
# Putting it into Practice: Pediatric Environmental Health Training Resource

## Mercury, Arsenic, and Cadmium Toxicity in Children

Children's Environmental Health Network

# Author

This presentation was developed by:

**Shahram Yazdani, MD**

UCLA David Geffen School of Medicine

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# Mercury (Hg)

- Naturally occurring heavy metal (Hg)
- Shiny silvery-white liquid at 25 °C
- Has many industrial uses
- Found in three forms:


- Elemental: pure mercury, silvery white liquid
- Organic: methylmercury, ethylmercury
- Inorganic:  mercuric chloride, mercuric oxide

# Epidemiology

- Mass exposure:
  - Minamata Bay in Japan (1959): contaminated fish
  - Iraq (1970's): fungicide-treated grain
- Sporadic exposure:
  - Contaminated fish: (all fish have some mercury)
  - Breast milk of exposed mothers
  - Vapor inhalation: broken fluorescent bulbs, thermometers
  - Transdermal: contaminated diapers, skin bleach

# Sources of Exposure

- Elemental (Hg)
  - Production of/Broken fluorescent light bulbs, manometers, thermometers, batteries
  - Small scale gold mining outside the US and Europe
  - Contaminated water and food source (i.e. contaminated soil)
  - Folk remedies or religious ceremonies (Santería)

# Sources of Exposure

- Inorganic (Hg):
  - Folk medicine such as Ayurvedic medicine (from India)
  - Folk skin lightening creams
  - Mercuric cyanide & other compounds: Extremely rare in children.

# Sources of Exposure

- Organic (Hg):

  -Methylmercury: Found in seafood, particularly larger, longer living animals[1]

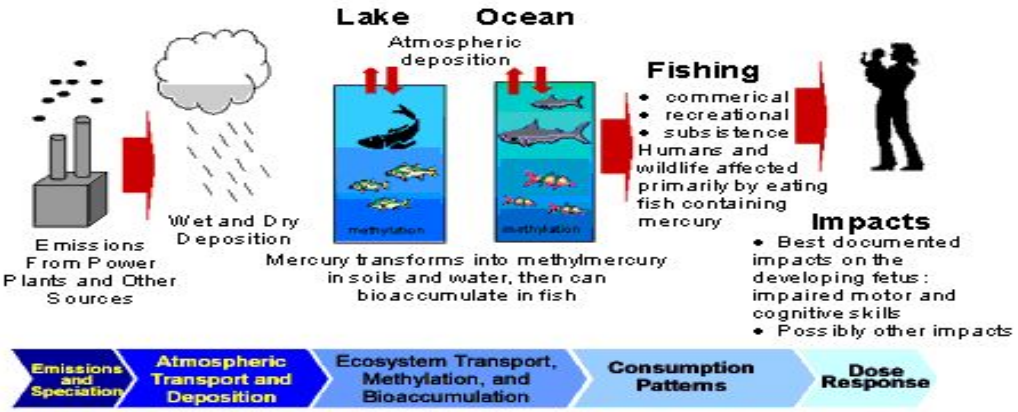



*Figure: EPA*

  -Thiomersal (Ethyl mercury): Mostly discontinued; Some multi-dose vaccines may contain the preservative[2,3]


1-US EPA; 2001. publication No EPA-823-R-01-001. http://www.waterboards.ca.gov/water_issues/programs/tmdl/records/region_1/2003/ref1799.pdf.
2- AAP, Committee on Infectious Diseases, Committee on Environmental Health. *Pediatrics*. 1999.
3-AAFP, AAP, Advisory Committee on Immunization Practices, Public Health Service. *MMWR*, 2000.

# Clinical signs and symptoms ( Prenatal exposure)

- High dose exposure:
  - Mental retardation
  - Cerebral palsy
  - Cerebellar ataxia and reflex anomaly
  - Failure to thrive
- Lower dosage from fish may cause neurocognitive deficit, but controversial.

Bose-O'Reilly, S. et al, *Curr Probl Pediatr Adolesc Health Care*, 2010.

# Clinical Signs and Symptoms (Chronic Exposure)

- Neurologic symptoms (in the order of progression from low to high dose exposure)
  - Paresthesia leading to ataxia
  - Generalized weakness
  - Ptosis, visual impairment
  - Hearing impairment and aphasia
  - Tremor mercurialis and muscle spasm
  - Cachexia
  - Incontinence
  - Stupor and coma

Mergler D, et al. *Ambio*, 2007.

# Clinical Signs and Symptoms (Chronic Exposure)

- Dermatotoxic reactions: range from chronic dermatosis to Acrodynia.
  - Seen in both organic and inorganic poisoning
  - Acrodynia (AKA Pink's Disease) includes triad of:
    - Skin: exanthema, edematous erythematous painful desquamating hands and feet.
    - Neurologic: paresthesia, irritability, photophobia, weakness
    - Hypertension

Harada M. *Crit Rev Toxicol*, 1995.
Gotelli CA, et al. *Science*, 1985.

# Acrodynia

# Clinical Signs and Symptoms (Chronic Exposure)

- Other organ damages include:
  - Neurodevelopmental: pre- and postnatal exposure
  - Nephrotoxic: proximal tubules with inorganic Hg
  - Teratogenic: mostly inorganic and methyl mercury
  - Cardiac: decreased Heart rate variability and hypertension
  - Carcinogenic: methylmercury associated with leukemia in adults

Clarkson TW, et al. *N Engl J Med*, 2003.
Bose-O'Reilly, S. et al, *Curr Probl Pediatr Adolesc Health Care*, 2010.
Yorifuji T, et al. Int Arch Occup Environ Health 2007;80:679-88.

# Clinical Signs and Symptoms (Acute Exposure)

- Usually due to vapor inhalation from broken fluorescent bulbs
- Cough
- Dyspnea
- Longer-lasting effects similar to chronic poisoning
- Inflammation of gums and oral mucosa
- Proteinuria

# Diagnosis

- History of possible exposure and physical findings
- Laboratory confirmation
  - 24-hour Urine testing: best suited for elemental or inorganic mercury (can use Hg/Cr ratio in kids)
  - Blood testing: for organic mercury; place whole blood in K-EDTA tubes
  - Hair: Most useful to quantify MeHg exposure for research purposes. Not useful in the clinical setting


WHO, 1996. Biological Monitoring of Chemical Exposure in the Workplace, Vol. 1. World Health Organization, Geneva.

UN Envir Program, WHO, International Atomic Energy Agency. The determination of methylmercury, total mercury and total selenium in human hair. In: Reference Methods for Marine Pollution Studies, 1987.

AAP Council on Environmental Health. [Mercury]. In: Etzel RA, Ed. Pediatric Environmental Health, 3rd edition, 2012.

# Diagnosis

Guidance levels of mercury concentrations in blood , urine, and hair

| Human bio-monitoring threshold limits | Hg in blood (µg/L) | Hg in urine (µg/L ) | Hg in urine (µg/L Crea) | Hg in hair (µg/kg/d ) |
|---|---|---|---|---|
| HBM I (alert value) | 5 | 7 | 5 | __ |
| HBM II (action level) | 15 | 25 | 20 | __ |
| US EPA bench mark | __ | __ | __ | 0.1 |

Commission on Human Biomonitoring of the Federal Environmental Agency. [Monograph Mercury—reference values and human bio- monitoring values]. *Bundesgesundheitsblatt*, 1999.

# Treatment

## **Chelation**: primary recommended treatment

- DMSA (Succimer):
  - First line treatment in the US for severe organic mercury poisoning.
  - No evidence of reduced methylmercury in human brain.[1]
  - Can be used as prophylaxis for metallic mercury exposure in children[2]
  - Does not remove inorganic mercury from the body and brain
- Dimercaprol (British anti lewisite(BAL in oil):
  - Effective in treating inorganic mercury poisoning
  - Should not be used in cases of methylmercury poisoning since it may increase the amount of mercury in the brain .
  - Available as intramuscular injection (painful)[3]


1-Louwerse, E.S., et al. 1995. *Int. Arch. Occup. Environ. Health*, 1995.

2-Forman, J., et al. *Environ. Health Perspect*, 2000.

3-Goyer, R.A., Clarkson, T.W. Toxic effects of metals. In: Klaassen, C.D., Ed., *Casarett & Doull's Toxicology: The Basic of Poisons, 6th Ed*, 2001.

# Treatment

## **Chelation**: primary recommended treatment

- D-Penicillamine:
  - Reduces blood Methylmercury[1]
  - High side effect profile
  - Reports of treatment failure in children with Acrodynia[2]
- DMPS ( 2,3-dimercapto-1- propane sulfonic acid ):
  - Recommended as the first-line treatment of inorganic mercury by WHO[3,4]
  - Not FDA approved
  - Does not remove inorganic mercury from the body and brain

1-Clarkson, T.W., et al. 1981. *J. Pharmacol. Exp. Ther*, 1981.
2-Karagol, U.et al. *Eur. J. Pediatr,* 1988.
3- WHO. *JAMA* , 1991.
4-Campbell, J.R. et al. *JAMA*, 1986.

# Prevention

- Prevention is both effective and practical
- Never vacuum spilled mercury/broken fluorescent light bulbs
- Pregnant/lactating mothers and children should:
  - Eat less than 12 oz/week of lower mercury fish (sardines, salmon, pollock, catfish)
  - Limit albacore tuna to 6 oz per week
  - Avoid swordfish, shark, king mackerel, or tilefish
  - Avoid whale blubber (used in some countries for cooking)
  - Avoid skin-lightening cream, industrial exposure or folk remedies

http://www.fda.gov/food/resourcesforyou/consumers/ucm110591.htm

# Arsenic (As)

- Extremely abundant in nature in the earth's crust
- Found in the southwestern states, eastern Michigan and parts of New England
- Found in three forms:
  - Elemental
  - Organic
  - Inorganic
- Children are susceptible to its antimetabolite and carcinogenic effect

# Arsenic

- Found in three major forms:
  - Elemental
    - Used as alloy and semiconductor industry
  - Organic
    - Organic arsenical pesticides are very toxic
    - Naturally formed organic arsenic is less toxic (in fish)
  - Inorganic
    - Trivalent (arsenite) is far more toxic and frequently used in the industry than arsenate.
    - Pentavalent (arsenate): mostly used as insecticide and poisons

# Epidemiology

- Mostly absorbed through ingestion
- May be transported through placenta
- Not absorbable through intact skin
- Less common in developed countries
- Continues to cause water poisoning in less developed countries
- Elemental and inorganic arsenic are more toxic than its organic form

# Sources of Exposure

- Well water: Levels may vary with earthquakes causing increased exposure of arsenic veins
- Anthropogenic (industrial, agricultural) and natural runoffs
- Incinerators
- Pressure-treated wood (copper chromium arsenate): found in many residential and kids' play areas (jungle gyms) despite FDA ban for residential wood treatment since 2003
- Pesticides: still found despite their ban in U.S.
- Rice: amounts to a minor factor in western diet
- Fish: less toxic organic As

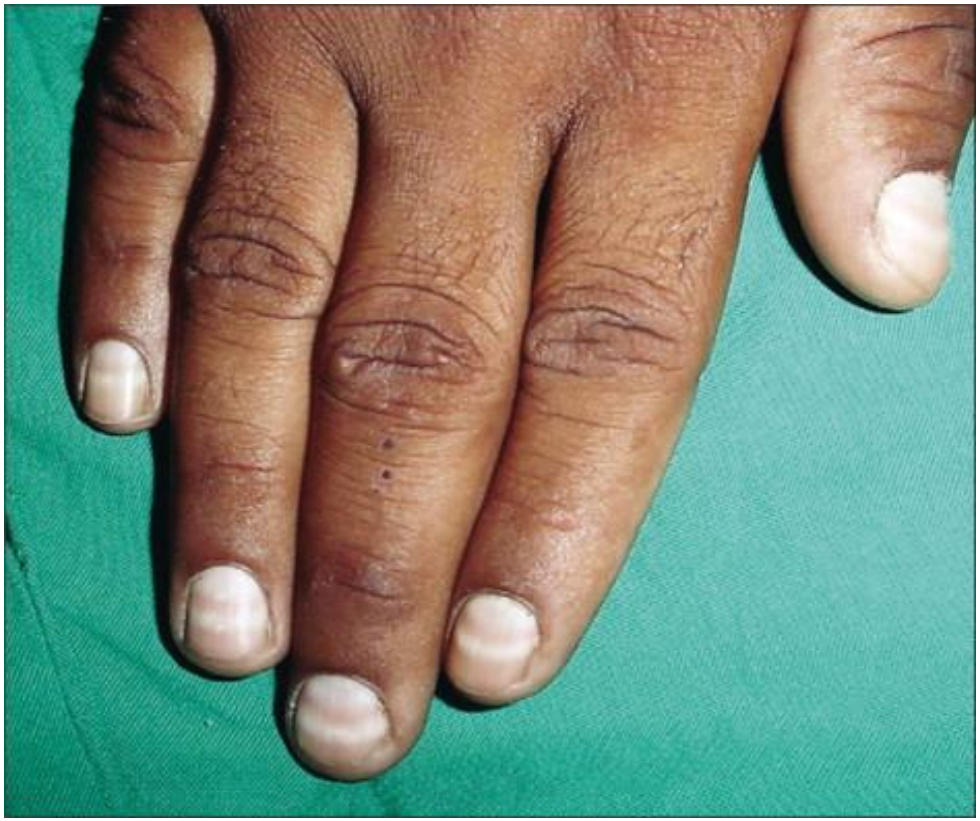
# Clinical signs and symptoms (Acute)

- High dose acute poisoning (>3-5mg/kg of elemental As)
  - Emesis within 30 minutes
  - Rapid progression to hematemesis
  - Abdominal cramping
  - Diarrhea (3% present as bloody/rice water)
  - Mees' lines: white transverse creases across the nails
  - Multi-organ failure (brain, kidney, liver)
  - Most die from shock or hypovolemia

Xu Y, et al. *Toxicological Sciences*, 2008.

# Mees' lines

Seen both in acute and chronic arsenic poisoning



# Clinical signs and symptoms (Acute)

- Lower dose acute poisoning (<3 mg/kg of elemental As)
  - A more protracted course
  - Facial edema and transient flushing
  - Intertriginous erythema/maculopapular rash
  - Hypotension
  - T-wave inversion
  - Congestive heart failure □ shock
  - Pulmonary edema
  - Sensorimotor peripheral axonal neuropathy
  - Other: proteinuria, hematuria, bone marrow suppression, rhabdomyolysis and conjunctivitis

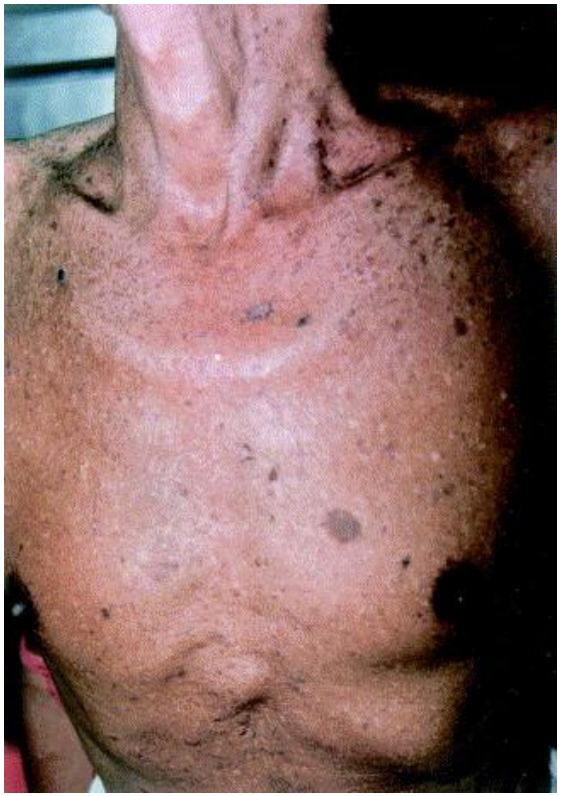
AAP Council on Environmental health. Chapter 22: Arsenic. In: Etzel, RA, Ed. *Pediatric Environmental Heath, 3rd Edition*, 2012.

# Clinical signs and symptoms (Chronic)

- Chronic exposure in children (can present with a wide range of symptoms):
  - Low-grade bone marrow depression
  - Generalized fatigue
  - Severe skin changes: include Mees' lines, eczematoid eruption, hyperkeratosis, melanosis
  - Liver dysfunction
  - Neurologic dysfunction
  - Cancer: risk in children not clear; mostly adult onset, skin, lungs, bladder, liver

# Chronic Arsenic skin changes

**Hyperkeratosis**



**Hypermelanosis of the chest**

# Clinical signs and symptoms

- Chronic exposure in pregnant women:
  - Spontaneous abortion
  - Still birth
  - Low birth weight
  - Preterm delivery

# Diagnosis

- Arsenic is mostly excreted through the kidneys
- 24-hour urine test (must be fractionated)
- Spot urine is not recommended in children
- Fractionation distinguishes highly toxic inorganic AS from the less toxic organic form
- If fractionation is not available, patient must avoid seafood for 2-5 days prior to urine test

# Treatment

- For significant exposure, chelation is recommended
- All treatments should be in consultation with a toxicologist and close observation
- D-Penicillamine
  - 100mg/kg/d po divided q6h x 5 days
- Dimercaprol (BAL)
  - Mild poisoning: 2.5mg/kg IM q6h x 8 doses, then q12h x 2 doses, then q24h x 10 doses
- Succimer (DMSA)
  - Approved and dosed based on lead poisoning treatment
  - 10mg/kg po q8h x 5 days, then q12h x 14 days

Franzblau A, Lilis R. *Arch Environ Health*, 1989.

# Prevention

- Drinking water: test all well water (<10 ppb recommended by WHO)
- Avoid As-contaminated water or soil in agriculture (i.e. rice)
- Consider the following when kids may be in contact with treated wood (copper chromium arsenate (CCA))
  - Never burn or saw treated wood
  - Avoid old wooden cribs
  - Seal old wooden jungle gyms and decks every 6 months or annually
  - Children should avoid hand to mouth contact after accidental contact with CCA treated wood and thoroughly wash their hands ASAP.

# Cadmium (Cd)

- A heavy metal found in earth's crust
- Natural sources
  - Rock erosion
  - Forest fires
  - Volcanic eruptions
- A recent anthropogenic contaminant (19$^{th}$ century)
  - Byproduct of zinc production
  - Mining
  - Smelting/incineration of waste

# Epidemiology

- Less of a problem in developed countries
- Still a significant burden in developing countries
- Mainly absorbed through:
  - Inhalation of cadmium dust (industrial)
  - Ingestion of contaminated food
  - Tobacco smoke inhalation

# Sources of Exposure

- Animal food sources (if exposed to Cd)
  - Sea food: oysters, mussels, certain species of fish
  - Mammalian kidney
  - Mammalian liver
- Grains from contaminated soil: wheat, rice
- Root plants: onion, potatoes
- Jewelry: gold and silver soldering
- Tobacco smoke

# Features of Toxicity

- Kidneys: may cause failure
- Liver: along with kidneys may comprise 50% of the total body Cd
- Lungs: worse with inhalation; affected both in acute and chronic cases
- Bone: 3$^{rd}$ depot of Cd poisoning; mainly chronic poisoning
- Half-life of 10-20 years in the tissue
- Cd does not readily cross placenta or blood-brain barrier

# Clinical signs and symptoms (Acute)

- Ingestion
  - Salivation
  - Emesis and abdominal pain
  - Painful spasm of the anal sphincter
  - Vertigo
  - Loss of consciousness

AAP Council on Environmental health. Chapter 24. In: Etzel, RA, Ed. *Pediatric Environmental Heath, 3rd Edition*, 2012.

# Clinical signs and symptoms (Acute)

- Inhalation
  - Cough
  - Dry throat
  - Headache and chills
  - Muscle weakness
  - Leg pain
  - Chest pain
  - Pulmonary edema
  - Bronchospasm
  - Pneumonitis

# Clinical signs and symptoms (Chronic)

- Kidney damage
  - Microproteinuria (mild cases)
  - Nephropathy (severe cases)
- Bone pain
  - Osteomalacia
- Lung damage
  - Restrictive lung changes

Friberg L. *Acta Med Scand,* 1950.
Bernanrd A. *Indian J Med Res,* 2008.

# Diagnosis

- Blood
  - Reflects recent exposure
  - Half-life 75-128 days
  - Normal value for non-smoker <1 μg/l, for smoker <5μg/l
- Urine
  - 24-hr urine or Cd/Cr ratio
  - Gold standard measure of toxicity
  - No child standards available
  - Normal <10 μg/g creatinine. Renal damage begins at 2 μg/g creatinine in adults.
  - Mean Urine [Cd] in 6-11 y.o. 0.075 μg/g

# Prevention

- Prevention is more effective than treatment
  - Avoid crops grown in contaminated soil or water
  - EPA maximum contaminant level for Cd is set at 0.005mg/L
  - Limit liver and kidney consumption in children
  - Avoid second hand smoke
  - Avoid playing with metal jewelry

AAP Council on Environmental health. Chapter 24. In: Etzel, RA, Ed. *Pediatric Environmental Heath, 3rd Edition* , 2012.

# Treatment

- No effective treatment available
- Chelation may worsen renal toxicity by mobilizing Cd from other tissues and further exposing the kidneys
- Supportive care for renal damage/failure
- Large doses of Vitamin D to treat osteomalacia

Johri N, et al. *Biometals* , 2010.

# Contact Information

Nsedu Obot Witherspoon, MPH
Executive Director
Children's Environmental Health Network
Email: nobot@cehn.org
Phone: 202-543-4033

www.cehn.org

Children's Environmental Health Network