Metals and Metalloids

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Treatment of Metal Poisoning

Old School Approaches

"The treatment of acute [*insert metal here*]-poisoning consists in the evacuation of the stomach, if necessary, the exhibition of the sulphate of sodium or of magnesium, and the meeting of the indications as they arise. The Epsom and Glauber's salts act as chemical antidotes, by precipitating the insoluble sulphate of [*insert metal here*], and also, if in excess, empty the bowel of the compound formed. To allay gastrointestinal irritation, albuminous drinks should be given and opium freely exhibited…"

Wood, HC: Therapeutics Materia Medica and Toxicology, 1879

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Treatment of Metal Poisoning

Old School Approaches

"If possible, the rapid administration of 2 oz. (6-7 heaping teaspoonfuls) of Magnesium sulfate (Epsom Salts) or Sodium sulfate (Glauber's Salt) in plenty of water. Alum (aluminum potassium sulfate) will also be useful in 4 gm (60 gr.) doses (dissolved) repeated. Very dilute Sulfuric acid may be employed (30 cc of a 10 % solution diluted to 1 quart). All soluble sulfates precipitate [*metal*] as an insoluble sulfate…"

Lucas, GW: The Symptoms and Treatment of Acute Poisoning; 1953

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Overview of Metals

- Iron
- Lead
- Arsenic
- Mercury
- … a whole bunch of other ones

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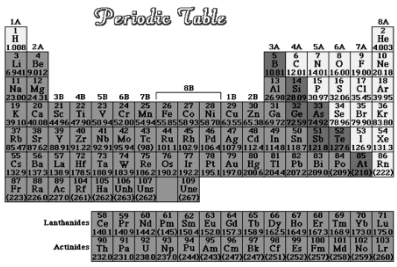
What's a Metal?
What's a Metalloid?



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Iron Poisoning
Introduction

- Essential for normal tissue and organ function
- In toxic doses, iron salts (ferrous sulfate, fumarate or gluconate) cause corrosive gastrointestinal effects followed by hypotension, metabolic acidosis, and multisystem failure.

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Iron Poisoning
Historical Data

- From 1999-2001
  - 10852 cases of iron poisoning were reported to the AAPCC – 60% occurred in children under 6 years
  - 30% of all pediatric pharmaceutical-related deaths reported to the AAPCC during that time period were a result of iron ingestion
- In 1997, the FDA mandated child-proof "strip packaging" & warning labels to be placed on all iron-containing products

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Iron Poisoning
Elemental Iron Content

Ferrous Gluconate	11.6%
Ferrous Lactate	19%
Ferrous Sulfate	20%
Ferrous Chloride	28%
Ferrous Fumarate	33%
Iron dextran	50mg Fe/mL

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Iron
Sources

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Supplement Facts
Serving Size: [illegible]

Amount per Serving	For 2-3 yrs old 1/2 Tablet % Daily Value for 2-3 yrs old	For Adults and Children 4 Years of Age and Older 1 Tablet % Daily Value for Adults and Children 4 Years of Age and Older
Vitamin A	5000 IU	100%	100%
Vitamin C	60 mg	75%	100%
Vitamin D	400 IU	50%	100%
Vitamin E	30 IU	140%	400%
Thiamin (B1)	1.5 mg	107%	100%
Riboflavin (B2)	1.7 mg	106%	100%
Niacin (B3)	20 mg	111%	100%
Vitamin B6	2 mg	143%	100%
Folate,Folic Acid,Folacin	400 mcg	100%	100%
Vitamin B12	6 mcg	100%	100%
Biotin	40 mcg	13%	13%
Pantothenic acid	10 mg	100%	100%
Calcium	100 mg	6%	10%
Iron (elemental)	18 mg	90%	100%
Phosphorus	100 mg	6%	10%
Iodine	150 mcg	107%	100%
Magnesium	20 mg	5%	5%
Zinc	15 mg	94%	100%
Copper	2 mg	100%	100%

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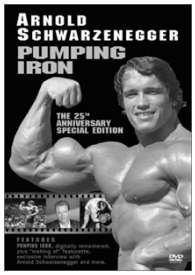
Iron
Other Sources



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Iron Poisoning
Range of Toxicity

- Minimum toxic dose: 20-60 mg/kg
- Fatal poisonings rare <60 mg/kg
- A 10-kg toddler can ingest 10 tablets of a 325mg preparation containing ferrous sulfate…

  Result: ingestion of 65 mg/kg of Fe

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Iron Poisoning
Pathophysiology – GI Effects

- Direct corrosive effects on the GI mucosa.
  - Emesis and stools may or may not be bloody
  - VS changes from volume losses, as well as vasodilation due to absorbed iron
- Mild metabolic acidosis may ensue, secondary to lactate production from dehydration.

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Iron Poisoning
Pathophysiology – Liver Failure

- Portal vein transports iron to the liver
- Iron travels the portal triad and comes into immediate contact with hepatocytes → resulting in hemorrhagic *periportal* injury and necrosis (direct hepatotoxin)
- *This process takes several hours!*

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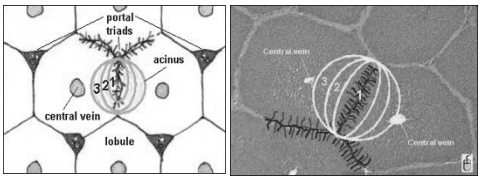

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Iron Poisoning
Pathophysiology – Metabolic Acidosis

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I – Iron
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Sidenote: Metabolic Acidosis after Tox Fellowship…

BEJRWFGKJLVDNRSVJLNWRJKLGJRW
VBLJNJNJNLSRVJNSWBRJNDEVGKJS
NDLGJVNWSDLJVNWLEJRNFGWDNV
KJUDNFRKUMUDPILESKFKHUJGWOS
UHVLKENRILHSLIFGNEIRUSDVWIRH
NBVINSWRIGCL…*HOLY@#$%ALOTOF*
THINGSCAUSEMETABOLICACIDOSIS…J
GRLUINBDFKGHJEJBDIVKUBELVAJV

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Iron Poisoning
Pathophysiology – Metabolic Acidosis

- Excess Fe in the blood is converted from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form
- Fe^{3+} builds up in mitochondria and attracts electrons from the electron transport chain, disrupting oxidative phosphorylation
- *Process takes several hours!*

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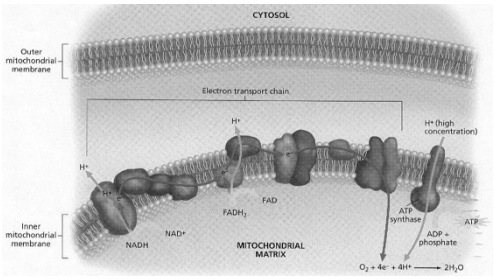

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Iron Poisoning

Pathophysiology – Metabolic Acidosis

- Pool of hydrogen ions (H+) earmarked for the conversion of ADP to ATP is liberated, exacerbating metabolic acidosis
- Multisystem failure: cell death and necrosis from to injury to the GI mucosa, the liver and the lung. Elevated tissue levels of iron also be found in the kidneys and brain

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Iron Poisoning

Clinical Presentation – "The 5 Stages"

- Stage I – vomiting, diarrhea, and abdominal pain resulting from the direct effects of iron on the GI mucosa in the first 6 hours of toxicity
- Stage II – "latent" period during which patients can experience an apparent recovery that may last 6-18 hours

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Iron Poisoning
Clinical Presentation – "The 5 Stages"

- Stage III – shock from volume losses, decreased tissue perfusion, and metabolic acidosis in 24 h. MS changes, abnormal respirations, seizures
- Stage IV – severe hepatic injury, apparent clinically and biochemically 2-3d after exposure
- Stage V – gastrointestinal strictures and scars that manifest weeks after exposure

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Iron Poisoning
Clinical Presentation – "The 5 Stages"

- Patients may go directly from Stage I (GI) to Stage III (shock/acidosis) if they do not receive appropriate therapy – can occur well before the described time frames
- Stage IV (hepatic injury) can be concurrent with Stage III (shock/acidosis)

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Iron Poisoning
Diagnostics

- Serum iron level
  - Initial levels may not accurately predict the severity of toxicity
  - May rise during treatment if a significant amount of iron remains in the GI tract
  - Best for *following progression*
- Patients with serum iron levels lower than 300 mcg/dL are rarely symptomatic

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Iron Poisoning
Diagnostics

- *May* see evidence of radio-opaque pills or pill fragments in the GI tract (negative KUB is an unreliable indicator)
- Elixir preparations are *not* visible on X-Ray
- Chewable tablets appear on 5% of KUB's

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Iron Poisoning
Diagnostic Pearls

- Consider Fe poisoning in *any* patient with:
  - GI symptoms
  - Mental status changes
  - Unexplained anion-gap metabolic acidosis
- Anemia, bloody emesis/stools may be absent or unreported
- *Unreliable*: WBC>15.0, glucose>150 to predict Fe>300
- *Useless*: TIBC

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Iron Poisoning
Treatment - Decontamination

- Syrup of Ipecac – NO (vomiting confounds)
- Gastric Lavage – NO (pills usually too big)
- Activated Charcoal – NO (does not bind)
- Whole Bowel Irrigation – possible benefit

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Iron Poisoning
Treatment

- Symptomatic and general supportive treatment with close monitoring of vital signs and aggressive IVF, $NaHCO_3$
- Initial labs CBC, lytes, and serum Fe level
- ABG, transaminases, and PT may be useful in patients who continue to be symptomatic

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Iron Poisoning
Treatment

- Asymptomatic
  - observe for at least 4 hours
  - start workup with onset of any GI symptoms
- Symptomatic
  - start workup immediately
  - watch for several hours after fluid resuscitation

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Iron Poisoning
Treatment – Deferoxamine Chelation

- DFO + Fe^{3+} → ferrioxamine
- Turns urine red-brown: "vin rose"
- Consider in patients with metabolic acidosis, mental status changes, or shock (base on symptoms, not levels)
- 100 mg DFO chelates only 8.5 mg Fe

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Iron Poisoning
Treatment – Deferoxamine Chelation

- Start infusion at 15 mg/kg/h
- May need to increase to 30-45 mg/kg/h
- Rate limit: histamine-mediated hypotension
- Little effect from H1-blocker premedication
- Treatment duration until *symptoms* resolve
  - Don't base on color reversion
  - Don't use non-validated published time limits

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Iron Poisoning
Extra Credit

What infectious side effect is most commonly documented with deferoxamine infusion?

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Iron Poisoning
Extra Credit

Yersinia septicemia

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Iron Poisoning
Take-Home Points!

- Must think of diagnosis early
  - Ask about recent pregnancies and presence of household iron for *EVERY PATIENT WITH GI SYMPTOMS!*
  - Always suspect Fe (and get a level!) in any patient with GI symptoms, MS changes, and unexplained metabolic acidosis
- Don't rely on KUB/WBC/Glucose/TIBC
- Symptomatic treatment is most important

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Lead Poisoning
Sources

- Children
  - History of pica (FE deficiency often concurrent)
  - Paint chips, dirt, folk remedies ("Azarcon"), candy, pottery, makeup
- Adults
  - Inadvertent occupational exposure
  - Pottery, folk remedies ("Litargirio")

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Lead Poisoning
Clinical Effects

- Can affect almost every organ system.
  - Central and peripheral nervous systems
  - Cardiovascular
  - Gastrointestinal
  - Renal
  - Endocrine
  - Hematologic systems
- Teratogenicity

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Lead Poisoning
Acute Toxicity

- Young children: history of pica
- Adults: inadvertent occupational exposure
- Reversible renal injury – mild-to-moderate exposure
- Acute Lead Encephalopathy:
  - Most often from rapidly absorbed lead salts
  - Hepatic injury, hemolysis, anorexia, vomiting, malaise, and seizures due to increased intracranial pressure; chronic exposure effects may also be present

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Lead Poisoning
Chronic Toxicity

- Diagnosis much more vague
- Children
  - Weight loss, weakness, abdominal complaints, anemia
  - Abnormal cognitive development: first signs in children may be subtle neurobehavioral deficits adversely affecting classroom behavior and social interaction;
- Adults
  - Vague gastrointestinal and CNS complaints
  - Hypertension
  - Wrist-drop/foot-drop and colic quite rare

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Lead Poisoning
Pathophysiology

- Anemia
  - Heme synthesis – several enzymes inhibited via binding to sulfhydryl groups
  - Build-up of delta-aminolevulinic acid, coproporphyrin and zinc protoporphyrin
  - Microcytic, hypochromic; Fe deficiency
- Neuronal effects
  - Inhibition of dendritic arborization, especially in developing brains

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Lead Poisoning
Treatment

- Removal from source of exposure
- Whole bowel irrigation for retained metal
- Chelation if indicated (BAL, EDTA, DMSA)… BAL for encephalopathy (well documented). Role for others is still not fully determined.

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Mercury Poisoning
Sources

- Elemental:
  - Thermometers, paints, ceramics, batteries, amalgams
  - Inhaled Hg vapor
- Inorganic:
  - Industry (photography, explosives, inking, cosmetics)
- Organic:
  - Bactericides/Fungicides
  - Fish
  - Farming
  - Embalming preparations

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Mercury Poisoning
Clinical Effects

- Can affect almost every organ system.
  - Central and peripheral nervous systems
  - Cardiovascular
  - Gastrointestinal
  - Renal
  - Hematologic systems
- Teratogenicity

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Mercury Poisoning
Clinical Effects

- Elemental:
  - Acute pneumonitis, corrosive bronchitis, embolism
  - May be preceded by stomatitis, colitis, lethergy, confusion, fever/chills, dyspnea, metallic taste
  - Chronic Triad: *tremor, gingivitis, erethism* (insomnia, shyness, memory loss, emotional lability, nervousness, anorexia
  - Other findings
    - Corneoscleral junction, lens damage
    - Peripheral neuropathy

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Mercury Poisoning
Clinical Effects

- Inorganic:
  - Acute corrosion – patient may die within hours
  - Shock, electrolyte imbalances, protein loss
  - Chronic effects similar to elemental mercury
    - Long-term behavioral impairment
    - Subclinical psychomotor and neuromuscular changes
    - Renal effects may resemble chronic renal failure

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Mercury Poisoning
Clinical Effects

- Organic: (may take weeks)
  - Fatigue, ataxia, dyscoordination, tremor, spasticity, weakness (hands, face, legs)
  - Numbness: mouth, stocking-glove
  - Deafness, tunnel vision, visual field constriction, scanning speech, dysphagia
  - poor concentration/memory, emotional lability, depression

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Mercury Poisoning
Pathophysiology

- Binding to enzymatic sulfhydryl groups
  - Enzymes of cellular function
  - Impaired metabolism of carbohydrates at pyruvic acid level
- Binding to carboxyl, amide, amine, phosphoryl groups

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Mercury Poisoning
Pathophysiology

- Elemental mercury
  - Lung is primary target for mercury vapor
    - Poor GI absorption
    - Moderate absorption via alveoli (remains in elemental form
  - Some systemic absorption
    - Oxidized by RBC's and tissues to Hg^{2+}
    - Some elemental Hg passes through blood-brain-barrier
    - Accumulation in kidney – renal dysfunction RARE

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Mercury Poisoning
Pathophysiology

- Inorganic mercury:
  - 10-15% absorbed from GI tract
    - Much remains bound to mucosa
  - Remains in ionized form post absorption
    - Very little passes into CNS
    - High renal accumulation (terminal portion of proximal tubule), leading to ATN (anuria within 24h in 50% of cases)
    - Some liver/spleen accumulation (mild)

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Mercury Poisoning
Pathophysiology

- Organic mercury:
  - 90% absorption from GI tract
  - Distribution: liver, kidney, RBC, brain, hair, epidermis
  - Rapid crossing over blood-brain barrier likely after conjugation to glutathione: depostion in cerebellum, occipital lobe, precentral gyrus;
  - Binds to typical enzyme moieties
    - Also inhibits choline acetyltransferase, may lead to some anticholinergic signs and symptoms, muscular weakness

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Mercury Poisoning
Treatment

- Removal from source of exposure
- Whole bowel irrigation for retained metal (need to perform early)
- Supportive care for fluid/electrolyte disturbances, renal failure, and pulmonary injury
- Chelation if indicated (BAL, EDTA)

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Arsenic Poisoning
Sources

- Food and water contamination
  - Pesticides (seafood, well water)
  - Production of arsenicals
- Microelectronic manufacturing
- Smelting, fossil fuel combustion
- Wood preservatives manufacturing
- Opium inhalation

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Arsenic Poisoning
Clinical Effects

- Can affect almost every organ system.
  - Central and peripheral nervous systems
  - Cardiovascular
  - Gastrointestinal
  - Renal
  - Hematologic systems
  - Skin
- Teratogenicity

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Arsenic Poisoning
Acute Toxicity

- Inhaled:
  - Cough, dyspnea, chest pain, resp. failure
- Ingestion:
  - Hemolysis and increased vascular permeability
  - Dehydration, intense thirst, vomiting, diarrhea, electrolyte imbalance
  - Burning/dry mucous membranes
  - Confusion, delirium, encephalopathy, seizures
  - Ventricular tachydysrhythmias
  - Delayed peripheral neuropathy

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Arsenic Poisoning
Chronic Toxicity

- Hematologic changes
  - Leukopenia, anemia, pancytopenia
  - Basal and squamous cell cancer, lung cancer
- Eczematous skin lesions, hyperkeratosis, warts, Mee's lines
- Renal failure
- Sensorimotor peripheral neuropathy
  - 1-3 weeks after exposure
  - Distal-to-proximal progression (days to weeks)

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Arsenic Poisoning
Pathophysiology

- Airborne As2O3 – deposited mostly in upper airways (most is ingested); AsH3 (arsine gas) easily inhaled
- 90% of ingested doses are absorbed
- Dilation of small blood vessels in splanchnic circulation causes vesiculation with or without rupture
- Mechanism of tissue injury not well-described
- Organic forms not very toxic (fund mostly in seafood)

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Arsenic Poisoning
Treatment

- Removal from source of exposure
- Whole bowel irrigation for retained metal (need to perform early)
- Supportive care for fluid/electrolyte disturbances, hypotension, dysrhythmias, renal failure, and pulmonary injury
- Chelation if indicated (BAL, EDTA)

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Thallium

- Sources: Rat poison (Russia, China), homicidal poison, semiconductors, jewelry manufacturing
- Mechanism: likes to go where potassium goes, disrupts Na-K ATP transport enzymes – likely explanation for neuropathy (functional, not structural damage)
- Dose: 15 mg/kg. Salt forms more toxic. May absorb through skin.

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Thallium

- Clinical: GI distress (12-24h), THEN painful neuropathy (24-72h), THEN alopecia (2-4 weeks later)
- Lab: urine >20mcg/L
- Treatment: Charcoal (MDAC?) & Dialysis for acute exposures, Prussian Blue; BAL may help, but little evidence

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Cadmium

- Sources: Mining, smelting, electroplating, soldering, batteries, water contamination
- Mechanism: corrosive; binds to metallothionein, deposits in kidney
- Dose: oral (>5gm); inhaled cadmium is worse-case (>5mg/m3)

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Cadmium

- Clinical: cough/wheezing, NCPE (inhaled); GI distress, renal failure (ingested); “itai-itai” (chronic)
- Lab: whole blood (>1 mcg/mL); minimal urinary excretion
- Treatment: supportive; chelators don’t work

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Chromium

- Sources: Electroplating, chrome yellow paint,
- Mechanism: hexavalent form is corrosive and an oxidizer
- Dose: inhaled (0.05mg/m3); ingested form mostly turns into trivalent form – rarely toxic unless acute ingestion >500mg

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Chromium

- Clinical: airway irritation, nose/throat/lung cancer; GI corrosion, renal failure, hemolysis in massive ingestion
- Lab: urine >> 1mcg/L
- Treatment: supportive; ascorbic acid may accelerate hexavalent → trivalent in GI tract; light evidence for N-Ac in animal models

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Antimony (Stibine)

- Sources: alloy, rubber manufacturing; flame retardant,
- Mechanism: corrosive; poorly understood cellular mechanisms – may bind to sulfhydryl groups; hemolysis from stibine
- Dose: antimony 100mg/kg; stibine 0.1ppm

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Antimony (Stibine)

- Clinical: antimony – GI distress, hepato-renal insufficiency; stibine – hemolysis, jaundice, renal failure
- Lab: urine >> 2mcg/L
- Treatment: supportive

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Barium

- Sources: depilatories, fireworks, glass-making
- Mechanism: shifts K+ into cells and prevents efflux
- Dose: 200mg of non-sulfate salts

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Barium

- Clinical: hypokalemia with weakness/ flaccid paralysis, dysrhythmias, GI distress; pneumoconiosis from inhalation
- Lab: blood >1 mg/L
- Treatment: potassium replacement; sodium/ magnesium sulfate to ppt insoluble salt

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Boron

- Sources: Boric acid – pesticide, fungicide
- Mechanism: irritant; cellular mechanisms poorly understood
- Dose: >2gm in children; >10gm in adults

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Boron

- Clinical: GI distress with blue-green emesis and renal failure (immediate); agitation/ seizures (1 day); lobster rash (5 days) with alopecia
- Lab: levels obtainable, but correlate poorly
- Treatment: supportive

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Copper

- Sources: pennies, plumbing, pesticides,
- Mechanism: irritant; cellular mechanisms poorly understood
- Dose: >200mg ingestion; 100mg/m3 inhalation

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Copper

- Clinical: GI distress with blue-green emesis and renal failure; centrilobular hepatic necrosis; hemolysis
- Lab: serum >4mg/L
- Treatment: supportive; BAL and d-penicillamine

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Manganese

- Sources: welding, mining, smelting
- Mechanism: unknown
- Dose: highly variable – 10,000ppm IDLH

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Manganese

- Clinical: pneumonitis acutely; atypical psychosis/schizophrenia ("manganese madness") followed by parkinsonism
- Lab: serum or urine >2mcg/L
- Treatment: supportive; poor response to chelators and anti-parkinson drugs

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Selenium

- Sources: “Gun Blue”, copper refining, supplements
- Mechanism: poorly understood
- Dose: “one swallow” in children (gun-blue) may be fatal; about 5mg/kg is toxic in most cases

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Selenium

- Clinical: onion/garlic odor; GI corrosion; coma, hypotension, cardiac depression with T-wave inversion, seizures
- Lab: whole blood >> 1mg/L
- Treatment: supportive; minimal animal evidence for N-Ac; ascorbic acid may turn salts into elemental selenium (poor proof)

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