague and non-specific (e.g. fatigue, irritability)
 - >> hence, lead poisoning is *diagnosed* by the blood lead level (BLL)
- Children are more susceptible to lead poisoning than adults
- Lead is absorbed through ingestion and inhalation
- BLL may not reflect the total body lead burden
- It can take years for a child's elevated BLL to decrease below the reference level

THE BEST MEDICINE = PREVENTION

THANKS FOR YOUR HARD WORK

