Heavy metals

TOXICOLOGY (1&2)

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Definitions

- **Metals**: originally included only gold, silver, copper, iron, lead.
  - Conduct heat and electricity

- **Metalloids**: are elements with features intermediate between metals and non-metals. Example: arsenic

- **Heavy metal**: A metal having an atomic weight greater than sodium, a density greater than 5 g/cm3 Arsenic 5.7; cadmium 8.65; lead 11.34; mercury 13.54

- Usually includes lead, cadmium and mercury

Many of the metals are essential for proper functioning of biological systems where they are usually required in trace amounts.

Metals such as Na, K, and Ca operate as essential charged molecules (ions) critical for neurotransmission and muscle contraction

Substances are toxic with excess exposure.

Blood, urine, and hair are the most accessible tissues for measuring metal exposure

Sources of heavy metal pollutants

Properties of heavy metals

They occur near the bottom of the periodic table

Have high densities

Toxic in nature

Nondegradable

Note: Arsenic is not actually a metal but is a semimetal i.e. its properties are intermediate between those of metals and nonmetals.

Toxic exposure to metals and metallic elements depends on:

1) The type of exposure (inhalation, dermal absorption, or ingestion)
2) The species (salt, element, vapor)
3) Dose and duration.
4) Host-based factors that can impact metal toxicity include (age at exposure, gender, and capacity for biotransformation)

Young: sensitive, consume more food, higher absorption in GI, rapid growth

5) Lifestyle factors such as smoking or alcohol ingestion may have direct or indirect impacts on the level of metal intoxication.

Metals are redistributed naturally in the environment by both geologic and biological cycles.

Rainwater dissolves rocks and transports materials, including metals, to rivers and underground water (eg, arsenic), depositing and stripping materials from adjacent soil and transporting these substances to the ocean to be precipitated as sediment or taken up into forming rainwater to be relocated elsewhere

Biological cycles moving metals include biomagnification by plants and animals resulting in incorporation into food cycles.

Human activity often intentionally shortens the residence time of metals in ore deposits, and can result in the formation of new, non-naturally occurring metallic compounds.

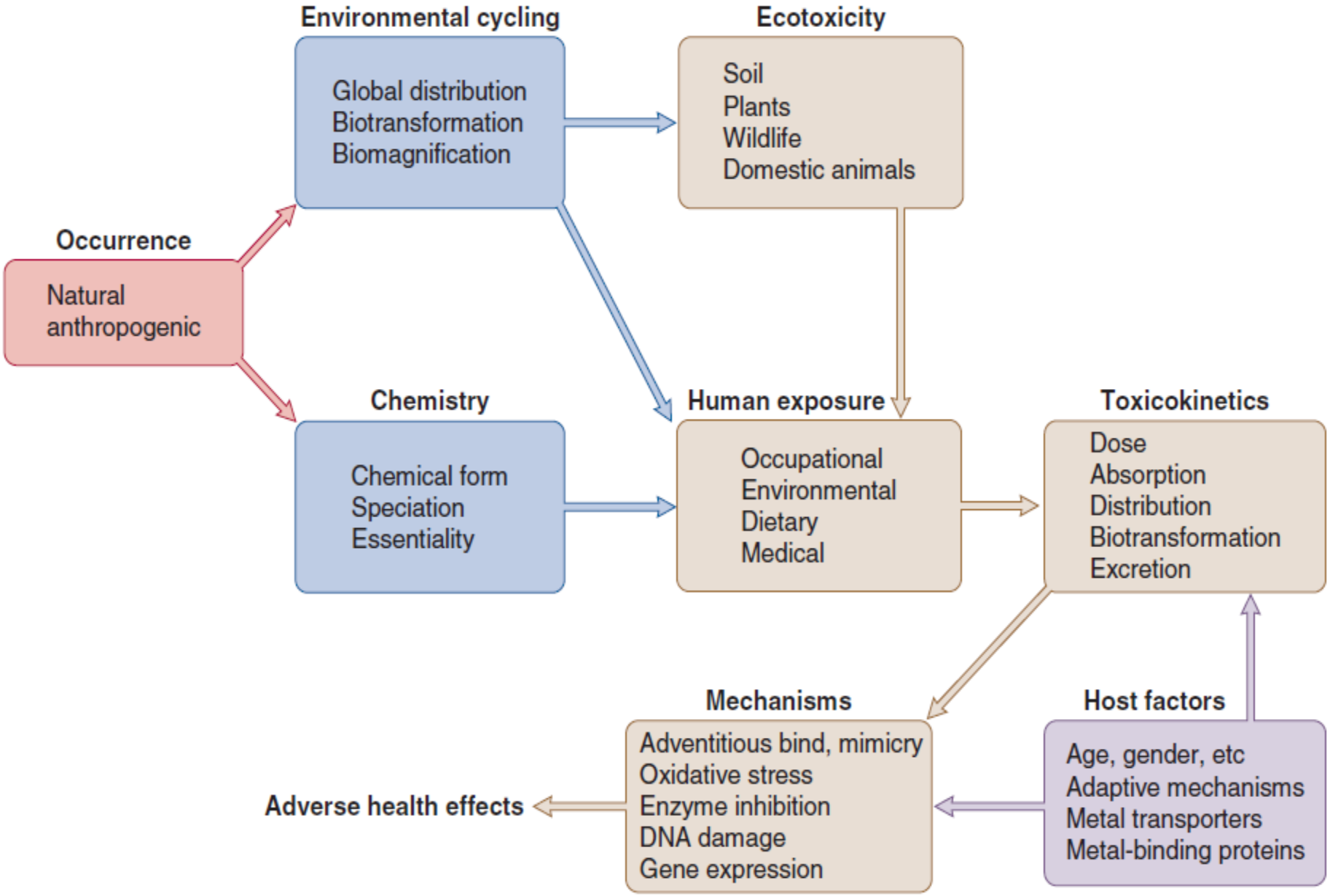

Figure 23-1. *Overview of metal toxicology.*

Absorption

- **Respiratory Absorption**

- Metal may be inhaled as vapor or aerosol (fume or dust)
  - Fume or vapor of some metals & compound are readily absorbed in from alveolar space (cadmium, 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

Gastrointestinal Absorption

- Metal may introduce into GI tract through food, water, mucociliary clearance
- Metal are absorbed into the cells lining the intestinal tract by:
  - Passive or facilitated diffusion
  - Specific transport process
  - Pinocytosis

Absorption 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)

Excretion

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 filtered in glomerulous into fluid of the renal tubule
- Some metals (Cd & Zn) are effectively resorbed by tubular epithelia before they reach the urinary bladder where very little resorption occur

Enterohepatic Circulation

- Absorbed metal may also excreted into intestinal tract in bile, pancreatic secretion or saliva

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Minor Pathways

- Hair (Hg, Zn, Cu and As)
- Nails
- Saliva
- Exhaled air
- Lactation
- Skin

Chemical Mechanisms of Metal Toxicology

1. **Metal binding ligands**

- Ex: Cadmium and mercury attach to sulfur in proteins.

2. inhibition of biologically critical enzymes

- Ex: Lead inhibit haem synthesis enzymes

3. Replacement of essential metal in the body

- Ex: Thallium mimics potassium and manganese mimics iron as a critical factor in their toxicity.

4. Metal mediated oxidative damage.

Producing oxidative modification of biomolecules such as proteins or DNA

carcinogenicity of certain metals

Ex: Nickel and chromium

A critical indicator of retention of a metal is its biological half life, or the time it takes for the body or organ to excrete half of an accumulated amount.

Ex: the biological half-lives of cadmium in kidney and lead in bone are 20 to 30 years

Management

1. Initial **stabilization of the patient**. This most often entails instituting the **ABCs** of emergency treatment
2. In the case of a few chemical agents, **antidotes** are available for neutralizing.
3. **Chelation therapy** decreases the body burden of metals that have been absorbed and distributed to body tissues

Chelators have one or more binding sites for the metal, the affinity of which varies according to the structure and properties of the metal.

Chelators:

a) Should have minimal risks involved with their therapeutic use.

b) Complex should be water soluble to enhance elimination through the kidneys without causing additional toxicity.

c) Oral administration is desirable, especially for treatment of chronic metal toxicity.

May bind to essential metals or cause the movement of metals from storage sites, thus increasing the probability for essential trace metal deficiency

TABLE 26.2 Chelators and Their Properties

Agent	Common or proprietary name	Metal-binding affinity	Indications[a]	Common ADRs
Dimercaprol	BAL	As, Hg	Acute As toxicity; Hg-induced renal damage	HT, tachycardia, NVD, HA
Ca-disodium-EDTA	Ethylene diamine tetraacetate	Ca^{+2}, Pb	Severe Pb toxicity	Renal damage
Penicillamine	Cuprimine®	Cu, Pb, Hg, Zn	Cu and Pb toxicity; Hg elimination; Wilson's disease	Allergic reactions
Deferoxamine	Desferal®	Fe^{+2}, Fe^{+3}	Fe toxicity	Allergic reactions
Succimer	DMSA, Chemet®	Pb	Pb toxicity	NVD, anorexia
Unithiol	DMPS	Hg	inorganic acute and chronic Hg poisoning	

[a]Approved for use in the treatment of the listed conditions or diseases.

Abbreviations: ADRs, adverse drug reactions; BAL, British anti-Lewisite; As, arsenic; Cu, copper; Ca, calcium; EDTA, ethylenediamine tetraacetate; Fe, iron; HA, headache; Hb, hemoglobin; Hg, mercury; HT, hypertension; NVD, nausea, vomiting, diarrhea; Pb, lead; Zn, zinc.

TOXIC METALS

1. Arsenic
2. Cadmium
3. Lead
4. Mercury
5. Iron
6. Zinc

Arsenic

- **Occurrence**: drinking water, food(Seafood and fish)
- **Uses**: wood preservatives, insecticides, and herbicides

- **Other Sources**
  - Industrial processes
    - Semiconductor manufacturing
    - Fossil fuels
    - Smelting (copper, zinc, lead)
    - Glass manufacturing
    - Antiparasitic drugs
    - Folk remedies

- **Mechanism of Toxicity:** accumulate in mitochondria and inhibiting succinic dehydrogenase activity and oxidative phosphorylation, a process that results in disruption of all energydependent cellular functions.

Trivalent forms:

- bind to sulfhydryl groups leading to inhibition of enzymatic systems
- inhibit the Krebs cycle and oxidative phosporylation. These lead to inhibition of ATP production

Pentavalent forms

- can replace the stable phosphate ester bond in ATP and produce an arsenic ester stable bond which is not a high energy bond

Endothelial damage, loss of capillary integrity, capillary leakage, volume loss, shock

Toxicokinetics: $t_{1/2}$ of inorganic arsenic in the blood is 10 hrs and of organic arsenic is around 30 hours

2-4 weeks after the exposure ceases, most of the remaining arsenic in the body is found in keratin-rich tissues (nails, hair, skin)

Renally excreted (30-50% of inorganic arsenic is excreted in about 3 days). Both forms are excreted depend on the acuteness of the exposure and dose

Signs and Symptoms of Acute Toxicity:

GI distress, watery or bloody diarrhea

Pulmonary edema, hemorrhagic bronchitis, and respiratory distress may be seen with acute oral poisoning

Hypotension, tachycardia

Complaint of a metallic taste in the mouth and garlic odor on the breath

Signs and Symptoms of Chronic Toxicity;

Changes in skin pigmentation

GI symptoms, anemia, skin cancers, and liver disease

Peripheral neuropathies

Nerve injury

Bone marrow depression resulting in anemia and leukopenia

Lung and skin cancer as result of long exposing to As

Treatment of Acute Poisoning:

consumption of large volumes of water, gastric lavage, or cathartics initiated within a few hours of exposure after oral ingestion of As

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Activated charcoal does not bind well inorganic arsenic

Whole bowel irrigation with polyethylene glycol

Skin decontamination in dermal exposure

Chelation therapy should be instituted promptly (minutes to hours)

- BAL (British anti-Lewisite)- IM
- Succimer (DMSA)- PO
- DMPS – PO, IV
- D-Penicillamine- less effective

CADMIUM

Occurrence : coal burning, waste incineration, and the use of phosphate fertilizers. cigarette smoke, food consumption, drinking water, and incidental ingestion of soil

Uses: pigmenting agents, resistant coating on metal, photography, nickel-Cd batteries, rubber……

Tobacco smoke (a one pack a day smoker absorbs roughly 5 to 10 times the amount absorbed from the average daily diet)

Mechanism of Toxicity:

The **liver** is the primary target in acute Cd exposure.

Oxidative stress or lipid peroxidation of cell membrane

Cd does not form stable DNA adducts but stimulates cell proliferation and inhibits DNA repair……. cancer

Effect on body

Affects lungs & kidneys

2º effects on skeletal system

Binds to sulfhydryl groups, disrupting enzymes

Competes with calcium for binding sites on regulatory proteins

Lipid peroxidation has been demonstrated

Respiratory Effects

Acute inhalation

- Fever, chills & decreases in FVC and FEV1

Initial symptoms: flu-like symptoms

- Later: chest pain, cough, dyspnea
- Bronchospasm and hemoptysis may occur

Chronic inhalation MAY result in impairment of pulmonary function with reduction in ventilatory capacity

Renal Effects

May cause tubular and glomerular damage with resultant proteinuria

May follow chronic inhalation or ingestion

Latency period of ~10 yrs

Nephropathy is progressive & irreversible

Renal Effects

Chronic exposure – progressive renal tubular dysfunction

Toxic effects are dose related

Critical renal concentration

Decreased GFR

Chronic renal failure

Kidney stones more common

Skeletal Effects

Bone lesions occur late in severe chronic poisoning

- Pseudofractures
- Other effects of osteomalacia and osteoporosis
- Appear to be secondary to increased urinary calcium and phosphorus losses

Signs and Symptoms of Acute Toxicity:

Inhalation: flulike symptoms, lung damage and fatality in severe cases (dust more than fume because of large size of particles).

headache, chills, muscle aches, nausea, vomiting, and diarrhea

Respiratory symptoms may linger for several weeks, and impairment of pulmonary function may persist for months.

Signs and Symptoms of Chronic Toxicity:

Kidney: cancer

Lungs: decreased lung friction and emphysema

Bone: osteoporosis and osteomalacia.

damage to the olfactory nerve, and loss of the sense of smell

yellow discoloration of the teeth, rhinitis, occasional ulceration of the nasal septum

Evaluation

Inhalation

- Chest radiograph

Chronic exposure

- Renal tests
  - Serum electrolytes, BUN, serum and urinary creatinine, serum creatinine, cadmium in blood & urine, urinary protein
- Other tests – CBC & LFTs

Direct Biologic Indicators

24 hour urine cadmium – reflects exposure over time an total body

Blood cadmium

Cadmium in hair – not reliable

Urinary $ß_2$-microglobulin – evaluate urine levels > 300 μg/g creatinine

Urinary RBP

Urinary metallothionein (MT)

Treatment of acute poisoning:

- There is no effective clinical treatment for cadmium intoxication
- Supportive treatment includes fluid replacement, oxygen, mechanical ventilation. With ingestion, gastric decontamination by emesis or gastric lavage soon after exposure. Activated charcoal not proven effective

In certain cases (Itai-Itai disease, osteomalacia) vitamin D is prescribed, although its effects have not been satisfactory

In experimental systems some chelators can reduce acute cadmium-induced mortality, but chelation therapy for cadmium generally results in significant adverse effects

Lead

Occurrence and Uses:

batteries and in sheathing electric cables, protective shielding from X rays and radiation from nuclear reactors, pigments in paint, “antiknock” agent in gasoline, until it was banned as an environmental pollutant in the United States in the 1970s.

Sources of Exposure

Soil and dust

Paint chips

Contaminated water

Parents lead-related occupation

Folk remedies

Congenital exposure

Mechanism of Toxicity:

Principal targets for Pb intoxication are the bone marrow and blood-forming pathways, GI tract, CNS, and neuromuscular system.

Pb increases intracellular levels of Ca in brain capillaries, neurons, hepatocytes, and arteries that trigger smooth muscle contraction, thereby inducing hypertension.

Toxicocokinetics and Toxicoynamics

Absorption:

- Lungs: depends on size particle
- GI:
  - Inadequate intake of iron, calcium, and total calories are associated with higher lead levels
  - Children are at higher risk of absorption than adults
- Skin:
  - Inorganic lead is not absorbed
  - Organic lead is well absorbed

Lead is carried bound to the RBC

Distributed extensively throughout tissues: bone, teeth, liver, lung, kidney, brain, and spleen

Excretion: kidney

Effects of Pb on blood formation and heme biosynthesis, Effects of Pb on heme synthesis also impact skeletal, renal, and neurological functions

Pb is incorporated into Ca selective structures and mimics its action so as to interfere with vital proteins

In bone, Pb alters circulating levels of 1,25-dihydroxyvitamin D, affecting Ca homeostasis and osteocyte function

Pb substitutes for Ca as a secondary messenger in neurons, blocking voltage-gated Ca channels, inhibiting influx of Ca and subsequent release of neurotransmitter.

Lead crosses the BBB and concentrates in the gray matter

Lead crosses the placenta

Health effects of lead

Disruption of the biosynthesis of haemoglobin and anemia

A rise in blood pressure

Kidney damage

Miscarriages

Disruption of nervous systems

Brain damage

Declined fertility of men through sperm damage

Diminished learning abilities of children

Behavioural disruptions of children, such as aggression, impulsive behaviour and hyperactivity

Range of Lead-induced Health Effects in Adults and Children

Blood lead levels	Adults	Children
10 μg/dL	Hypertension may occur	•Crosses placenta •Impairment IQ, growth •Partial inhibition of heme synthesis
20 μg/dL	Inhibition of heme synthesis Increased erythrocyte protoporphyrin	Beginning impairment of nerve conduction velocity
30 μg/dL	•Systolic hypertension •Impaired hearing(↓)	Impaired vitamin D metabolism
40 μg/dL	•Infertility in males •Renal effects •Neuropathy •Fatigue, headache, abd pain	Hemoglobin synthesis inhibition
50 μg/dL	Anemia, GI sx, headache, tremor	Colicky abd pain, neuropathy
100 μg/dL	Lethargy, seizures, encephalopathy	Encephalopathy, anemia, nephropathy, seizures

N.B

Signs and Symptoms of Acute Toxicity:

Rare: result in cramping, colicky abdominal pain, and constipation, vomiting; bloody, black stools; and a metallic taste, Arthralgias and myalgias, neurotoxicity

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Signs and Symptoms of Chronic Toxicity:

Children and young adults

Plumbism

Fatigue and muscular weakness and incoordination.

Blue-gray pigmentation of the gingiva

Pb encephalopathy

Demyelination of nerves cells causes wrist and foot drop

Diagnosis

Evaluation of clinical symptoms and signs

CBC

Serum iron levels, TIBC, ferritin

Abdominal radiographs (for recent ingestion of lead-containing material)

Whole blood lead level

X-ray fluorescence (XRF)- to asses body burden

Treatment of Acute Poisoning

TABLE 26.3 Chelation Therapy for Chronic Pb Toxicity in Children in NYC

BLL (μg/dL)	Recommended action	Chelation therapy
<20	Provide education, testing, reporting to NYC DOHMH	No chelation therapy
20–44	Provide education, retesting, reporting to NYC DOHMH; follow-up in 3 mo	No chelation therapy
>45	As above, also confirm BLL with venous sample, perform FEP test + medical exams	Chelation therapy: Ca-EDTA for 3–5 days, followed by Ca-EDTA + BAL if BLL >69 μg/dL

Abbreviations: BLL, blood lead level; FEP, free erythrocyte protoporphyrin; NYC, New York City; DOHMH, Department of Health and Mental Hygiene; EDTA, ethylenediamine tetraacetate; BAL, British anti-Lewisite.
Source: From Ref. 1.

DMSA (succimer) is the only FDA-approved orally administered chelating agent for treating children with Pb blood levels more than 45 mg/dL.

In patients with kidney impairment, BAL is recommended since excretion is primarily in bile rather than urine

EDTA also mobilizes Pb from bone to soft tissue and may aggravate acute toxicity if not given in conjunction with BAL

N.B

Clinical Monitoring

Erythrocyte protoporphyrin (EP) test

determine the accumulation of protoporphyrin in erythrocytes.

insensitive to Pb levels in the 10 to 25 mg/dL range

Free erythrocyte protoporphyrin (FEP) or **Zn protoporphyrin (ZPP)** tests are more sensitive, especially at concentrations as low as 1 mg/dL

Radiographic techniques of bones

MERCURY

Three toxic forms of Hg: elemental, inorganic, and organic.

Occurrence and Uses:

earth's crust and the leaching of sediment.

Used in thermometers, barometers, velectrical apparatus, paints

both organic and inorganic Hg undergoes environmental transformation.

Conversion of inorganic Hg to methyl Hg results in its release from sediment at a relatively fast rate and leads to its wider distribution.

Inorganic Hg may be methylated and demethylated by microorganisms.

Elemental Hg at ambient air temperatures volatilizes and is extremely dangerous

TABLE 26.4 Hg Poisoning and Its Pathophysiologic Characteristics

Characteristics	Elemental Hg (Hg°)	Inorganic Hg	Organic Hg
Form and chemical properties	Lipophilic, converted to charged cations	Salt forms, water soluble	Methyl Hg, lipophilic
Occurrence	Industrial, thermometers	Industrial, chemical laboratories, marine life	Pesticide, industrial
Absorption	Inhalation	GI tract	GI tract
Target organs	Pulmonary, CNS	Kidneys, GI	CNS
Elimination	Fecal, enterohepatic	Urinary, fecal	Fecal, enterohepatic

Abbreviations: Hg, mercury; GI, gastrointestinal; CNS, central nervous system.

Most human exposure to Hg is by **inhalation** because it readily diffuses across the alveolar membrane due to its lipid solubility. Because of this property it has a high affinity for RBCs and the CNS.

Oral absorption of organic Hg is nearly 100%.

Transfer through the placenta and the blood-brain barrier is complete.

Inorganic Hg is eliminated in urine and feces, while organic Hg is eliminated primarily in the feces.

Mechanism of Toxicity:

high-affinity binding of divalent mercuric ions to thiol or SH groups of proteins.

Inactivation of various enzymes, structural proteins, and alterations of cell membrane permeability.

Increased oxidative stress, disruption of microtubule formation, interference with protein synthesis, DNA replication, and Ca homeostasis

Health effects of mercury

Disruption of the nervous system

Damage to brain functions

DNA damage and chromosomal damage

Allergic reactions, resulting in skin rashes, tiredness and headaches

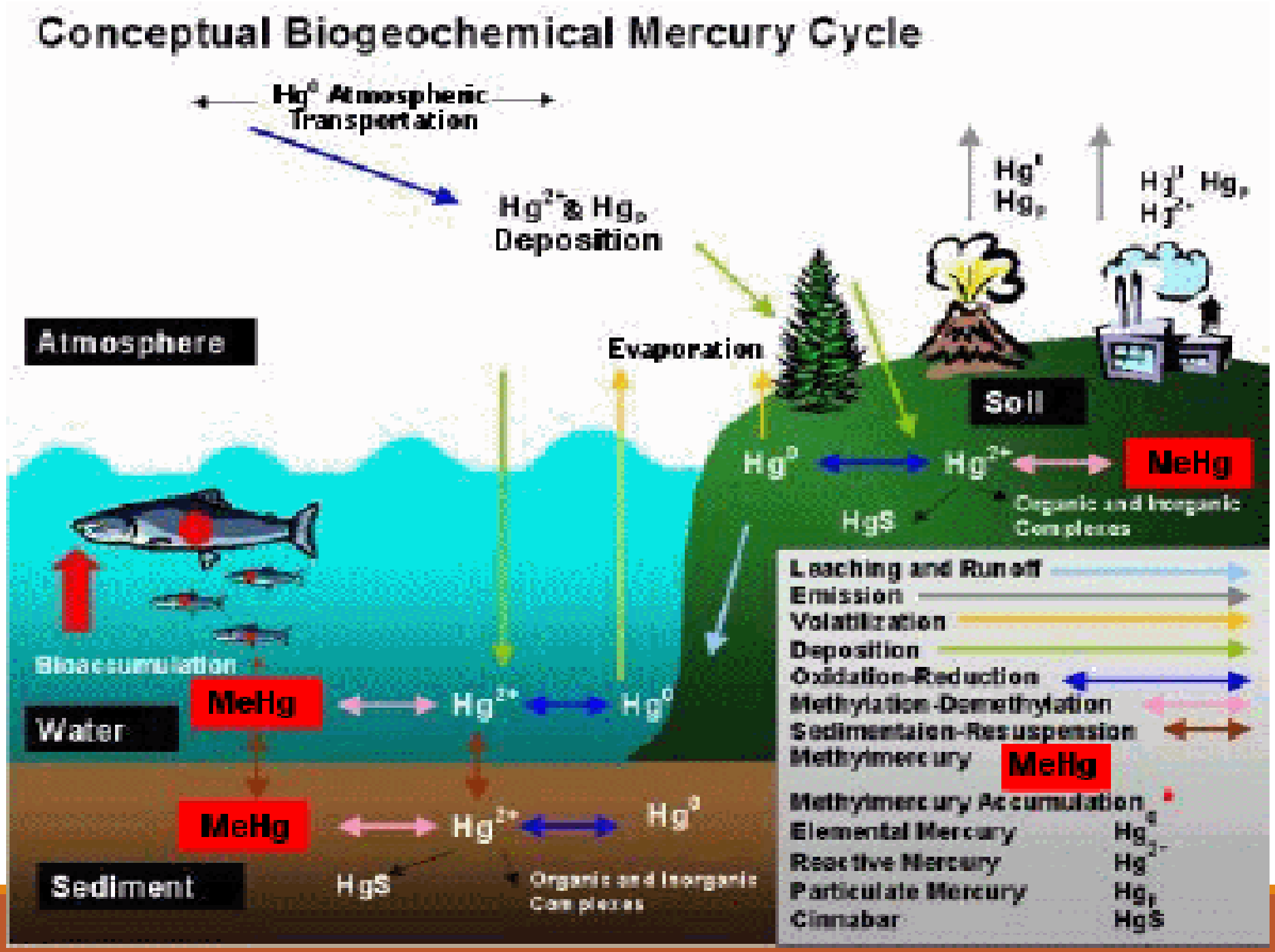
Negative reproductive effects, such as sperm damage, birth defects and miscarriages

Environmental effects of mercury

Fish are organisms that **absorb** great amounts of **methyl mercury** from surface waters every day (**mercury can accumulate** in fish and in the food chains)

The effects that mercury has on animals are: kidneys damage, stomach disruption, damage to intestines, reproductive failure and DNA alteration

Conceptual Biogeochemical Mercury Cycle



Signs and Symptoms of Acute Toxicity (Inhalation and Ingestion)

Lungs: cough, dyspnea, and tightness and burning pain in the chest.

GI: acute inflammation of the oral cavity, abdominal pain, nausea, and vomiting.

Cardiovascular: heart rate and blood pressure.

Renal: proteinuria, hematuria, and oliguria

Ingestion of inorganic mercurial salts

GI irritation, including pain, vomiting, diarrhea, and renal failure. Contact dermatitis, acrodynia (pink disease), shock, and cardiovascular collapse.

Subacute or Chronic Poisoning:

Neurologic: damage to small neurons in the cerebellum and visual cortex.

Clinical Management of Hg Poisoning

For dermal or ocular exposure, washing of exposed areas are suggested.

Oral administration of a protein solution has been suggested to reduce absorption, depending on Hg's affinity for binding to SH groups.

Administration of activated charcoal: acute high-dose

Gastric lavage and induction of emesis(not used in caustic Hg)

Chelation therapy: depends on the form of Hg, route of exposure, and possible side effects that might be experienced.

BAL is one of the more effective chelators for inorganic Hg salts, while D-penicillamine is marginally effective as a chelator for elemental and inorganic Hg.

IRON

Fe forms ferrous and ferric compounds.

The ferrous and ferric ions combine with cyanides to form complex cyanide compounds.

Occurrence and Uses

pigment in paint… blue color, red

Physiological Role:

Fe-containing enzymes and proteins

important component of hemoglobin, myoglobin, and cytochrome enzymes.

The average adult human stores about 3.9 to 4.5 g of Fe.e Of this, 65% is bound to hemoglobin, 20% to 30% is bound to the Fe storage proteins ferritin.

Mechanism of Toxicity:

usually occurs after about a few days of 20 to 60 mg/kg of continuous administration

chronic Fe overload affects the liver, heart, and pancreatic beta cells.

Amplify oxidant damage via the Fenton reaction.

accumulation within the cellular lysosomal compartment sensitizes lysosomes to damage and rupture

- **Signs and Symptoms of Acute Toxicity**

1. **GI toxicity** occurs within a few hours of ingestion. Symptoms include nausea, emesis, and diarrhea.
2. **Relative stability period** begins approximately 6 to 12 hours after ingestion in severely poisoned patients.
3. **Shock and acidosis** may occur a few hours, and up to 48 hours, after ingestion.

- Hypovolemic shock occurs in response to fluid and blood losses from the gut.

Cardiogenic shock usually occurs 26 to 48 hours after ingestion and represents a depressant effect of Fe on myocardial cells.

4. Hepatotoxicity within two days of ingestion and is the second-most common cause of death in Fe poisoning.

The liver is at risk because its portal circulation exposes it to the highest concentrations of Fe. Liver cells have a high metabolic activity that favors production of free radicals.

5. GI scarring occurs two to four weeks after ingestion. Patients present with partial or complete bowel obstruction, as the initial injury to the gut lumen heals by scarring and stenosis.

Signs and Symptoms of Chronic Toxicity:

hereditary hematochromatosis

Disturbances of liver function, diabetes mellitus, endocrine disturbances, and cardiovascular effects.

Treatment of Acute Poisoning:

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induction of vomiting and gastric lavage

Deferoxamine is an Fe chelator and is the treatment of choice for acute Fe overload

Repeated phlebotomy has also been suggested, as it is effective in removing as much as 20 mg of Fe per year.

ZINC

Zn is used extensively as a protective coating or galvanizer for iron and steel.

Zn oxide has antiseptic and astringent properties.

rodenticides, herbicides, pigments, and wood preservatives; and as solubilizing agents.

Zn deficiency results in dermatitis, growth retardation, impaired immune function, and congenital malformations

The metal has a role in the maintenance of nucleic acid structure of genes through the formation of “Zn finger” proteins.

The highest content is found in muscle, bone, the GI tract, brain, skin, lung, heart, and pancreas. In blood, about two-thirds of Zn is bound to albumin.

The principal route of excretion is in the feces

Mechanism of Toxicity:

it enters cells via channels that are shared by Fe and Ca. This pathway may be a prerequisite for cell injury.

Signs and Symptoms of Acute Toxicity:

inhalation of Zn oxides, causes chest pains, cough and dyspnea

Zn chloride is more damaging and corrosive to the mucous membranes

Oral ingestion of large doses of Zn sulfate has been associated with GI distress and alterations of GI tissue, including vomiting, burning in the throat, abdominal cramps, and diarrhea.

Clinical Management of Poisoning:

Inhalation: removal of the victim from the immediate area

Ocular and dermal: irrigation with water

Oral :ipecac to induce vomiting is not recommended in the presence of caustic Zn compounds.

Ingestion of large amounts of milk and cheese may reduce Zn absorption in the GI tract due to the high levels of phosphorus and Ca present in these products.

To reduce body burdens of Zn, administration of Ca-disodium-EDTA is the treatment of choice, while BAL has also been recommended.

Thank you