

Metals

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Sources

- Information taken from:
 - Basic Toxicology, 3rd edition, Frank Lu, pages 294-311
 - Industrial Toxicology, edited by Phillip Williams and James Burson
 - www.emedicine.com

Introduction

- Number of metals and metalloids in the periodic table = 80
- Many industrial uses
- May also be found as essential elements in the body, in the environment, food or workplace

Introduction

- Metals donate one or more electrons to form a cation in aqueous solutions
- Heavy metal – generally seen as toxic and have a specific gravity of greater than 4 or 5

Introduction

- Exposure to metals occurs through the continuum from mining, extraction of ore, refining, manufacturing, use, or disposal.
- Target organ can be the site of contact (example – chromium), system toxicant (example - lead)

Introduction

- Ability of metal to cross membranes (example lungs, GI tract) varies greatly
- Generally organic metal compounds tend to pass membranes much easier than inorganic metals
- Lipophilic metal compounds move readily across membranes

Introduction

- Metals cross membranes by passive diffusion, pinocytosis or specialized transport mechanism
- Toxicity varies greatly from metal to metal
 - Example aluminum vs. mercury

Metal Biological Activity

- Biological Activity
 - Inhibit enzymes – especially in the sulfhydryl (SH) group, histidyl or carboxyl group
 - Displaces an essential metal cofactor in the enzyme, vitamins and substrate
 - Inhibit synthesis of proteins
 - Substitutes for essential metals

Metal Biological Activity

- Intracellular structures that are affected by metals
 - Endoplasmic reticulum (enzymes affected)
 - Lysosomes
 - Mitochondria – respiratory enzymes inhibited
 - Nucleus – stimulates DNA, RNA and protein synthesis (e.g. lead)

Metal Toxicity

- Dietary factors – low levels of protein in the diet or deficiencies of vitamins C and D can impact uptake
- Old and young at greatest risk
 - Lead and young children
 - Lead and mercury can cross the placenta barrier

Metals - Biomarkers

- Some metals may be found in blood, hair, nails and other excreta

Excretion of Metals

- Renal excretion (kidney) is the primary means by which the body rids itself of metals
- Kidney is often the site of injury from metals and metabolites
- GI tract – also an important route of excretion

Kidney

- Cd – renal proximal tubular cells = excretion of small-molecule proteins, amino acids and glucose in the urine
- Inorganic Hg, Pb, Cr and PI – proximal tubule damage

Excretion of Metals

- Enterohepatic Circulation- metals excreted into the intestinal tract in bile, saliva and pancreatic secretions are reabsorbed back into the GI track and return to the liver

Immune System and Metals

- Be, Cr, Ni, Au, Hg, Platinum and Zirconium induce hypersensitive reactions

Nervous System

- Organic mercury, mercury vapor and organic lead compounds readily enter the nervous system
- Other neurotoxic metals include: Cu, Au, Li, Mn

Mercury

- Elemental form is liquid
- Release from earth's crust =25k-125k tons/yr
- Man-made activities produce 10k tons/yr.
- Fossil fuel combustion, mining, smelting, production of steel, cement and phosphate

Mercury

- Air and water are small sources of mercury with respect to human exposure
- Fish is the highest single source of Hg in food
- Tuna and swordfish

Mercury

- “Mad Hatters Disease” – England
- Mercury was used in the making of felt hats as a biocide

Lead

- Background levels
 - 5-25 mg/kg in soil
 - 1-60 $\mu\text{g}/\text{L}$ in water
 - $>1 \mu\text{g}/\text{m}^3$ in air

Lead

- Organ systems impacted by lead
 - Hemopoietic (blood forming organs)
 - Nervous system
 - GI tract
 - Kidneys
 - ┆ Reproductive

Lead

- Hemopoietic – heme synthesis – anemia. Blood levels are the best single indicator of recent high exposures to lead. However, blood levels are rough estimates of exposure and don't always correlate well with lead intoxication
- Nervous systems – impact start when blood lead levels reach 80 $\mu\text{g}/\text{dl}$
 - encephaphy

Lead

- Nervous system – lead impacts the velocity of nerve conduction along an axion

Lead

- Signs and Symptoms of Plumbism include:
 - Colic, constipation
 - Paralysis of extensor muscles of the wrist (wrist drop)
 - Lead lines of gingivas
 - ┆ Non-specific = headaches, irritability, insomnia, muscle weakness, lassitude, anemia

Lead

- Storage – up to 90% of the human total body burden is in the bones, with 10% in liver and kidney
- Biological half-life of lead in the body is 10-20 yrs in bones and several months in soft tissue

Cadmium

- By-product of smelting lead and tin
- Used in electroplating, batteries, pigments, fasteners
- Exposure to general population is via food and smoking

Cadmium

- Main toxic effect:
 1. Displaces or replaces Zn in enzymes that require it as a catalyst or component
 2. Reacts with SH group

Cadmium

- Long biological half-life (15-30 years)
- Causes damage to the proximal tubules resulting in kidney lesions
- Itai-Itai disease – bone deformity, Japan, rice - questionable

Beryllium

- Main source of environmental Be is combustion of fossil fuels
- Used as an alloy in metals in the nuclear and space industries
- Berylliosis- long-term inhalation – granulomas in the lungs which eventually become fibrotic

Beryllium

- Dermal exposure – cell mediated hypersensitivity reaction
- Potential human carcinogen

Chromium

- Used in making pigments, stainless steel and alloys
- Major environmental sources include combustion of fossil fuels and cement producing plants
- Hexavalent Cr (Cr^{+6}) is a lung carcinogen
- Hexavalent Cr is water soluble and corrosive

Chromium

- Cr^{6+} causes ulceration of nasal passages
- It has been suggested that Cr^{6+} converts to Cr^{3+} inside cells, which is more biologically active – binds with nucleic acid and initiating cancer formation
- Kidney damage = renal tubular necrosis

Nickel

- Used in storage batteries, electroplating and as a catalyst
- Human carcinogen – nasal cancer mostly, but also lung, larynx, stomach and perhaps the kidneys
- Dermal sensitivity – Nickel itch for cashiers and those who sell jewelry

Zinc

- Used as a surface coating – corrosion inhibitor
- Galvanized steel
- Metal fume fever – results from exposure to newly formed (nascent) fumes
- Fume is a very small particle generated during welding or torch cutting

Zinc

- Metal fume fever is also known as zinc shakes or brass founders ague
- Metal fume fever is similar to the flu- characterized by chill, headache, cough, fever and last about 24 hours
- Onset is 3-10 hours

Metal Fume Fever

- May also be caused by fumes (oxides) of Cobalt, Magnesium or Copper

Treatment

- Chelation Agents – provide SH groups, which the metals attach to and are more readily excreted
 - BAL- British Anti-lewisite
 - Edetate disodium EDTA
 - Succimer

Summary

- Exposure to metals can occur from a variety of natural and man-made sources
- Metals vary great with respect to toxicity
- Organic metals and lipophilic metals pass membranes in the body more readily than inorganic metals
- The kidney is often the target organ