HEAVY METAL POISONING

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LEARNING OBJECTIVES

- Define/identify Toxicology of selected heavy metals that have impacts on human health – Lead, Arsenic, Mercury, & Iron
- Identify laboratory values impacted in heavy metal poisonings
- Identify/recognize clinical signs and symptoms of heavy metal poisonings
- Define treatments for heavy metal poisonings

Heavy metals

Heavy Metals

- Arsenic
- Bismuth
- Cadmium
- Chromium
- Copper
- Iron
- Lead
- Manganese
- Mercury
- Nickel
- Selenium
- Silver
- Thallium
- Zinc

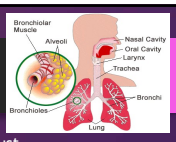
HEAVY METALS

- Heavy metal are chemicals elements with a specific gravity that is at least 5 times the specific gravity of water
  - Arsenic 5.7; lead 11.34; mercury 13.54
- Metal having an atomic weight greater than Na, a density greater than 5 g/cm^3
- Bottom of the periodic table –high densities
- Physical properties
  - High reflectivity, electrical and thermal conductivity, strength
  - Easily traced and measured and fate determined
- Toxic and non-biodegradable
- Toxicity arises from strong affinity of the heavy metal cations for sulfur

Metal Toxicity

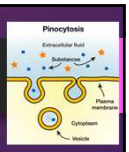
- Classification of the metal
- Absorption, storage and excretion
- Mechanism of action

Absorption - Respiratory



- Metal may be inhaled as vapor or aerosol (fume or dust particulate)
  - Fume or vapor of some metals & compound are readily absorbed in from alveolar space (mercury, tetraethyl lead)
- Large particles trapped in upper respiratory tract, cleared by mucociliary transport to pharynx and swallowed (equivalent to oral exposure)
  - Small particles may reach alveolar/gas exchange. Water soluble metal aerosols are rapidly absorbed from alveoli into the blood

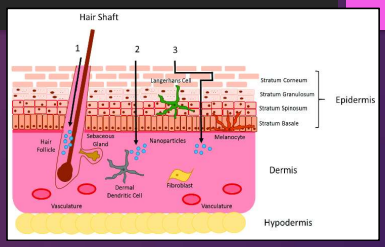
Absorption –Gastrointestinal



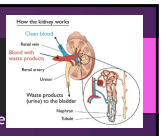
- Metal may introduced into GI tract through food, water
- Metals are absorbed into the cells lining the intestinal tract by:
  - Passive or facilitated diffusion
  - Specific transport process
  - Pinocytosis
- Depends on many factors
  - Solubility of metal in fluids of the intestinal tract
  - Chemical forms of metal (lipid soluble methyl mercury is completely absorbed compare to inorganic mercury - poorly absorbed)
  - Presence and composition of other materials in GI tract
  - Composition for absorption sites between similar metals (zinc & cadmium or calcium & lead)
  - Physiological state of the person exposed (Vitamin D enhance the absorption of lead)

Absorption - skin

- 1. Appendageal route
- 2. Intracellular route
- 3. Intercellular route



Excretion



1. Kidney - Important route of excretion
   - Metals in blood plasma are bound to plasma proteins and amino acids
   - Metals bound to low molecular weight proteins and amino acids are filte glomerulus into fluid of the renal tubule
   - Some metals are effectively resorbed by tubular epithelia before they reach the urinary bladder where very little resorption occur
2. Enterohepatic Circulation
   - Absorbed metal may also excreted into intestinal tract in bile, pancreatic secretion or saliva
3. Minor Pathways
   - Hair (Hg, Zn, Cu and As)
   - Nails
   - Saliva
   - Perspiration
   - Exhaled air
   - Lactation
   - Exfoliation of skin

Acute toxicity

- Organs and tissue affected are those involved in the absorption and elimination
- Result of the accumulation of critical high concentrations of metal that at these sites with little opportunity to detoxify, eliminate or adapt to metal
- Treatment of acute metal intoxication is designed to:
  - Enhance the elimination of the metal through neutralization
  - Prevent irreversible damage to organs and tissue
  - Treat the symptoms of acute toxicity

Chronic toxicity

- Duration of initial exposure to the onset of signs and symptoms months to years
  - Diagnosis of chronic metal intoxication is more difficult than acute intoxication
- Diagnosis – presence of excessive metals in blood and urine
- Organ system not involved in absorption or elimination of metal such as hematopoetic or immune system may be affected

Metals in workplace

- Metals are extensively used in industrial operation thus resulting in a high risk of exposure to workers and environment:
  - Welding
  - Grinding
  - Soldering
  - Painting
  - Smelting
  - Storage battery
  - Recycling
  - Smoke

Medicinal uses of heavy metals

- Treatment of helminths, protozoa, syphilis –Arsenic (no longer or rarely used)
- Anti-emetic – Copper -(no longer used)
- Antacids –aluminum
- Rheumatoid arthritis –gold
- Food supplements –zinc and selenium
- Leukemia and some homeopathic remedies – Arsenic

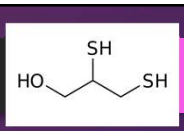
Laboratory Testing

- Samples should be sent in metal free containers
- Pts should abstain from seafood and seaweed products which contain nontoxic organic forms)for 1-2 weeks (arsenic and mercury testing).
  - Elevated concentrations can be sent for speciation
- To help in diagnosis and gauge severity
  - CBC with peripheral smear
  - Renal function tests
  - Urine analysis – metals and/ or proteinuria
  - Urine electrolytes
  - Liver function studies
- Imaging studies

How to treat (get rid of) heavy

- In the body:
  - Chelators - small molecules that bind very tightly to metal ions
  - Chelating agents convert metal ions into a chemically and biochemically inert form that can be excreted
  - Bidentate Chelating agent has 2 or more electronegative groups that can form stable complexes with multivalent cationic metal atoms
- In the environment:
  - Removal of lead pipes, paints, etc.
  - Addition of new uncontaminated soil to site
  - Home water filters

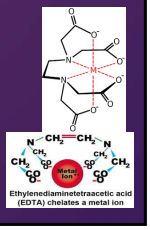
Some Chelators



- **Dimercaprol (BAL)**
  - Acute arsenic and mercury poisoning
  - In combination with EDTA for lead poisoning
  - High incidence of adverse effects, highly lipophilic and enters cells – tachycardia, headache, N & V, parasthesias, fever, pain and hematoma at injection site, long term –thrombocytopenia and increased PT
- **Succimer** –water soluble analog of Dimercaprol
  - Oral treatment of lead toxicity in children and adults
  - Often effective in arsenic and mercury poisoning if early
  - Less toxic, but GI distress, CNS effects, skin rash, elevated LFT's may occur
- **Unithiol** –water soluble derivative of Dimercaprol
  - Initial treatment of inorganic mercury or arsenic
  - Oral form may be used for lead poisoning
  - Vasodilation & hypotension if rapidly infused; skin reactions

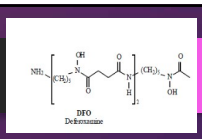
More chelators

- **Penicillamine,** a water soluble derivative of Penicillin (also bidentate)
  - Treatment of copper poisoning
  - Adjunctive therapy for arsenic and lead
  - Severe side effects common –nephrotoxicity, proteinuria, pancytopenia, hemolytic anemia, autoimmune dysfunction
- **EDTA** –**polydentate chelator** of many cations, including calcium & trivalent cations
  - Lead poisoning; must give as the calcium disodium salt to prevent hypocalcemia
  - Adverse effects – Nephrotoxicity, Renal tubular necrosis, EKG changes



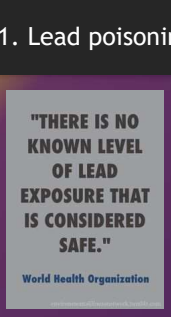
Ethylenediaminetetraacetic acid (EDTA) chelates a metal ion

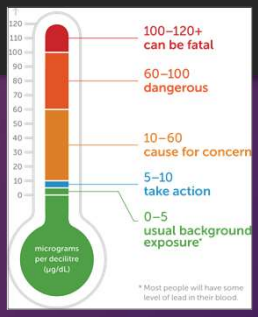
More chelators

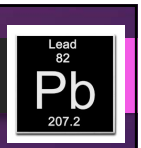


- Deforoxamine (IV)
  - Treatment of acute iron toxicity due to iron overload caused by blood transfusions in pts with thalassemias or MDS
- Deferasirox (oral)
  - Treatment of iron overload
- Adverse reactions –erythema, urticaria. Long term use – neurotoxicity, hepatic & renal dysfunction, severe coagulopathies
- Rapid IV administration can cause histamine release and hypotensive shock

1. Lead poisoning



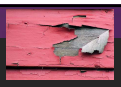




https://www.cdc.gov/nceh/lead/default.htm

Sources of lead

- Used in pipes – Lead toxicity "Plumbism"
- Paints (older houses); ALSO, Lead chromate (yellow pigment); corrosion-resistant paints (red)
- Commonly used in the building industry for roofing and flashing and for soundproofing
- Bullets
- Batteries and sinkers in fishing
- Ceramics and dishware
- Coloring agents in various foods
- Some types of PVC mini-blinds
- When combined with tin, it forms solder, used in electronics and in other applications to make connections between solid metals-food cans, vending machine children's toys &n jewelry
- Gasoline (before the 1970's)



- 95% percent of the body burden of lead in adults are found in calcified tissue (bone and teeth); however toxicity is manifest primarily in the nervous systems, renal systems and hematopoetic systems
- Inorganic lead oxides and salts enter the body
  - Absorbed through gastrointestinal & respiratory tracts; minor skin absorption
  - Target organs for toxicity: Hematopoietic; CNS; Kidney
  - Treatment –Dimercaprol, EDTA, Succimer, Unithilol
- Tetraethyl lead –organic lead
  - Absorbed through skin; minor GI absorption
  - Target organ –CNS
  - Treatment – Seizure control

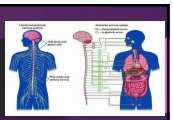
Clinical signs and symptoms

Exposure to even low levels of lead can cause damage over time, especially in children. The greatest risk is to brain development, where irreversible damage can occur

Newborn	Children	Adult
Premature	Developmental delay	High blood pressure
Low birth weight	Learning difficulties	Joint and muscle pain
Slowed growth, FTT	Irritability	Difficulties with memory or concentration
	Loss of appetite	Headache
	Weight loss	Abdominal pain
	Sluggishness and fatigue	Mood disorders
	Abdominal pain	Reduced sperm count and abnormal sperm
	Vomiting	Miscarriage, stillbirth or premature birth in pregnant women
	Constipation	
	Hearing loss	
	Seizures	
	Eating things, such as paint chips, that aren't food (pica)	

https://www.mayoclinic.org/diseases-conditions/lead-poisoning/symptoms-causes/syc-20354717

Susceptibility of Nervous System to effects of toxins



- Large surface area of nervous system –increases exposure to toxins
- High lipid content (myelin) – accumulate and retain lipophilic toxins
- Neuron is sensitive to shortage of Oxygen
- Electrochemical transmission - At the synapse – toxins disrupts synaptic function
- Nerve cells killed by toxins cannot regenerate

Investigation tools for neurological toxicity

1. WHO Neurobehavioral Core Test Battery
Detects subtle, mild neurological changes in early stage of intoxication

TEST	FUNCTIONAL DOMAIN
Simple reaction time	Attention/domain
Digit span	Auditory memory
Santa Ana dexterity test	Manual dexterity
Digit symbol	Perceptual-motor speed
Benton visual reaction	Visual perception
Aiming	Motor steadiness

2. Nerve conduction velocity
   - Lead decreases the velocity at which nerve impulse is conducted along the arm

Laboratory testing

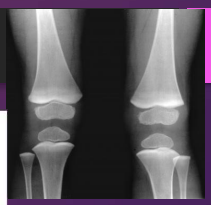
- Blood lead level (BLL) Currently 5 ug/dL action level
- Heme metabolism
  - Lead inhibits delta-amino-levulinic acid dehydratase (enzymes involved in synthesis of porphyrins and heme)
  - Inhibition of the enzymes result in accumulation of the substrate aminolevulinic acid (ALA) in blood or urine
- Calcium EDTA mobilization test – estimate body burden of lead

Lead

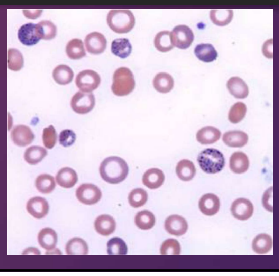
Transport and storage
- Lead is transported to all organs and tissue of body by blood
- 95% of Lead in blood is associated with the erythrocytes
- Lead accumulates in bone throughout life
- Biological half-life of lead bone is 10-20 years, while half life of lead in soft tissues is several months

- Organ systems
  - Hematopoietic
  - Nervous & neuromuscular
  - Renal and cardiovascular
  - GI
  - Reproductive system – low sperm count, abortions, stillbirths, low sperm motility, premature baby
- Signs and symptoms include
  - Muscle weakness, anemia, Insomnia, loss of memory, headache, paralysis of extensor muscles of the wrist

Lead lines in gums and bone



Basophilic stippling



Lead – preventive measures – home & school

- Prevent childhood lead poisoning – removal of lead paints and pipes
- Filter systems for pipes

Workplace measures

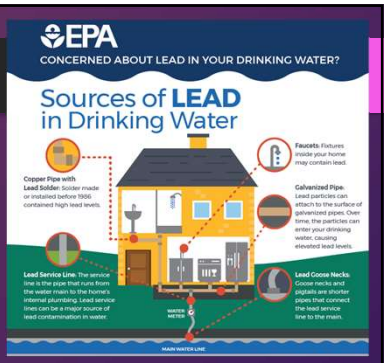
Engineering controls

- Local exhaust ventilation system
- Water spray to control dust or
- Airborne chemical removal and containment equipment
- Maintenance requirements
  - During operational conditions
  - Monthly inspection
  - Annual examination and testing
  - Record keeping

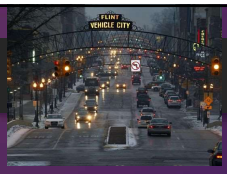
Industry regulations

- Exposure monitoring
  - Full shift personal samples, at least 1 sample per work area
  - If below action level no further assessment needed unless there has been a change in production, process, control or personnel
  - If at or above action level, should repeat every 6 months
  - If at/above PEL, repeat every 3 months
- Medical surveillance
  - For all workers exposed above action level for more than 30 days per year
- Biological monitoring
  - At least every 6 months for exposed workers
  - Every 3-months if blood Pb 40-60 ug/100 gm blood
  - Monthly if 60-80, during removal period for female worker of

Lead Pipes



Flint, Michigan Water Crisis



Flint, Michigan Timeline

- **April 2013:** Facing severe financial pressures, the city of Flint decides to change the source of the city's water
- **April 2014:** Flint begins using water from the Flint river until the KWA pipeline from Lake Huron is completed
- **May 2014:** Flint residents begin to complain about the water
- **August 2014:** Water tests positive for *E. coli* bacteria; a boil-advisory is issues in parts of Flint
- October 2014 – Flint's GM Truck assembly plant discontinues using Flint tap water due to corroding engine parts from high levels of chlorine

Timeline continued, 2015

- January 2015: Flint announces that the water contains high levels of trihalomethanes, in violation of the Safe Drinking Water Act, but city officials tell residents that the water is safe
- Flint residents complain of health issues caused by city water. Residents bring bottles of discolored tap water to a community meeting
- February 2015: Flint resident LeAnne Walters's son develops rashes. High levels of lead are detected in the water in her home by the EPA and Va. Tech team
- March 2015 Flint City Council members vote to reconnect to Detroit water. Emergency manager Jerry Ambrose overrules the vote.

2015 Continued

- September 24, 2015 - Dr. Mona Hanna-Attisha releases a report that shows that childrens' BLL have increased since the switch in water sources.
- September 2015 Virginia Tech's water study team reports that 40% of Flint homes have elevated levels of lead
- October 2, 2015 - The Michigan Department of Health and Human Services (MDHHS) reviews the data from Hurley Medical Center and verifies the findings. The state begins testing drinking water in schools and distributing free water filters
- October 2015: Flint switches back to using water from Detroit with financial aid from state
- Something in 2015 –deadly Legionella Outbreak 87 cases/12 deaths

https://www.bridgemi.com

TRUTH TELLING

"FLINT HAS A VERY SERIOUS LEAD IN WATER PROBLEM."

"We believe that in the weeks and months ahead MDEQ and Flint will be forced to admit they failed to protect public health as required under the Federal Lead and Copper Rule."

- Virginia Tech water expert Marc Edwards

OUTRAGEOUS STATEMENTS

"Apparently, it is going to be a thing now."

- MDEQ public info officer Karen Tommasulo

"Let me start here – anyone who is concerned about lead in the drinking water in Flint can relax."

"(T)he bottom line is that residents of Flint do not need to worry about lead in their water supply, and DEQ's recent sampling does not indicate an eminent health threat from lead…"

- MDEQ spokeman Brad Wurfel

TRUTH TELLING

The City of Flint's lead-in-drinking-water sampling procedures (which are supervised by the Michigan Department of Environmental Quality) are "smoke and mirrors."

- Virginia Tech water expert Marc Edwards

Since the switch to Flint River water, the percentage of Flint infants and young children with elevated blood lead levels has nearly doubled citywide and has nearly tripled in areas of the city with high-risk for lead exposure. Flint should stop using the Flint River for drinking water as soon as possible. Flint should declare a health advisory to trigger additional government response to the crisis.

- Hurley Medical Center
Dr. Mona Hanna-Attisha study

OUTRAGEOUS STATEMENTS

"Bottom line is that folks in Flint are upset – because they pay a ton for water and many of them don't trust the water they're getting – and they're confused, in no small part because various groups have worked hard at keeping them confused and upset… (I)t's been rough sledding with a steady parade of community groups keeping everyone hopped-up and misinformed."

Virginia Tech researchers "only just arrived in town and (have) quickly proven the theory they set out to prove, and while the state appreciates academic participation in this discussion, offering broad, dire public health advice based on some quick testing could be seen as fanning political flames irresponsibly."

- MDEQ Communications Director Brad Wurfel

2016 Continued…..

- January 2016: Michigan Gov. Rick Snyder declares a state of emergency in Flint. Then, President Barack Obama signs an emergency declaration and orders federal aid for Flint.
- Volunteers from around the country donate water and supplies to Flint residents.
- Governor announces there was an outbreak of Legionella between 6/2014 and 11/2015
- March 2016: The Flint water task force, appointed by Governor Snyder, finds that state agencies within Michigan are mainly responsible for the crisis
- December 20, 2016 - Four officials charged with felonies

2017

- January 30, 2017 - A $722 million class action lawsuit is filed against the EPA on behalf of more than 1,700 residents impacted by the water crisis.
- February 17, 2017 - The Michigan Civil Rights Commission issues a report: "The Flint Water Crisis: Systemic Racism Through the Lens of Flint."
- March 17, 2017 – EPA awards 100 million to Flint for drinking water infrastructure upgrades.
- March 28, 2017 - Federal judge approves a $97 million settlement in which the state of Michigan agrees to replace lead and galvanized steel water lines in the Flint
- October 12, 2017 - House oversight committee requests clarification about Gov. Snyder's sworn testimony that he did not know of the Legionella outbreak until 2016.

2018

- February 5 – A study on the causes of an outbreak of Legionnaires' disease in Flint in 2014 and 2015 found that low chlorine levels were the cause. Chlorine, which kills microbes responsible for the disease, also reacts with heavy metals like lead and iron. High levels of lead and iron in Flint's water may have been responsible for the decreased amount of chlorine available
- April 2 - A new study by the MDEQ reports that elevated lead levels were found in 4 percent of final water samples from Flint schools. One school's results show lead levels at 100 ppb, six times the federal action level
- April 26 - The EPA approves a $1.9 million grant to Va Tech professor Marc Edwards for nationwide research of lead contamination in drinking water. A groundbreaking step, resulting from the Flint Water Crisis, to ensure of the safety of future generations
- September 28 - A report by the Michigan Department of Health and Human Services says the Genesee County Health Department failed to help 85% of children diagnosed with high blood lead levels in 2016
- October 5 – Elon Musk donates approximately $480,000 to the Flint school system to pay for UV filtration devices in all 12 schools; installation is expected to be completed by January 2019.[82]
- December 26 - In a published interview, governor-elect Gretchen Whitmer pledged to restore free water distribution to Flint residents.
-

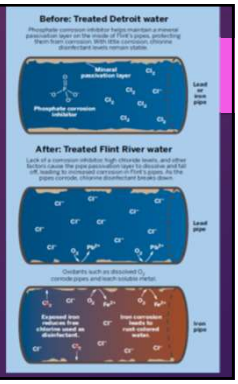
2019
Mlive.com

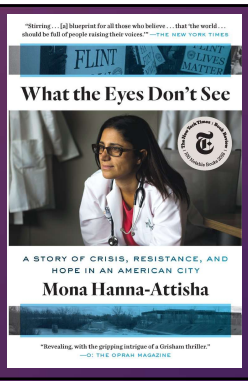
- Jan 2 – In her first act as Governor, Gretchen Whitmer signs an executive directive requiring state employees to immediately report to their department or agency director any threat to public health or safety, an action inspired by the mistakes made by her predecessor's administration that led to the water crisis
- Jan 18 - Flint was told people would be jailed for the water disaster. Three years later, it hasn't happened (LA Times)
- Feb 4 -Executive order - Reorganize the Michigan Department of Environmental Quality and dissolve industry-led environmental rule review panels
- Feb 6 - House votes to overturn DEQ restructuring plan, Whitmer says she won't back down
- Feb 11 - Flint Water Crisis lessons remain unlearned with attacks on environmental executive orders (M Hanna-Attisha)
- April 25 - Residents still furious after 5 years of Flint water crisis

https://www.acs.org/content/acs/en/education/resources/highschool/chemmatters/past-issues/2016-2017/december-2016/flint-water-crisis.html

Flint's Water Crisis Should Raise Alarms for America's Aging Cities
Fortune Magazine, ROB CURRAN January 25, 2016

Lead pipes are prevalent in cities that were developed in the 19th and early 20th centuries, meaning all the major metropolitan areas



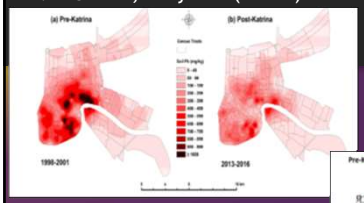


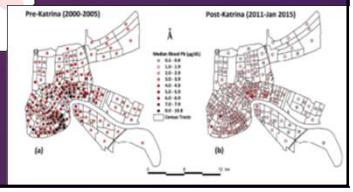
New Orleans, LA.

- Newkirk II, V.R. " The Poisoned Generation" The Atlantic, May 21, 2017
- In 1985, kids were regularly testing at levels well above 25 ug/dL (standard at the time); was worse in the projects
- Casey Billieson and her 2 sons, 5 & 3. Boys began struggling with childhood learning goals -learning disabilities,
- 1994, Lawyer, Gary Gambel and team came to visit & test soils for lead. She had her boys tested -they were > 4x the action level
- Suits against HANO; Back and forth
- 2005 Katrina
- Legal war of attrition that spanned 20 years

Hurricane Katrina side effect: Dramatically lower rates of lead in New Orleans, study finds (7/2016)

https://www.theadvocate.com/new_orleans/news/article_29f329b6-55c0-11e6-a3fc-1bb6de67683b.html





Int. J. Environ. Res. Public Health 2017, 14, 407

Tulane University Tulane University | New Orleans Tulane researcher finds profound improvements in soil lead levels following Katrina August 26, 2016

Adverse Childhood Experiences (ACEs)

- 2017 DC Public Health Case Challenge Lead and Adverse Childhood Experiences: Neurological and Behavioral Consequences for Youth in the District of Columbia

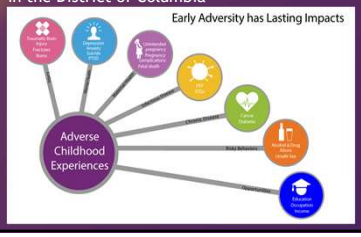


Table 1. ACE-Related Odds of Having a Physical Health Condition

Health Condition	0 ACEs	1 ACE	2 ACEs	3 ACEs	4+ ACEs
Arthritis	100%	130%	146%	155%	236%
Asthma	100%	115%	118%	160%	231%
Cancer	100%	112%	101%	111%	162%
COPD	100%	120%	161%	220%	399%
Diabetes	100%	128%	132%	116%	201%
Heart Attack	100%	148%	144%	287%	232%
Heart Disease	100%	123%	149%	250%	205%
Kidney Disease	100%	83%	166%	179%	263%
Stroke	100%	114%	117%	180%	281%
Vision	100%	167%	181%	199%	354%

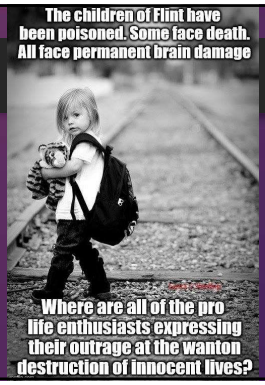
New Orleans 7th grader's lead test results prompt district to speed up filter installation at French Quarter school

By Marta Jewson | March 29, 2019

https://thelensnola.org

Home prevention

- The American Academy of Pediatrics recommends no more than 1 part per billion of lead in children's drinking water



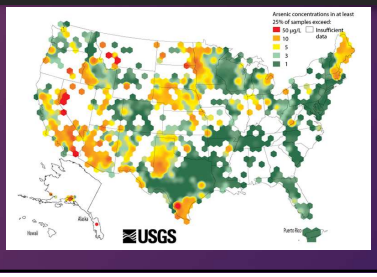
2. Arsenic

33 74.92
As
Arsenic

Sources of Arsenic

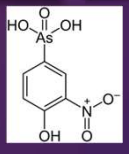
- Plants and animal tissues (shrimp)- organic form -less toxic & is detoxified in body
- Rocks, soil, well water – inorganic form - most toxic
- Industrial
  - Byproduct of smelting copper, lead, zinc
  - Pesticides
  - Wood preservatives
  - Burning fossil fuels
- Tobacco smoke
- Wallpaper paste/pigments
- Chemical warfare "Lewisite"

Arsenic in US water supply -US Geological Survey

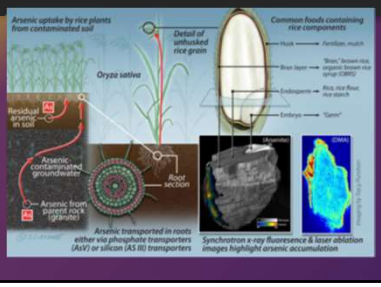


Current uses

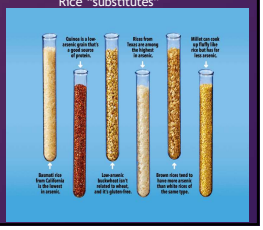
- Use is DROPPING because of toxicity
- Silicon-based computer chips
- Manufacture of glass
- Feed additive to prevent parasitic infections for poultry and swine (!) 3 out of 4 banned in 2013
- Arsenic pesticides
- Anti-leukemia drugs - FDA approval of arsenic trioxide for relapsed or refractory APL in September 2000
- Homeopathic medicines



Rice -Arsenic uptake from soil



Rice "substitutes"

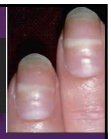


Arsenic – mechanisms of toxicity

- Induces ROS and oxidative stress; alters balance of antioxidants
- Binds to thiols
- Alters signaling cascades
- Apoptosis and cell death

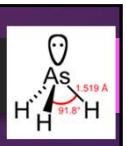
- Developmental defects – Crosses placenta
  - Epigenetic effects, endocrine, immunosuppressive, neurotoxic, interference with enzymes needed for fetal programming and development

Arsenic



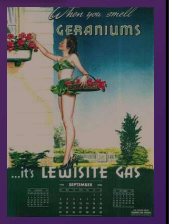
- Inorganic arsenic salts -highly toxic, potent hemolytic agent
  - Absorption through intestinal tract; also through skin (lipid soluble)
  - Targets – Capillaries, gastrointestinal tract, hematopoietic system; bound to RBCs and globulins; long term concentration in bone and keratinized tissues
- Acute or chronic toxicity
- Excreted by the kidneys 3-5 days
- Crosses placenta and causes stillbirth

Arsine gas



- Arsine gas -Inhalation
  - Targets erythrocytes -hemolysis
  - Hemoglobinuria, jaundice, heart failure
  - Immediate death at 150 ppm
  - Treatment -supportive

Lewisite



http://wmdindc.blogspot.com

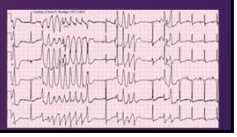
Parental Smoking –additional source of arsenic exposure for children

Parental Smoking	Mean arsenic in children's urine (Ug/gr/cr)
Not smoking	4.2
One parent smokes	5.5
Both parents smoke	13

WHO Bulletin 1992

Arsenic –signs of acute toxicity

- Constriction of throat, difficulty swallowing
- Severe thirst
- Garlic taste
- Severe abdominal pain, vomiting, diarrhea
- Muscle cramps
- Cardiac arrhythmias
- Coma and death



Arsenic –signs of chronic toxicity

- Main source –drinking water
- Clinical manifestations:
  - Garlic odor on breath
  - Excessive perspiration
  - Muscle soreness and weakness
  - skin hyperpigmentation in raindrop pattern
  - Parasthesias of hands and feet
  - Peripheral vascular disease
  - Gangrene in feet
  - Cancer –skin, kidney, bladder

3. Mercury

Traces of Mercury have been found in nutella…

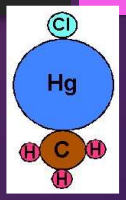
Mercury

- Elemental
  - Inhalation
  - Targets CNS & kidneys
- Inorganic salts
  - GI tract
  - Targets Kidneys & GI tract
  -
- Organic mercurial
  - GI tract
  - Targets CNS

"Mad as a hatter"

Mercury

- Major source of mercury is through meat or seafood, in the form of **methyl mercury**
- Highest in people who eat a lot of marine food
- Methyl mercury is easily taken up through the intestinal wall
- Major health concern is damage to the brain and nervous system, may also affect the immune system
- Methyl mercury easily passes through the placenta and can affect the fetus → may cause neurological damage



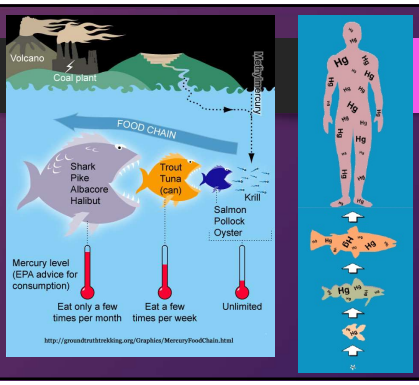
Coal-burning power plants are the most common source of mercury pollution.

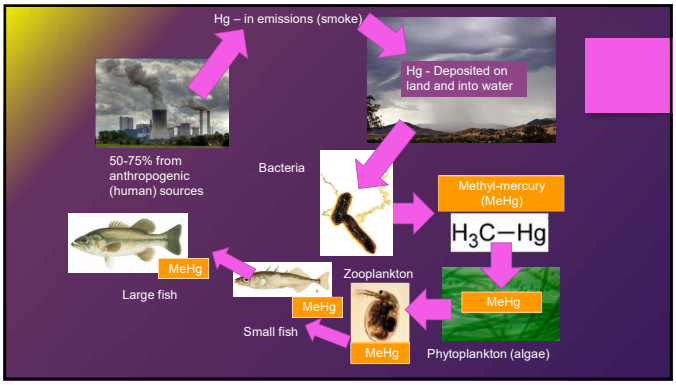
Coal contains mercury naturally, and when it is burned, the mercury travels up the smokestack and is released into the air.

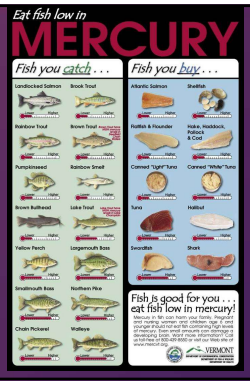
Mercury poisoning –Minamata Disease

Release of methyl mercury in waste water from a chemical factory 1932-1968.

Bioaccumulation







Two drops of death

- **Karen Elizabeth Wetterhahn,** Professor of Chemistry at Dartmouth
- She was using all proper safety precautions – protective clothing, gloves, and most important, a negative pressure fume hood
- She had spilled one or two drops of dimethylmercury from the tip of a pipette onto her latex-gloved hand
- She proceeded to clean up the area prior to removing her protective clothing
- Tests later revealed that dimethylmercury can rapidly permeate different kinds of latex gloves and enter the skin within about 15 seconds

Dangerous levels of mercury found in skin creams purchased on Amazon, Ebay
EWG, Nov 15, 2018

- Mercury is used in cosmetics as a skin lightening agent and preservative. Cosmetics with mercury are often marketed as skin lightening creams and anti-aging treatments that remove age spots, freckles, blemishes and wrinkles. Adolescents sometimes use these products as acne treatments.
- The FDA banned the use of mercury in most cosmetics at levels higher than 1 ppm in 1973
- Despite these actions, skin care products that contain mercury remain on the market, readily accessible to many consumers

CONTROVERSY – MERCURY IN VACCINES & AUTISM

- Mercury is a known neurotoxin
- Mercury affects neuronal development -cell migration & division, cell degeneration & death
- Ecological link? Rising incidence of autism in the 1990's – more exposure to mercury?
- Thimerosal, a preservative used in vaccines, contains ethyl mercury

Statement on thiomersal -2006

World Health Organization

- The Global Advisory Committee on Vaccine Safety concludes that there is no evidence of toxicity in infants, children or adults exposed to thiomersal (containing ethyl mercury) in vaccines July 2006
- The pharmacokinetic profile of ethyl mercury is substantially different from that of methyl mercury.

•Hertz-Picciotto I et al. Blood mercury concentrations in CHARGE Study children with and without autism. *Environ*

Ref:

•Hertz-Picciotto I et al. Blood mercury concentrations in CHARGE Study children with and without autism. *Environ Health Perspect.* 2010, 118(1):161-6.

Some authors have reported higher blood mercury (Hg) levels in persons with autism, relative to unaffected controls.

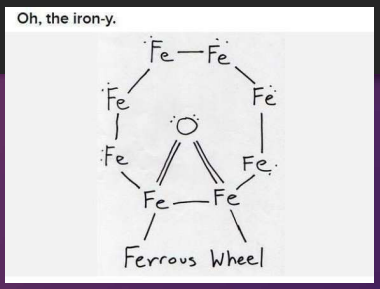
OBJECTIVES: We compared blood total mercury concentrations in children with autism or autism spectrum disorder (AU/ASD) and typically developing (TD) controls in population-based samples, and determined the role of fish consumption in differences observed.

METHODS: The Childhood Autism Risk from Genetics and the Environment (CHARGE) Study enrolled children 2-5 years of age. After diagnostic evaluation, we analyzed three groups: autism spectrum disorder (AU/ASD), non-autism spectrum disorder (non-AU/ASD) with developmental delay (DD), and population-based typically developing (TD) controls. Mothers were interviewed about household, medical, and dietary exposures. Blood Hg was measured by inductively coupled plasma mass spectrometry. Multiple linear regression analysis was conducted (n = 452) to predict blood Hg from diagnostic status controlling for Hg sources.

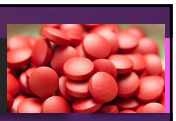
RESULTS: Fish consumption strongly predicted total mercury (Hg) concentration. Autism spectrum disorder (AU/ASD) children ate less fish. After adjustment for fish and other Hg sources, blood Hg levels in autism spectrum disorder (AU/ASD) children were similar to those of typically developing children (p = 0.75); this was also true among non-fish eaters (p = 0.73). The direct effect of autism spectrum disorder (AU/ASD) diagnosis on blood mercury not through the indirect pathway of altered fish consumption was a 12% reduction. Developmental Delay (DD) children had lower blood Hg concentrations in all analyses. Dental amalgams in children with gum-chewing or teeth-grinding habits predicted higher levels.

CONCLUSIONS: After accounting for dietary and other differences in Hg exposures, total Hg in blood was neither elevated nor reduced in CHARGE Study preschoolers with autism spectrum disorder (AU/ASD) compared with unaffected controls, and resembled those of nationally representative samples.

4. Iron



Overview - Iron



- Essential to the function of hemoglobin, myoglobin, many cytochromes, and many catalytic enzymes
- Extremely toxic when high levels after an overdose or from accumulation in disease states- Hereditary Hemochromatosis
- Approximately 10% of ingested iron is absorbed from the intestine and subsequently bound to **transferrin**, using only 15 to 35% of the iron-binding capacity of transferrin
- The acute ingestion of iron is especially hazardous to children. (Pills look like candy)
- Acute ingestion in adults -usually associated with suicide attempts
- Early recognition is necessary to ensure appropriate therapy and prevention of fatalities.

Lab Values

- **Normal serum iron levels range from 50 to 150 µg/dL**
- **The total iron-binding capacity (TIBC), ranges from 300 to 400 µg/dL**
- **TIBC is a crude measure of the ability of serum proteins—including transferrin—to bind iron**
- **Transferrin saturation = Iron/TIBC High**
- **When iron levels rise after a significant iron overdose, transferrin becomes saturated so that excess iron circulates as free, unbound iron in the serum**
- **This unbound iron is directly toxic to target organs**

Assessment of the severity of an iron exposure

- Important to refer to the amount of elemental iron ingested because the toxicity of an iron compound depends on the amount of elemental iron it contains
- The total amount of elemental iron ingested can be approximated by multiplying the estimated number of tablets by the fraction of elemental iron contained in the tablet

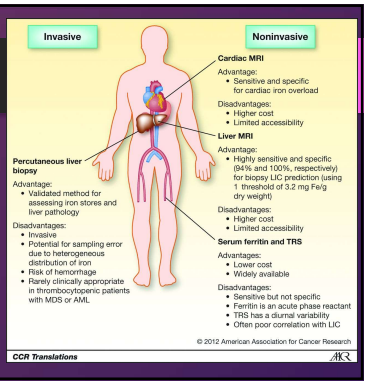
COMPOUND	PERCENTAGE OF ELEMENTAL IRON
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12
Ferric pyrophosphate	30
Ferrocholinate	14
Ferroglycine sulfate	16
Ferrous sulfate, dried	33
Ferrous carbonate, anhydrous	38
Carbonyl iron	100
Iron polysaccharide	46

A 325-mg tablet of ferrous sulfate heptahydrate has 65 mg (20%) of elemental iron

Toxic Levels

ELEMENTAL IRON (mg/kg)	PEAK SERUM IRON LEVEL (µG/DL)	TOXICITY
<20	50-150	None
20-40	150-300	Mild
40-60	300-500	Moderate
>60	>500	Severe

Iron – other testing



Clin Cancer Res; 18(23) December 1, 2012

Two toxic effects

- Causes direct caustic injury to the gastrointestinal mucosa
- Impairs cellular metabolism, primarily of the heart, liver, and central nervous system (CNS)

Clinical features

- The clinical effects of acute iron poisoning occur in **five stages**
- Not every patient goes through every phase

Stages of Iron Toxicity

Stage	Clinical Effect	Time Frame
Stage I	• GI Irritation	30 min - 6 hrs
Stage II Latent	• Recovery from GI symptoms	6 hrs - 24 hrs
Stage III Shock and metabolic acidosis	• Metabolic acidosis (anion gap) • Dehydration • Lactic acidosis	6 hrs - 72 hrs
Stage IV Hepatotoxicity/Hepatic necrosis	• Fulminant hepatic failure	12 hrs - 96 hrs
Stage V Bowel obstruction	• GI mucosa healing leads to scarring	2 wks to 8 wks

Early effects

Phase 1
- Reflects the corrosive effects of iron on the gut
- Vomiting occurs within 80 min of ingestion
- Diarrhea, often bloody, follows

Phase 2
- An apparent but not complete **recovery** that lasts less than **24 hours** but can extend up to 2 days
- Most patients recover after this point

Mid-late effects

Phase 3
Recurrence of GI symptoms
Severe lethargy or coma
Anion gap metabolic acidosis
Leukocytosis
Coagulopathy -DIC
Renal failure
Cardiovascular collapse

Serum iron levels may have fallen to normal during this phase because of distribution of iron into the tissues

Phase 4
Fulminant hepatic failure 2 - 5 days after ingestion

Rare, appears to be dose related, usually fatal

Phase 5
Represents the consequences of healing of the injured gastrointestinal mucosa

Characterized by pyloric or proximal bowel scarring, sometimes associated with obstruction

Labs

- A serum iron level measured at its peak, **3 to 5** hours after ingestion, is the most useful laboratory test to evaluate the potential severity of an iron overdose
- Labs:
  - CBC, peripheral smear
  - Coags
  - Urea and electrolytes
  - Blood gases
  - Glucose

X Ray

- Most tablets that contain a significant amount of elemental iron are radiopaque
- The presence of tablets on a radiograph correlates with the severity of the ingestion

Management of iron toxicity

- Supportive measures:
  - Airway
  - Breathing
  - Circulation
- Chelating agent, Deforoxamine – continuous infusion for up to 24 hours
- Deforoxamine binds with **ferric iron (Fe3+)** in the blood to form water-soluble ferrioxamine that is then **excreted** by the kidneys
- Significant adverse effects of IV Deforoxamine therapy include hypotension and the development of acute respiratory distress syndrome (ARDS)

Take Home Messages

- A history of exposure is the most critical aspect of diagnosing heavy metal toxicity. A complete history includes questions about potential occupational exposures, hobbies, recreational activities, and potential environmental exposure.
- A complete dietary history should be taken, especially the ingestion of fish, seafood, and seaweed products since these will frequently be implicated as dietary sources of organic (and relatively nontoxic) mercury, arsenic, or both. The timing of ingestion relative to the collection of urine samples is critical to interpreting the results.
- Herbal medications and dietary supplements are also potential sources of heavy metal exposure. Many Ayurvedic and Chinese patent medicines contain heavy metals
- The most important therapeutic maneuver in many cases of metal toxicity is to remove the source of exposure

Questions?