Absorption, Distribution, Metabolism and Excretion (ADME):

NST110: Advanced Toxicology

Lecture 2: Absorption and Distribution

NST110, Toxicology
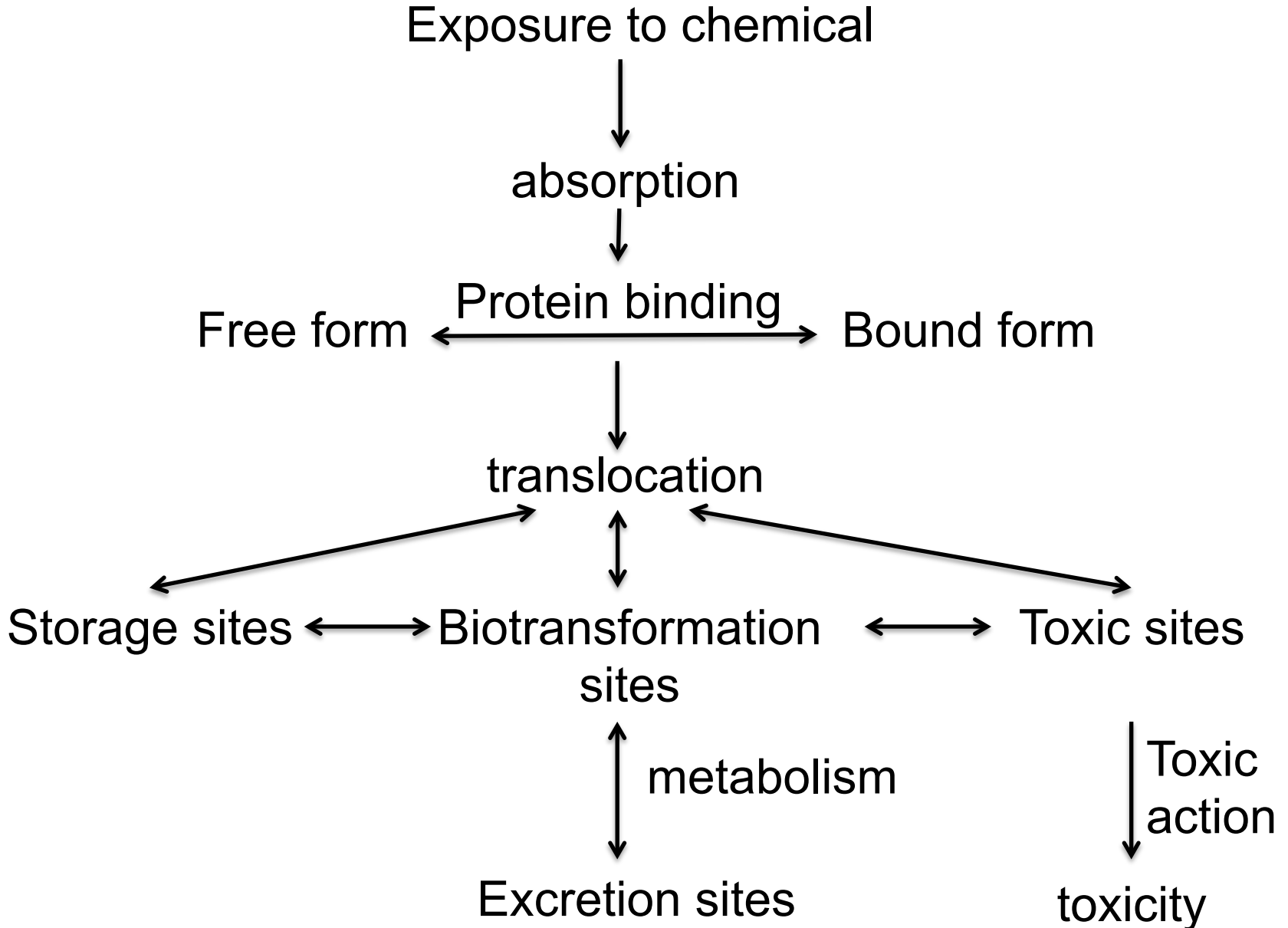
Department of Nutritional Sciences and Toxicology

University of California, Berkeley

Review and Forward

•**The toxicity of a substance depends on the dose.**

•However, it is ultimately not the dose but the **concentration of a toxicant _at the site of action_** (target organ or tissue) that determines toxicity.

•The concentration of a chemical at the site of action is often proportional to the dose, but the same dose of two or more chemicals may lead to **vastly different concentrations in a particular target organ of toxicity depending on the _disposition_ of the chemical.**

•Disposition of a chemical depends on **_absorption, distribution, biotransformation (metabolism) and excretion._**

Biological Factors that Determine Toxicity

Exposure to chemical

↓

absorption

↓

Protein binding

Free form ←――――――――→ Bound form

↓

translocation

Storage sites ←――→ Biotransformation sites ←――→ Toxic sites

metabolism

Excretion sites

Toxic action

toxicity

Absorption

Factors involved in absorbing a chemical:
1. Physicochemical properties of your chemical
   1. Hyrdrophobic? Hydrophilic?
   2. Ionized? Nonionized? Weak acid/base?
   3. Molecular weight? Volatility?
2. Route of exposure
3. Getting chemicals across cell membranes
   1. Diffusion/Passive transport
   2. Active transport

Routes of Absorption, Distribution and Excretion
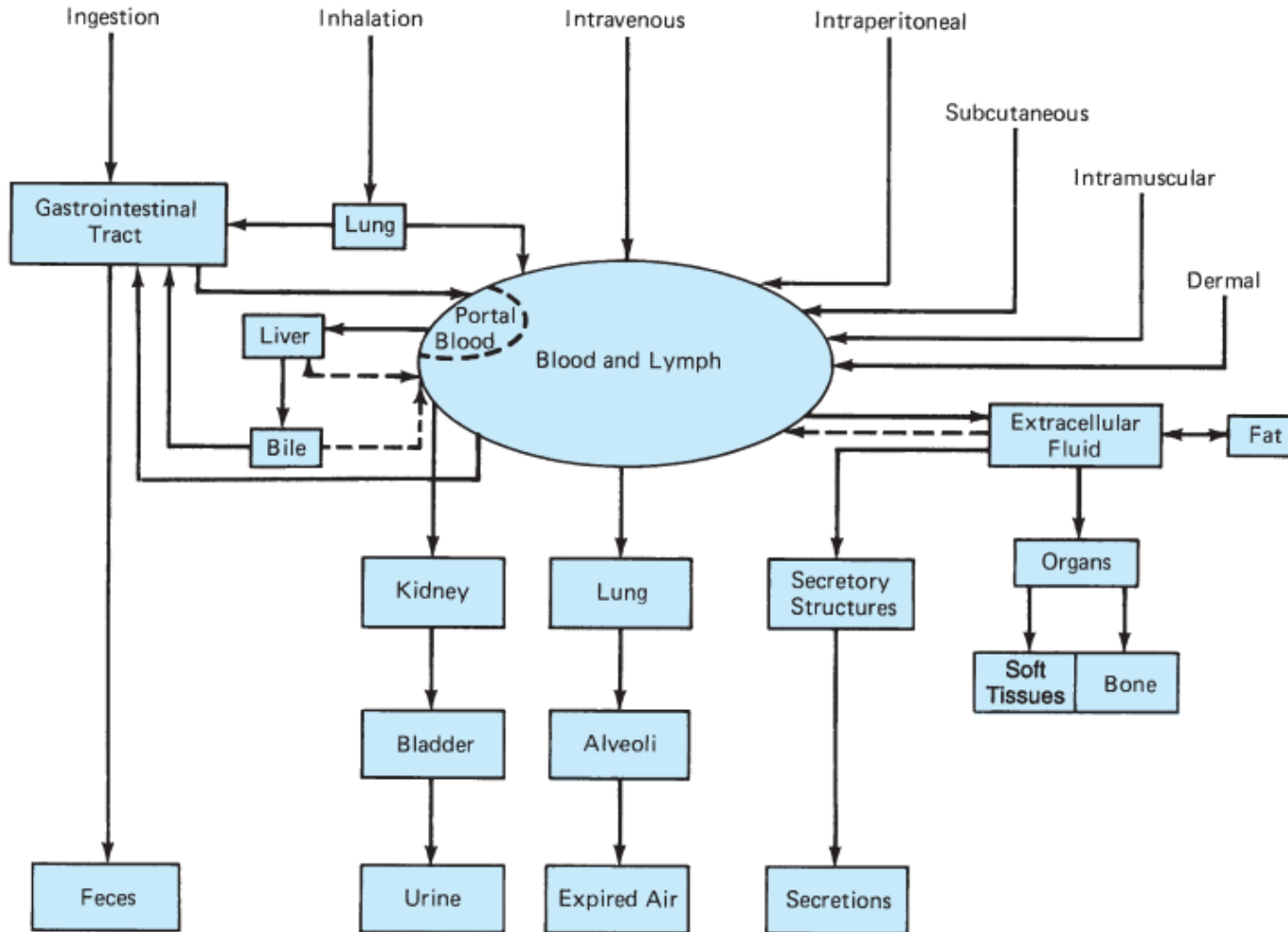
Routes of Absorption:
1. Ingestion
2. Inhalation
3. Dermal
4. Inhalation
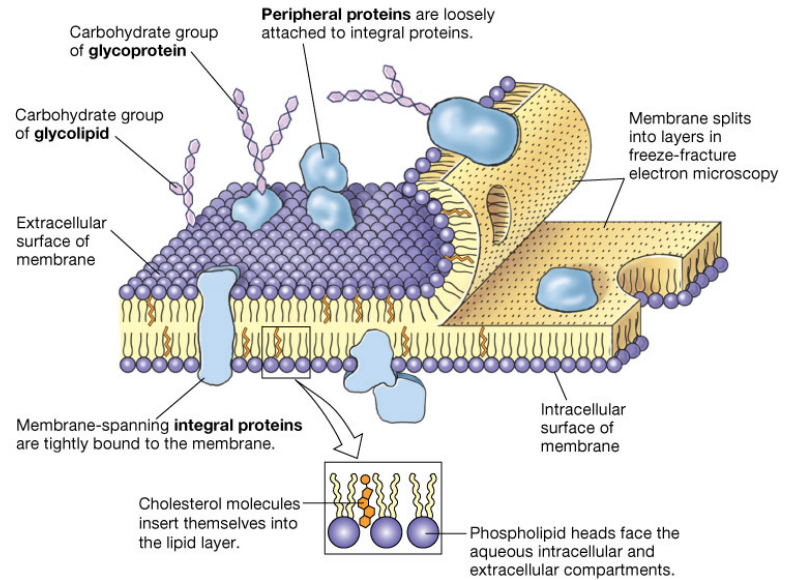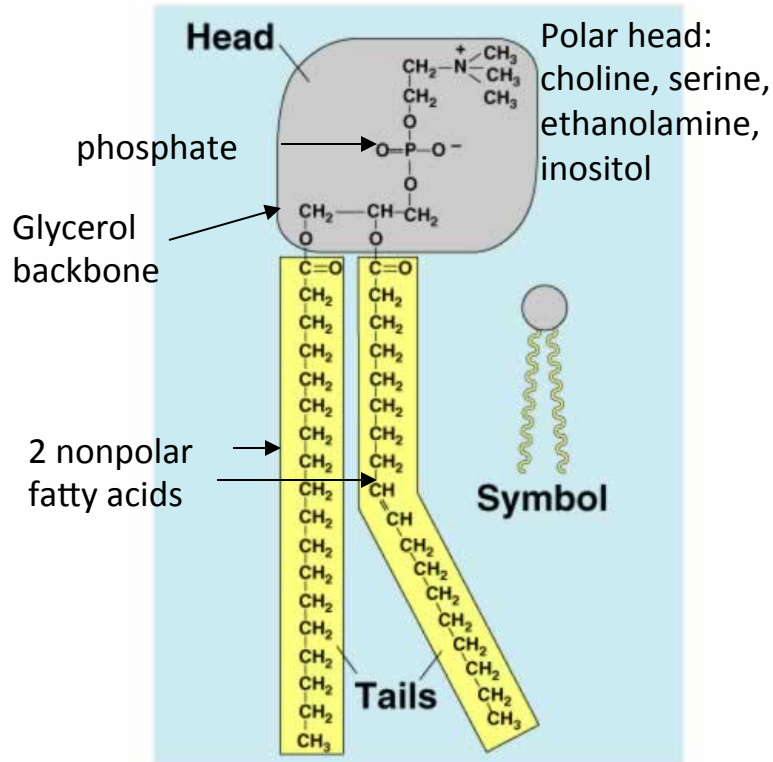5. Intravenous
6. Intraperitoneal
7. Intramuscular
8. Subcutaneous

Routes of Distribution:
1. Systemic circulation
2. Portal circulation
3. Lymphatic system
4. Fat
5. Extracellular fluid
6. Organs

Routes of Excretion:
1. Feces
2. Urine
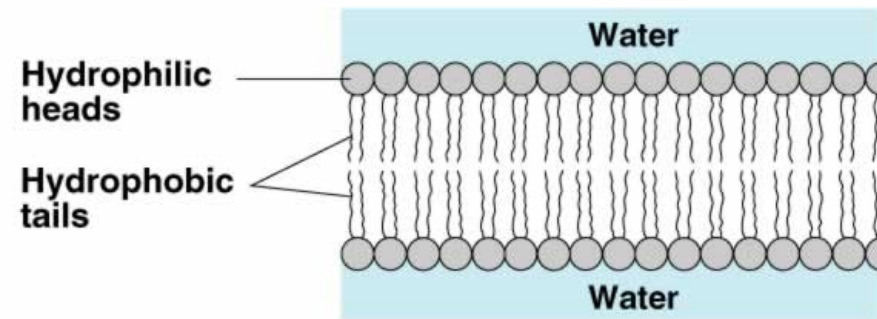3. Expired air
4. secretions

Absorption Across Membranes

Head

phosphate

Glycerol backbone

2 nonpolar fatty acids

Polar head: choline, serine, ethanolamine, inositol

Symbol

Tails

Peripheral proteins are loosely attached to integral proteins.

Carbohydrate group of glycoprotein

Carbohydrate group of glycolipid

Extracellular surface of membrane

Membrane splits into layers in freeze-fracture electron microscopy

Membrane-spanning integral proteins are tightly bound to the membrane.

Intracellular surface of membrane

Cholesterol molecules insert themselves into the lipid layer.

Phospholipid heads face the aqueous intracellular and extracellular compartments.

Copyright © 2004 Pearson Education, Inc., publishing as Benjamin Cummings.

Water

Hydrophilic heads

Hydrophobic tails
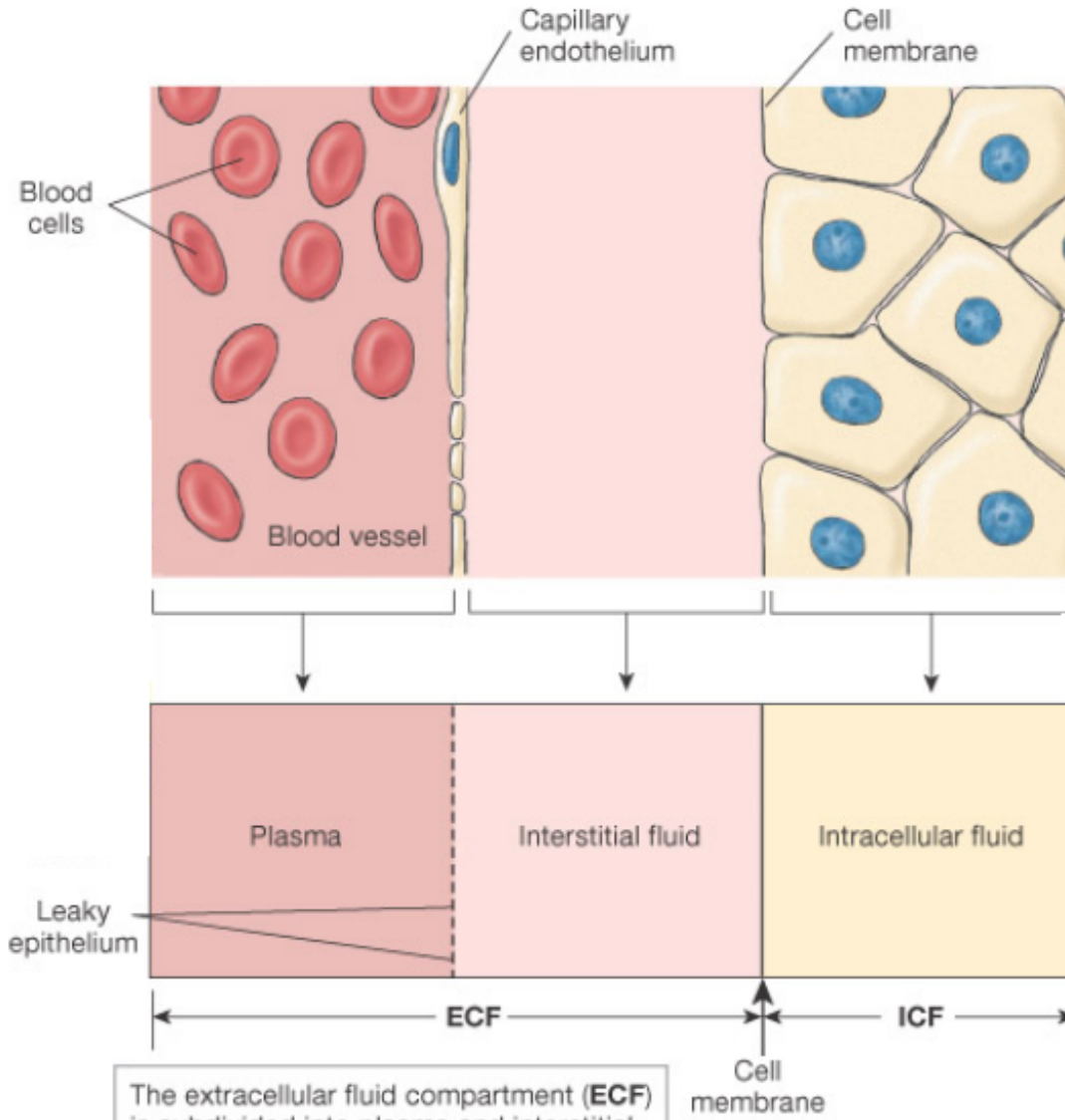
Water

©Addison Wesley Longman, Inc.

- The membrane is a phospholipid bi-layer consisting of a polar head group, phosphate, glycerol backbone and 2 fatty acid molecules esterified to the glycerol backbone.

- hydrophobic compounds can diffuse across the membrane

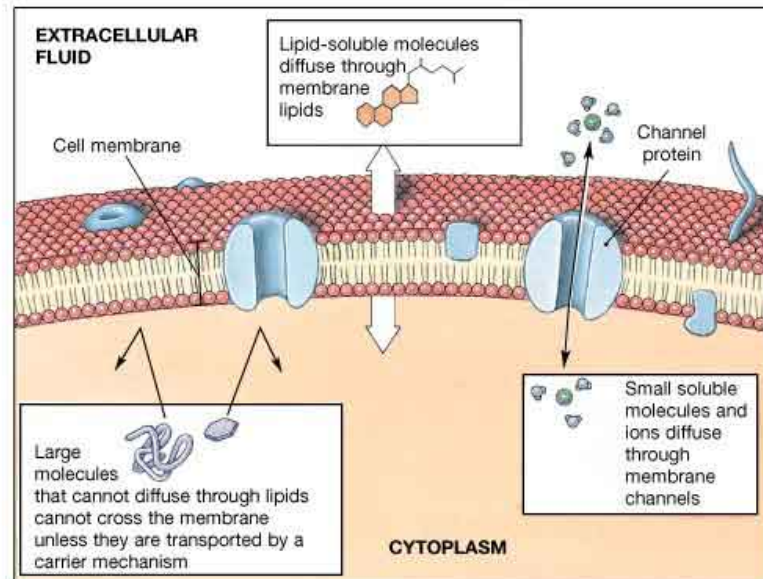- hydrophilic compounds will not diffuse across the membrane

Physical Barriers to Absorption

The extracellular fluid compartment (**ECF**) is subdivided into plasma and interstitial fluid. Material moving between cells and ECF must cross the cell membrane.

Types of Transport

1. Passive Diffusion—no ATP required; gradient driven

a. Simple Diffusion—hydrophobic molecules passively diffuse across the membrane. Rate of transport proportional to the octanol/ water partition coefficient or logP.

b. Facilitated Diffusion—saturable carrier-mediated transport (e.g. glucose transporter)

EXTRACELLULAR FLUID

Lipid-soluble molecules diffuse through membrane lipids

Cell membrane

Channel protein

Large molecules that cannot diffuse through lipids cannot cross the membrane unless they are transported by a carrier mechanism

Small soluble molecules and ions diffuse through membrane channels

CYTOPLASM

FIGURE 3-6 Diffusion across the Cell Membrane

Octanol/Water Partition Coefficients (P) of Different Molecules Expressed as log P

| COMPOUND	LOG P
Paraquat	Charged molecule
Sulfobromophthalein	Charged molecule
Cephalosporin C	−4.72
Cystine	−4.45
Glycine	−3.21
Glutathione	−3.05
Gluconic acid	−2.89
Cysteine	−2.35
Glucose	−2.21
Edetic acid	−1.93
Ethylene glycol	−1.37
Lead acetate	−0.63
Ouabain	−0.35
p-Aminohippuric acid	−0.25
Dimercaprol	0.18
Scopolamine	0.30
Sarin	0.45
Aspirin	1.02
Colchicine	1.19
Atropine	1.32
Benzoic acid	1.88
Benzene	2.14
Salicylic acid	2.19
Digoxin	2.27
Methyl salicylate	2.34
2,4-D	2.73
Warfarin	2.89
Digitoxin	3.05
Parathion	3.47
DDT	6.76
TCDD	7.05

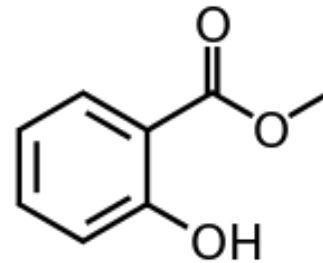# Simple Diffusion Based on LogP
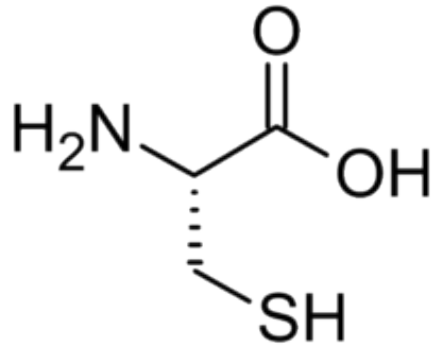
Cysteine (-2.2)
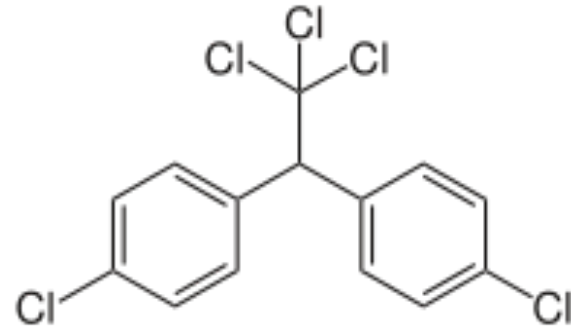
Dichloro**d**iphenyl**t**richloroethane
(DDT) (6.7)
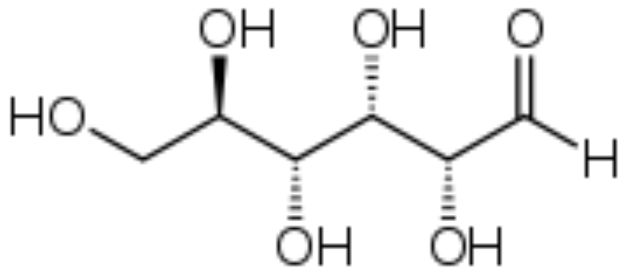
Glucose (-2.2)
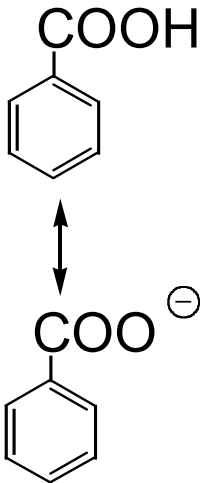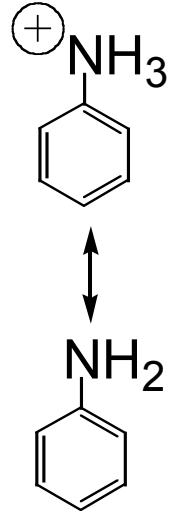
**Methyl salicylate
(2.19)**

Simple Diffusion of Weak Organic Acids and Bases

- The ionized form usually has low lipid solubility and does not permeate readily through the lipid domain of a membrane.

- The non-ionized form of weak organic acids and bases is more lipid soluble, resulting in diffusion across the lipid domain of the membrane.

- The pH at which a weak organic acid or base is 50 % ionized is its pK_a or pK_b.

The degree of ionization of a chemical depends on its pKa and on the pH of the solution, a relationship described by the Henderson-Hasselbalch equation.
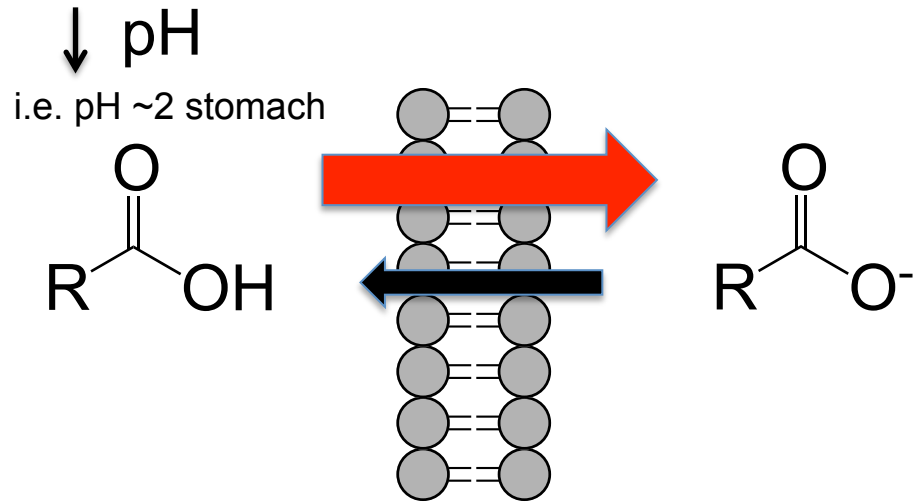
For acids: $pK_a - pH = \log [\text{non-ionized}]/[\text{ionized}]$

For bases: $pK_b - pH = \log [\text{ionized}]/[\text{non-ionized}]$

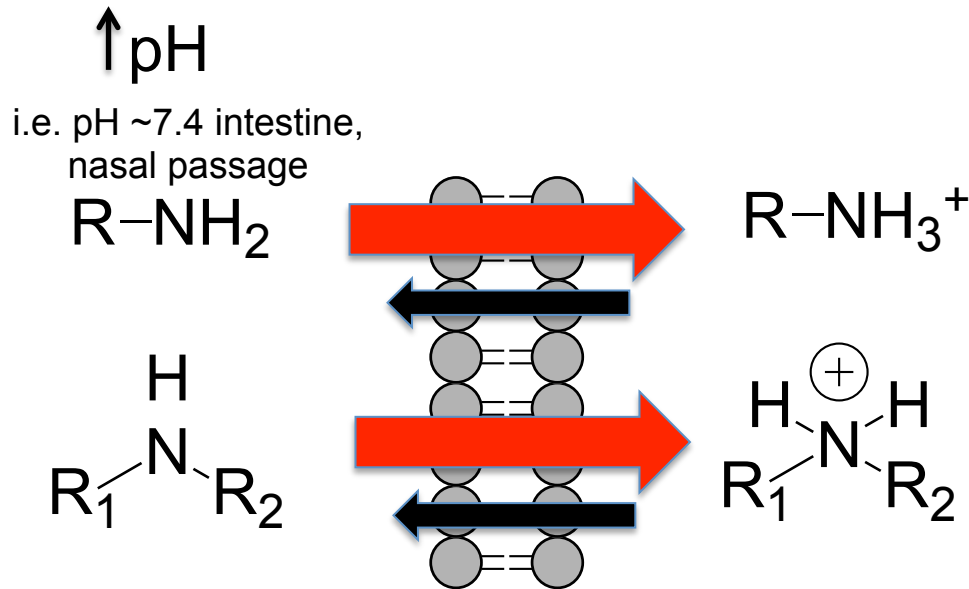| pH	benzoic acid	% nonionized	aniline	% nonionized
1		99.9		
2		99		0.1
3		90		1
4		50		10
5		10		50
6		1		90
7		0.1		99

pK_a of benzoic acid = 4.0; pK_b of aniline = 5.0

pH Effect: Acid/Base effect on absorption

↓ pH

i.e. pH ~2 stomach

$R-CO_2H$ ⟶ $R-CO_2^-$

- •R-CO_2H would be absorbed under acidic conditions (e.g. stomach).

↑pH

i.e. pH ~7.4 intestine, nasal passage

$R-NH_2$ ⟶ $R-NH_3^+$

$R_1-\overset{H}{N}-R_2$ ⟶ $R_1-\overset{\overset{\oplus}{H\,\,\,H}}{N}-R_2$

- •R-NH_2 would be absorbed at neutral pH (e.g. intestine, nasal passage).

Compounds will accumulate in total amount where there are more binding sites

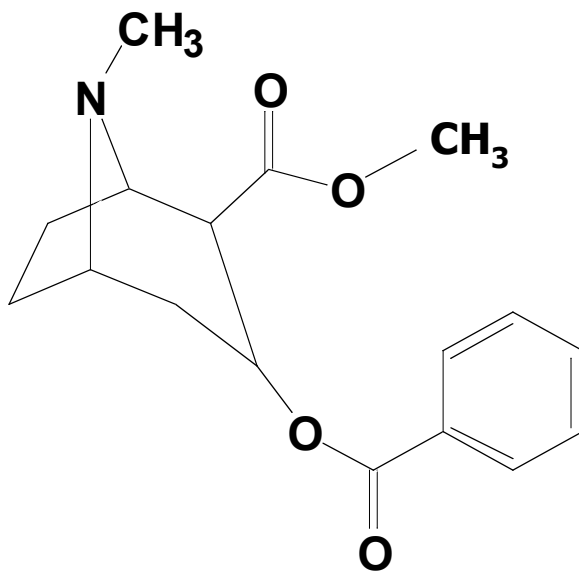higher
binding sites

lower
binding sites
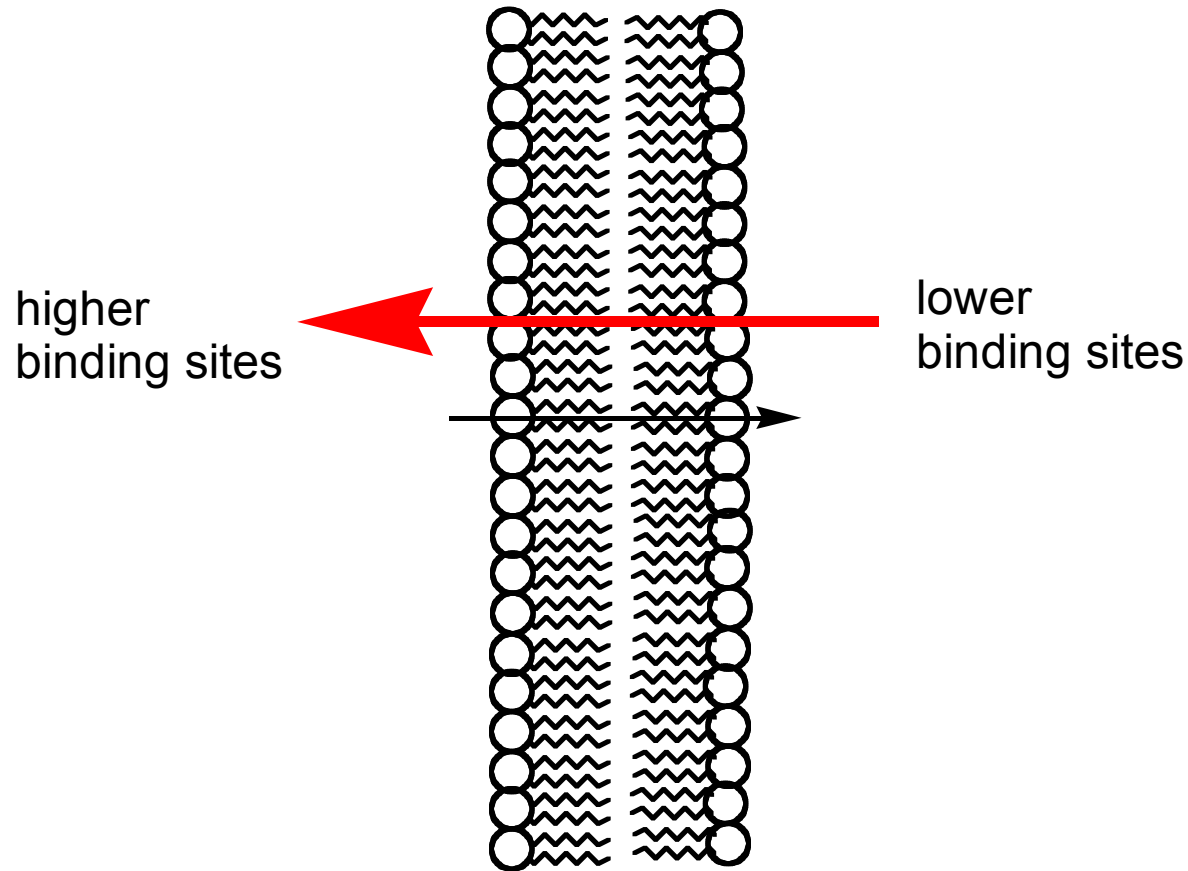
Applicable for the blood-brain barrier; toxicants with high affinity for binding proteins (e.g. albumin, hemoglobin) less likely to cross barrier.
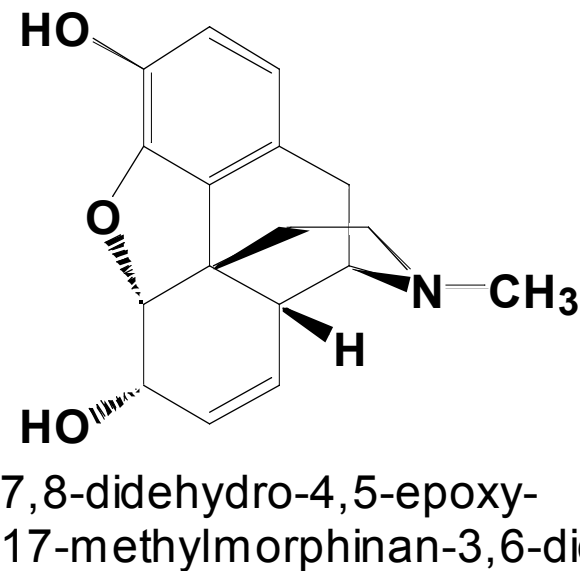
What are the common names for these chemicals and where are they likely to be absorbed?
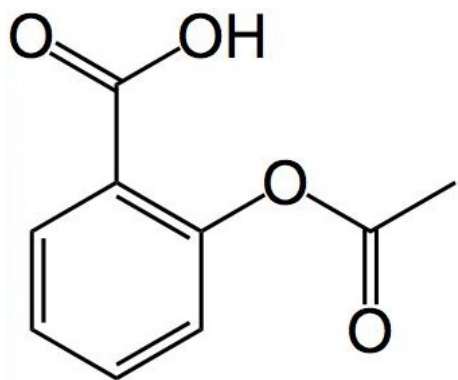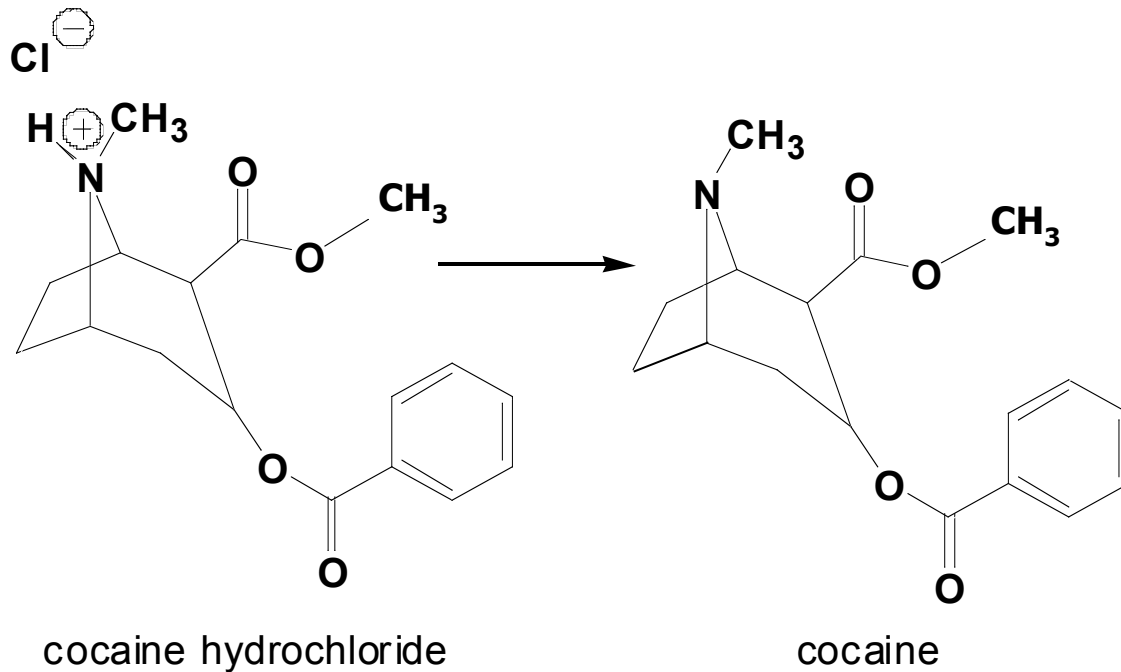

2-(acetyloxy)benzoic acid

methyl 3-benzoyloxy-8-methyl-8-azabicyclo [3.2.1]octane-4-carboxylate

7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol

Freebasing

cocaine hydrochloride

cocaine

Freebasing has been done with baking soda (sodium bicarbonate) or ammonia (NH_3) to increase absorption of cocaine (crack) via nasal installation.

Facilitated Diffusion

Facilitated Diffusion—saturable carrier-mediated transport (e.g. glucose transporter)

Extracellular space

Protein channel

Cell membrane

Carrier proteins

Intracellular space
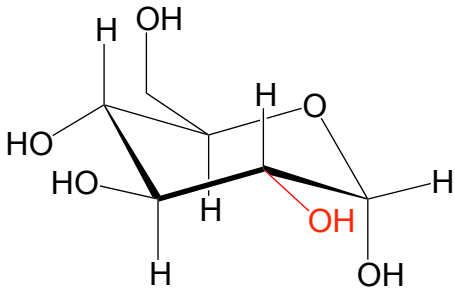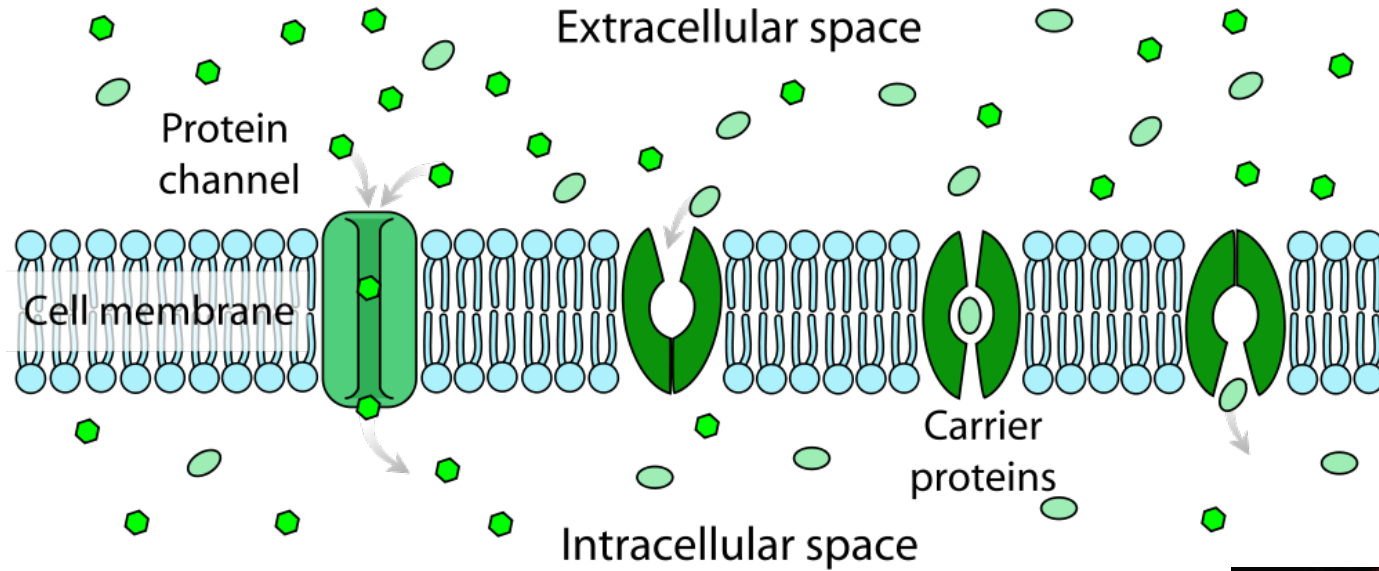
Glucose
(taken up by glucose transporters by facilitated diffusion)
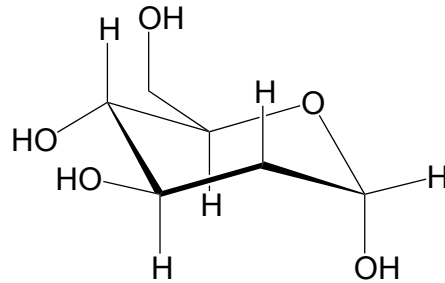
2-deoxy-glucose
(also taken up by glucose transporters— inhibits hexokinase-- chemotherapeutic)
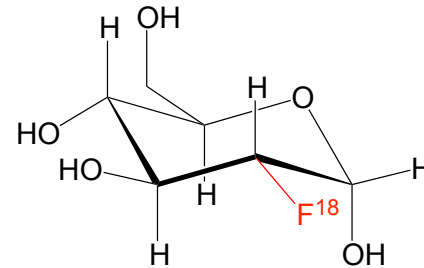
Fluorodeoxyglucose
(taken up by glucose transporters—imaging agent for tumors)

cancer

right lung   left lung

2. Active Transport--a) chemicals are moved against an electrochemical gradient; b) the transport system is saturable; c) requires the expenditure of energy.

Examples:

1. multi-drug-resistant protein (mdr)—decreases GI absorption, blood-brain barrier, biliary excretion, placental barrier

2. Multi-resistant drug protein (mrp)—urinary excretion, biliary excretion

3. Organic-anion transporting polypeptide (oatp)—hepatic uptake of organic anions

4. Organic anion transporter (oat)—kidney uptake of organic anions

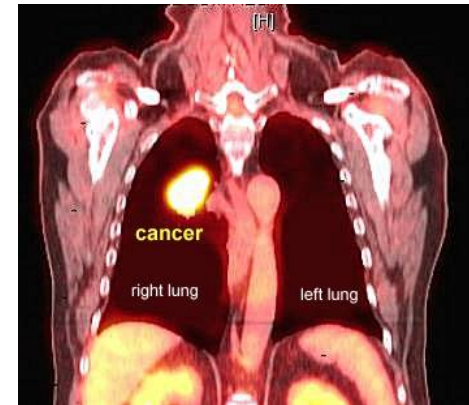5. Organic cation transporter (oct)—kidney, liver and placental uptake of organic cations

6. Divalent-metal ion transporter (dmt)—GI absorption of divalent metals (Fe^{2+}, Cu^{2+}, Mg^{2+}, etc.)

7. Peptide transporter (pept)—GI absorption of peptides

Routes of Exposure: Oral (GI tract)

The Digestive System

The Digestive System diagram showing Esophagus, Stomach, Gallbladder, Liver, Duodenum, Pancreas, Colon, Small Intestine, Anus, Rectum
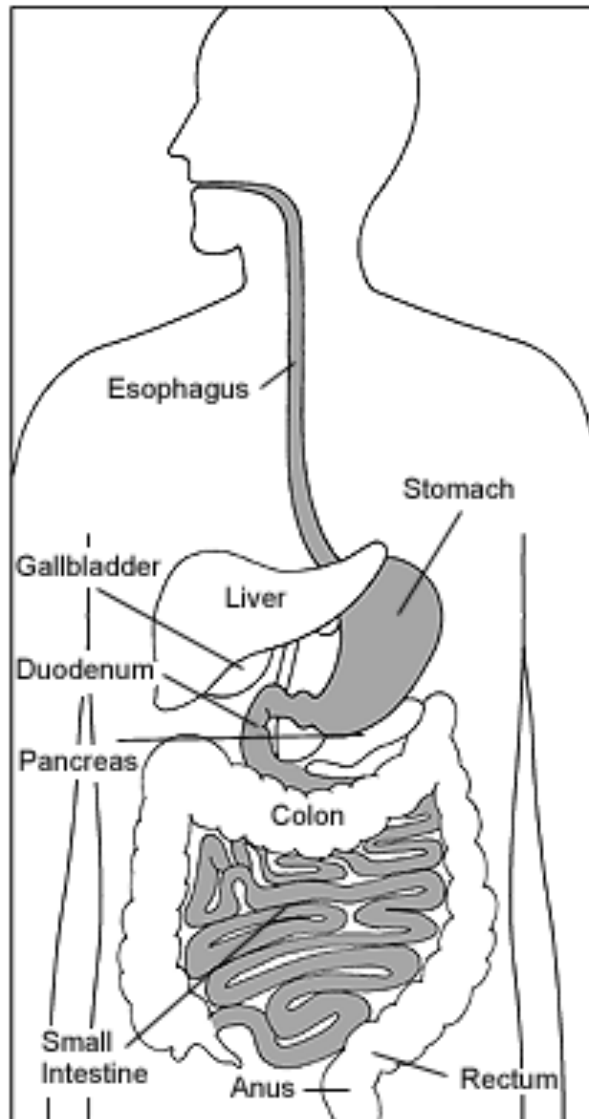
• GI tract can be viewed as a tube traversing the body.

• Although the GI tract is in the body, its contents can be considered exterior to most of the body's metabolism.

• Unless the toxicant is an irritant or has caustic properties, poisons in the GI tract do not produce systemic injury <u>until absorbed.</u>

• Absorption can occur anywhere in the GI tract including the mouth and rectum.

• Initial metabolism can

   occur in gastric cells.

Cross-section diagram labeled: Villi, Crypt, Mucosa, Submucosa, Circular muscle, Longitudinal muscle, Serosa, Submucosal artery and vein, Submucosal plexus, Peyer's patch, Myenteric plexus, Lymph vessel

GI Tract Absorption

- **<u>Weak acids and bases</u>** will be absorbed by simple diffusion to a greater extent in the part of the GI tract in which they exist in the most lipid-soluble (non-ionized) form—hydrophilic substances will be transported to the liver by the portal vein

- **<u>Highly hydrophilic substances</u>** may be absorbed through transporters (xenobiotics with similar structures to endogenous substrates).

- **<u>Highly hydrophobic compounds</u>** may be absorbed into the lymphatic system via chylomicrons and drained into venous circulation near the heart.

- **The greatest level of absorption** for most ingested substances occurs in the small intestine.
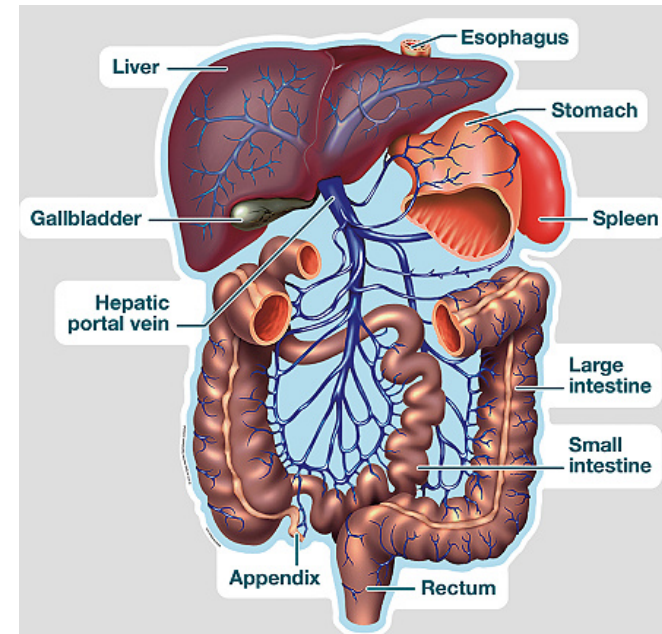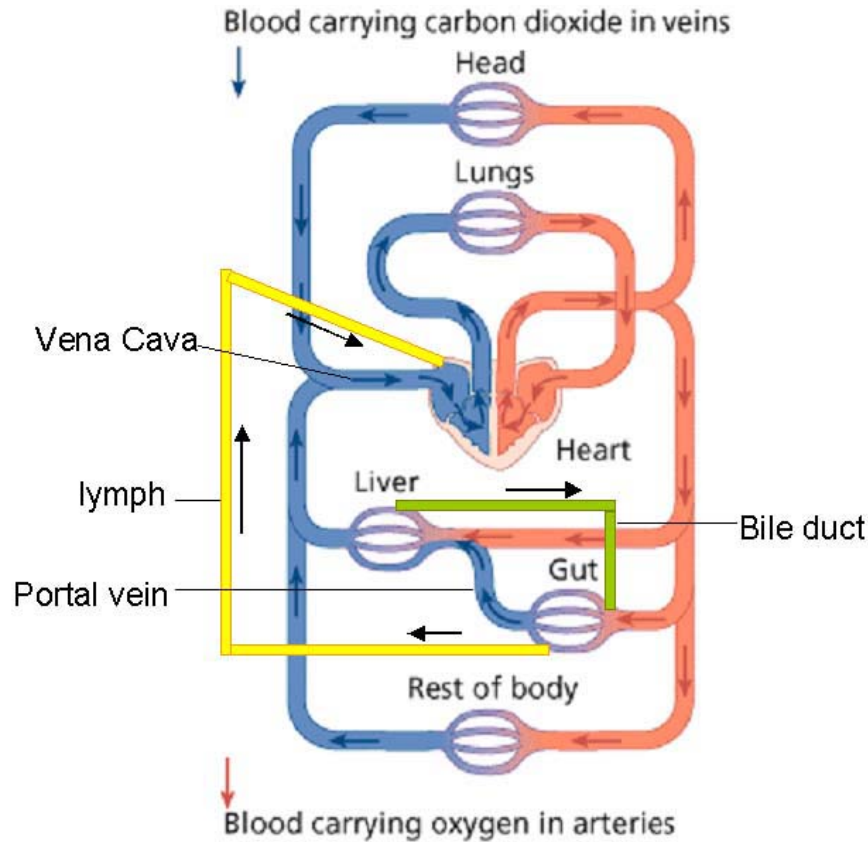
Polar versus Nonpolar GI Absorption

Polar substances that are absorbed:

1. go to the liver via the **portal vein.**

2. may undergo **first-pass metabolism** or **presystemic elimination** in gastric and/or liver cells where xenobiotics may be biotransformed.

3. can be excreted into the bile without entrance into the systemic circulation or enter the systemic circulation.

The liver and first-pass metabolism serve as a defense against most xenobiotics. The liver is the organ with the highest metabolic capacity for xenobiotics.

Polar versus Non-Polar GI Absorption
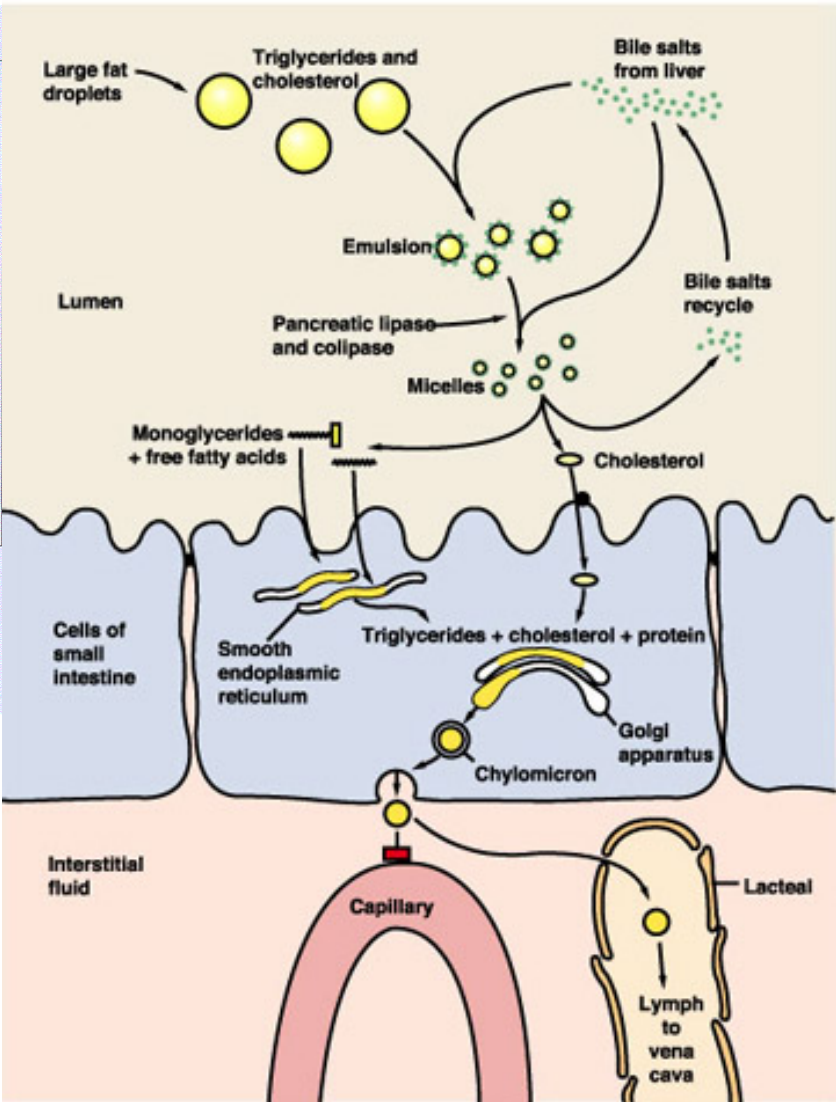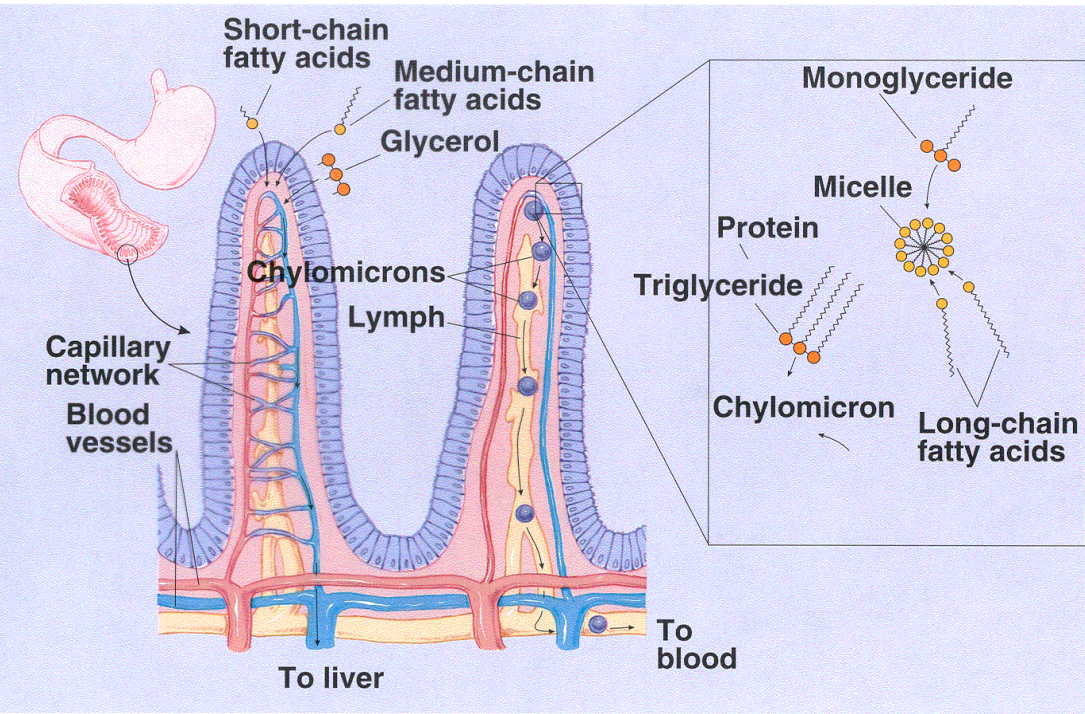
<u>Lipophilic, non-polar substances (e.g. polycyclic aromatic hydrocarbons)</u>

1. Ride on the "coat-tails" of lipids via micelles and follow lipid absorption to the lymphatic system (via chylomicrons) to the lungs.

2. Non-polar substances may by-pass first-pass metabolism. e.g. PAH have selective toxicity in the lung, where they may be metabolically activated.

Routes of Exposure: Inhalation (Lung)

Toxicants absorbed by the lung are:

1. Gases (e.g. carbon monoxide, nitrogen dioxide, sulfur dioxide, phosgene)

2. Vapors or volatile liquids (e.g. benzene and carbon tetrachloride)

3. Aerosols

The respiratory system
The respiratory system consists of the upper respiratory system (mouth, nasal cavity, pharynx, larynx) and the lower respiratory system (trachea, bronchi, lungs). The lower respiratory system is enclosed in the thorax, bounded by the ribs, spine, and diaphragm.

Pharynx
Vocal cords
Esophagus
Right lung
Right bronchus
Nasal cavity
Tongue
Larynx
Trachea
Left lung
Left bronchus
Diaphragm

Trachea

Cartilage rings

Cartilage plates

Left primary bronchus

Root of lung

Visceral pleura

Secondary bronchus

Tertiary bronchi

Smaller bronchi

Bronchioles

Terminal bronchiole

Respiratory bronchiole

Alveoli in pulmonary lobule

Gases and Vapors

The absorption of inhaled gases and vapors starts in the nasal cavity which has:

1. Turbinates, which increase the surface area for increased absorption (bony projections in the breathing passage of the nose improving smell).

2. Mucosa covered by a film of fluid.

3. The nose can act as a "scrubber" for water-soluble gases and highly reactive gases, partially protecting the lungs from potentially injurious insults (e.g. formaldehyde, SO_2).
   -Rats develop tumors in the nasal turbinates when exposed to formaldehyde.
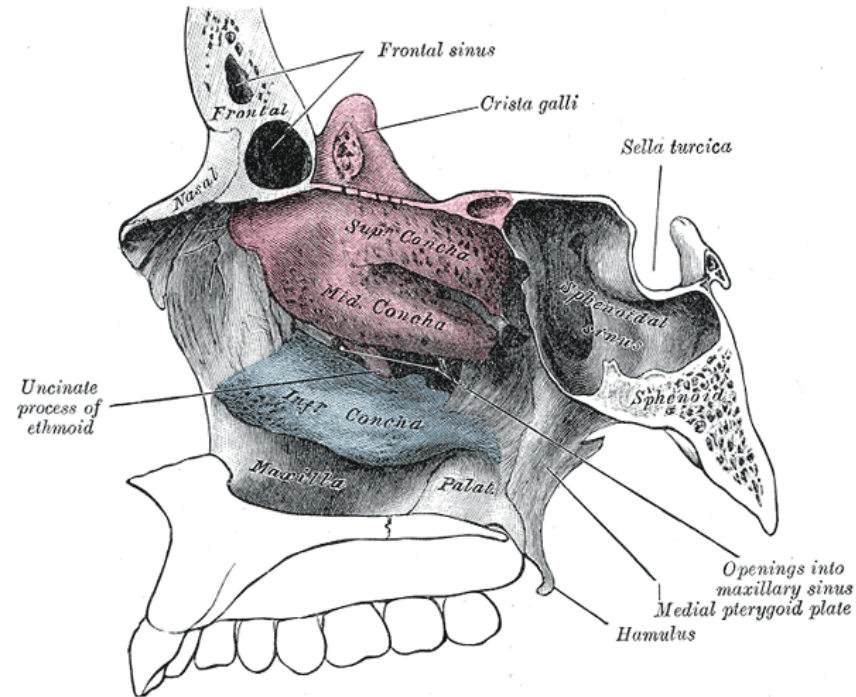
Absorption of Gases

Absorption of gases differs from intestinal and percutaneous absorption of compounds because:

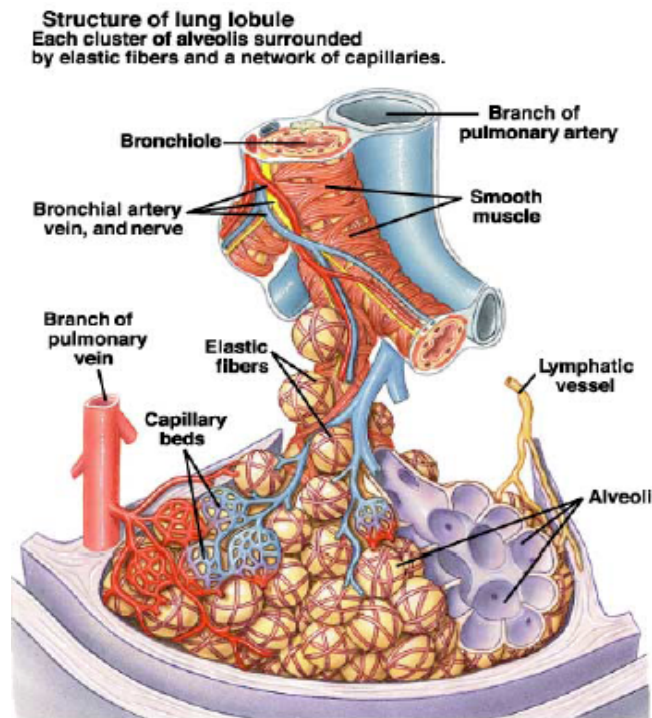1. Ionized molecules are of very low volatility, so their ambient air concentration is insignificant.

2. Epithelial cells lining the alveoli (type I pneumocytes) are very thin and the capillaries are in close contact with the pneumocytes, so the diffusion distance is very short.

3. Chemicals absorbed by the lungs are rapidly removed by the blood (3-4 seconds for blood to go through lung capillary network).

Structure of lung lobule
Each cluster of alveolis surrounded by elastic fibers and a network of capillaries.

Bronchiole

Bronchial artery vein, and nerve

Branch of pulmonary vein

Capillary beds

Branch of pulmonary artery

Smooth muscle

Elastic fibers

Lymphatic vessel
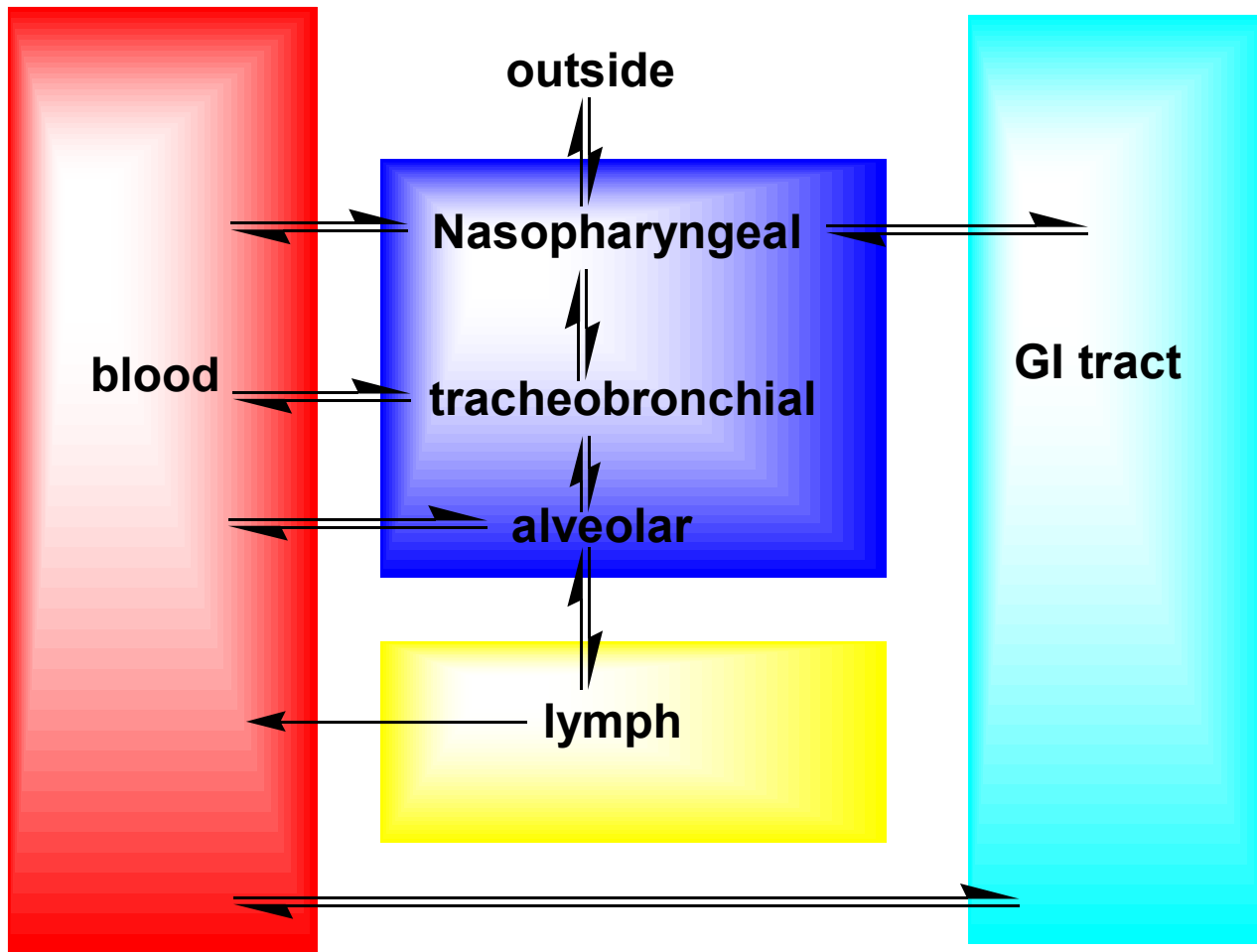
Alveoli

- When a gas is inhaled into the lungs, gas molecules diffuse from the alveolar space into the blood and then dissolve.

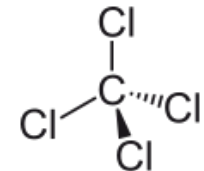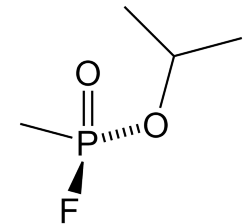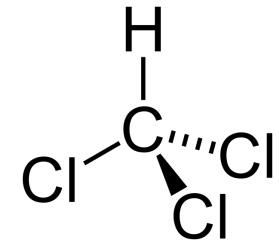- The gas molecules partition between the air and blood during the absorptive phase, and between blood and other tissues during the distributive phase.

- Note that **inhalation bypasses first-pass metabolism.**

Examples of Toxicant Gases or Volatile Liquids

$$:C \equiv O:$$

112.8 pm

1. **Carbon monoxide**—binds hemoglobin (with >200x affinity compared to O2) and displaces oxygen leading to impaired oxygenation of tissues, energy impairment, and death
2. **Chloroform**—anesthetic that depresses the nervous system, but can also be metabolized to phosgene, a reactive metabolite that modifies proteins and causes toxicity in lung, kidney, and liver.
3. **Sarin gas**—chemical warfare agent (recently used in Syria) that causes excessive neuronal excitation, convulsions, seizures, tearing, salivation, suffocation, and death through inhibition of acetylcholinesterase
4. **Carbon tetrachloride**—volatile liquid used widely as a cleaning agent and refrigerant, currently banned—greenhouse gas and carbon tetrachloride can be bioactivated in the liver to produce a potent hepatotoxin
5. **Benzene**—largely found in crude oil, but also found in tobacco smoke and used to be found in glues, paints, and detergents— benzene metabolism leads to bioactivated carcinogens that cause leukemia

Aerosols and Particles

Size   Location of Absorption

>5 µm   Deposited in nasopharyngeal region (or mouth).

    1. Removed by nose wiping, blowing or sneezing.

    2. The mucous blanket of the ciliated nasal surface can propel insoluble particles by movement of cilia and be swallowed.

    3. Soluble particles can dissolve in mucus and be carried to the pharynx or nasal epithelia and into blood. (asbestos-lung cancer)

2-5 µm   Deposited in tracheobronchiolar regions of the lungs.

    1. Cleared by retrograde movement of mucus layer in ciliated portion of respiratory tract.

    2. Coughing can increase expulsion rate.

    3. Particles can be swallowed and absorbed from the GI tract. (asbestosis—lung fibrosis, wheezing)

<1 µm   Penetrates to alveolar sacs of lungs and is absorbed into blood or cleared through lymphatic system after being scavenged by alveolar macrophages. (asbestos and silica dust can cause silicosis—cough, shortness of breath, inflammation, immunodeficiency through damaging pulmonary macrophages)

Pulmonary Clearance

- Particles trapped in fluid layer of conducting airway removed by mucociliary escalator.

- Particles phagocytized by alveolar macrophages removed by lymph.

- Substances dissolved from particle surface removed in blood.

- Small particles directly penetrate epithelial membranes.

Routes of Exposures: Dermal (skin)
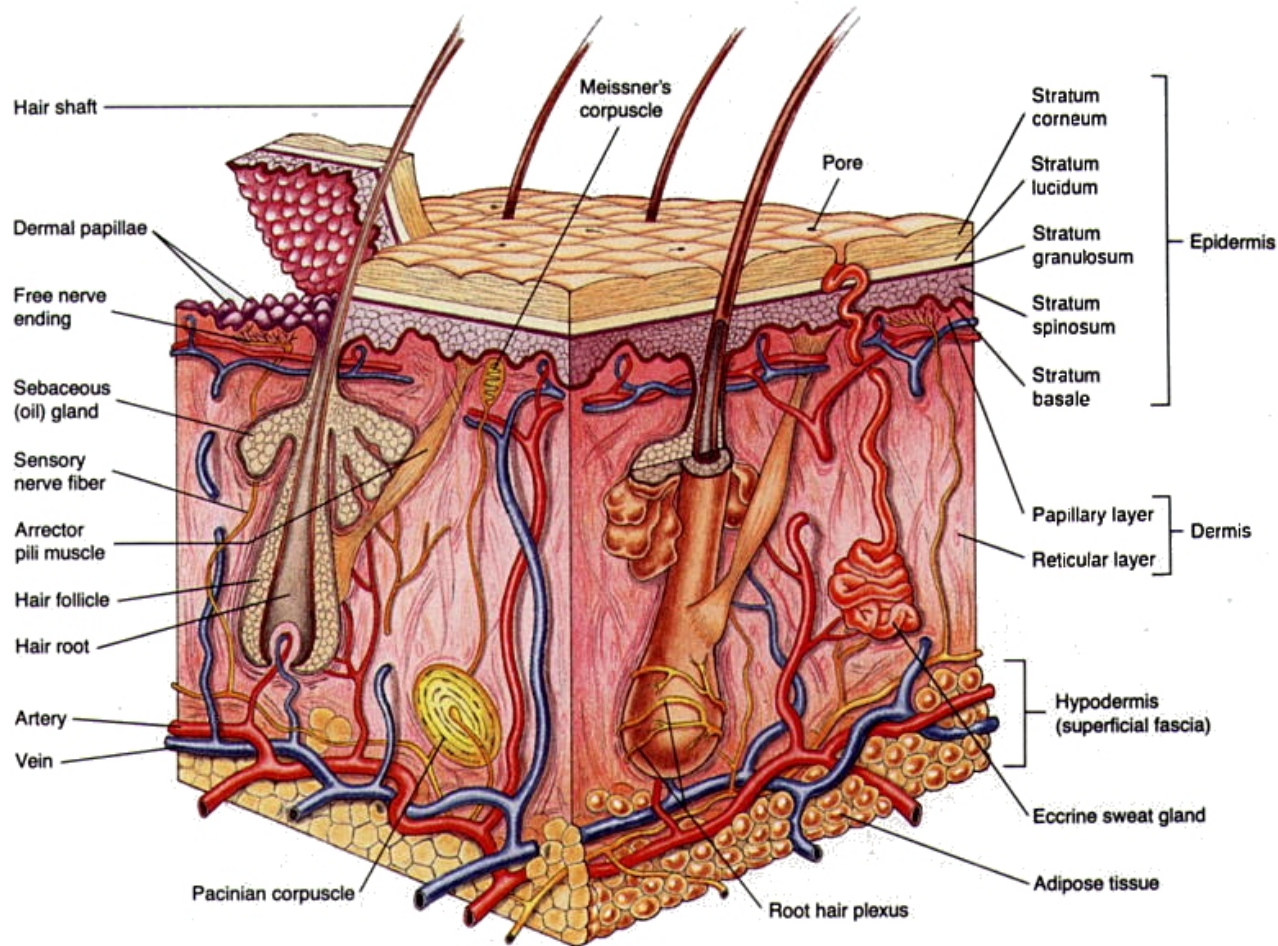
Human skin comes into contact with many toxic agents. Fortunately, the skin is not very permeable and is a good barrier for separating organisms from their environment.

Factors for Dermal Absorption

•To be absorbed through the skin, a toxicant must pass through the epidermis or the appendages (sweat and sebaceous glands and hair follicles).

•Once absorbed through the skin, toxicants must pass through several tissue layers before entering the small blood and lymph capillaries in the dermis.

Hair shaft · Meissner's corpuscle · Pore · Stratum corneum · Stratum lucidum · Stratum granulosum · Epidermis · Dermal papillae · Free nerve ending · Stratum spinosum · Stratum basale · Sebaceous (oil) gland · Sensory nerve fiber · Papillary layer · Dermis · Arrector pili muscle · Reticular layer · Hair follicle · Hair root · Hypodermis (superficial fascia) · Artery · Vein · Eccrine sweat gland · Adipose tissue · Pacinian corpuscle · Root hair plexus

•The rate-determining barrier in the dermal absorption of chemicals is the epidermis—especially the *stratum corneum* (horny layer), the upper most layer of the epidermis.

•The cell walls are chemically resistant, two-times thicker than for other cells and dry, and in a keratinous semisolid state with much lower permeability for toxicants by diffusion—the *stratum corneum* cells have lost their nuclei and are biologically inactive (dead).

•Once a toxicant is absorbed through the *stratum corneum*, absorption through the other epidermal layers is rapid.

All toxicants move across the *stratum corneum* by passive diffusion

•Polar substances diffuse through the outer surface of protein filaments of the hydrated *stratum corneum*.

•Non-polar molecules dissolve and diffuse through the lipid matrix between protein filaments.

•The rate of diffusion is proportional to lipid solubility and inversely proportional to molecular weight.

Once absorbed, the toxicant enters the systemic circulation by-passing first-pass metabolism.

Factors that Affect *Stratum Corneum* Absorption of Toxicants

1. ## Hydration of the *stratum corneum*

- The *stratum corneum* is normally 7% hydrated which greatly increases permeability of toxicants. (10-fold better than completely dry skin)

- On additional contact with water, toxicant absorption can increase by 2- to 3-fold.

2. ## Damage to the *stratum corneum*

- Acids, alkalis and mustard gases injure the epidermis and increase absorption of toxicants.

- Burns and skin diseases can increase permeability to toxicants.

3. ## Solvent Administration

- Carrier solvents and creams can aid in increased absorption of toxicants and drugs (e.g. dimethylsulfoxide (DMSO)).

Special Routes of Exposure

Toxicants usually enter the bloodstream after absorption through the skin, lungs or GI tract. Special routes include:

1. Subcutaneous injection (SC) (under the skin)

   -by-passes the epidermal barrier, slow absorption but directly into systemic circulation; affected by blood flow

2. Intramuscular injection (IM) (into muscle)

   -slower absorption than IP but steady and directly into systemic circulation; affected by blood flow

3. Intraperitoneal injection (IP) (into the peritoneal cavity)

   -quick absorption due to high vascularization and large surface area

   -absorbed primarily into the portal circulation (to liver—first-pass metabolism) as well as directly into the systemic circulation.

4. Intravenous injection (IV) (into blood stream) -directly into systemic circulation

Toxicity is Dependent on Route of Exposure

Often, if a toxicant undergoes first-pass metabolism, it will be less toxic if administered orally than IV.

More toxic ⟵————————————————⟶ Less toxic

IV > Inhalation > IM/SC > Dermal > IP > Oral

No first-pass metabolism	First-pass metabolism
Directly into systemic circulation	(metabolized in the liver first)

Caveat: This does not apply for toxicants that have selective toxicity towards the GI tract or the liver, or for toxicants that become selectively bioactivated in the liver.

Summary on Absorption

- Route of exposure and physicochemical properties of xenobiotic determine how a chemical is absorbed and whether it goes through first-pass metabolism or is subjected to systemic circulation.

- The degree of ionization and the lipid solubility of chemicals are very important for oral and percutaneous exposures.

- For exposure to aerosols and particles, the size and water solubility are important.

- For dermal absorption, polarity, molecular weight and carrier solvent of the toxicant and hydration of the epidermis are important.
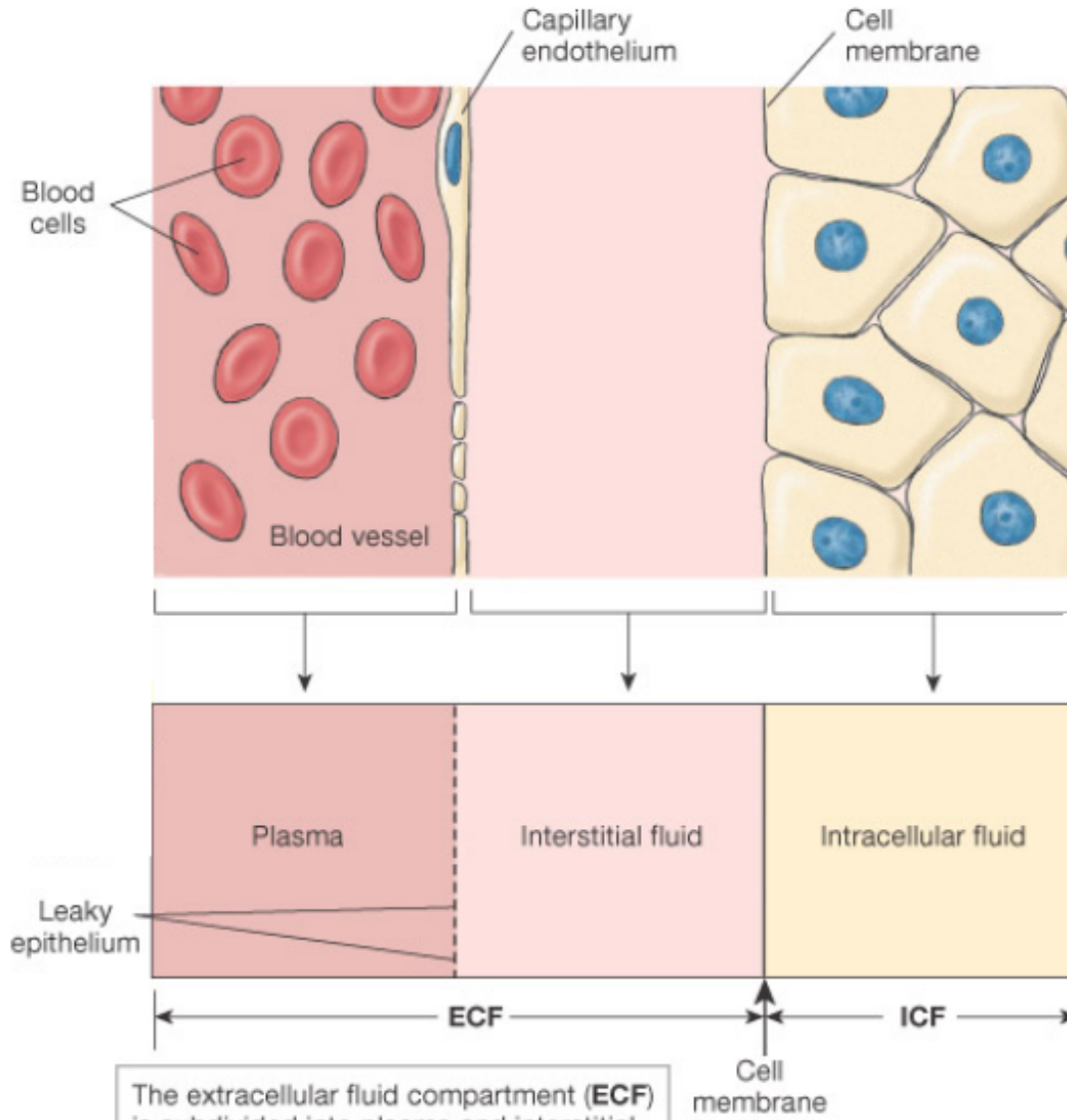
Distribution

After a toxicant enters portal circulation, systemic circulation, or lymph, it is available for distribution (translocation) throughout the body, which usually occurs very rapidly. The rate of distribution to organs or tissues is determined by:

1. Physicochemical properties of the chemical

2. Blood flow

3. Rate of diffusion out of the capillary bed into the cells of a organ or tissue.

4. Affinity of a xenobiotic for various tissues.

Penetration of toxicants into cells or tissues occurs by passive diffusion or active transport (as discussed earlier).

Physical Barriers to Distribution

The extracellular fluid compartment (**ECF**) is subdivided into plasma and interstitial fluid. Material moving between cells and ECF must cross the cell membrane.

Distribution of toxicants

Distribution can be highly localized, restricted or disperse depending on:

1. Binding and dissolution into various storage sites (fat, liver, bone)

2. Permeability through membranes

3. Protein binding

4. Active transport

If the toxicant accumulates at a site away from a toxic site of action, it is considered as a protective storage site

Storage of Toxicants in Circulation and Tissues

1. Plasma Proteins as Storage Depot:

    a. **<u>Albumin</u>** -the most abundant protein in plasma- can bind to a very large number of different compounds—(e.g. bilirubin, Ca^{2+}, Cu^{2+}, Zn^{2+}, vitamin C, fatty acids, digitonin, penicillin, sulfonamides, histamine, barbiturates, thyroxine, etc.)

    1. Contains 6 binding regions on the protein

    2. Protein-ligand interactions occur primarily through hydrophobic forces, hydrogen bonding, and van der Waals forces.

    3. Bilirubin, a heme byproduct, is neurotoxic at high levels, but is normally bound to albumin to make it less toxic.
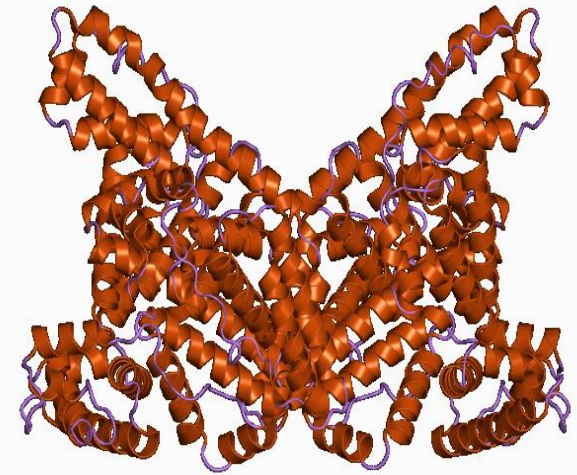
2. Liver and Kidney as Storage Depots—have the highest capacity for binding chemicals.

    1. **<u>Ligandin:</u>** this cytoplasmic protein in the liver is a high-affinity binding protein for many organic acids—can bind bilirubin, azodye carcinogens, steroids, etc.

    2. **<u>Metallothionein</u>**: found in the kidney and liver and has high affinity for cadmium and zinc--in the liver, metallothionein binds Lead (Pb) and concentrates it to 50-fold more than plasma.
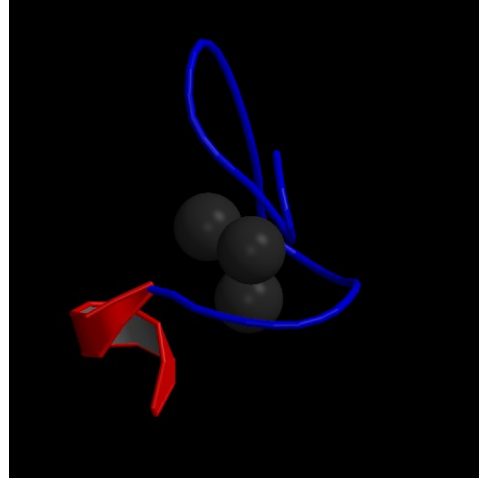
Human metallothionein bound to Cd2+
determined by NMR
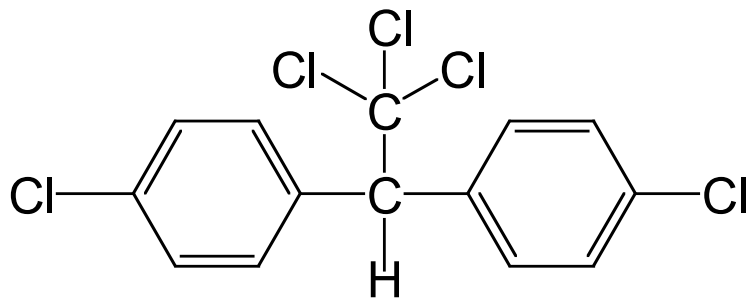
3. Fat as a Storage Depot

Many highly lipophilic toxicants are distributed and concentrated in fat (e.g. dioxin, DDT, polychlorinated biphenyls)
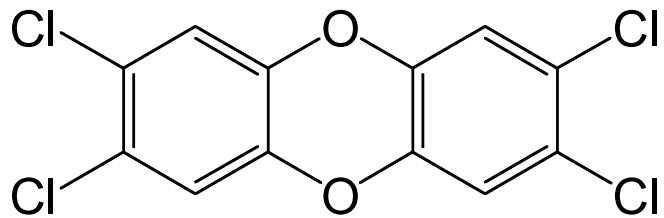
dioxin

-The LD_{50} of a fat-stored compound will be higher in an obese subject.

-However, a quick weight-loss can result in large release of toxicant and toxic effect.

DDT

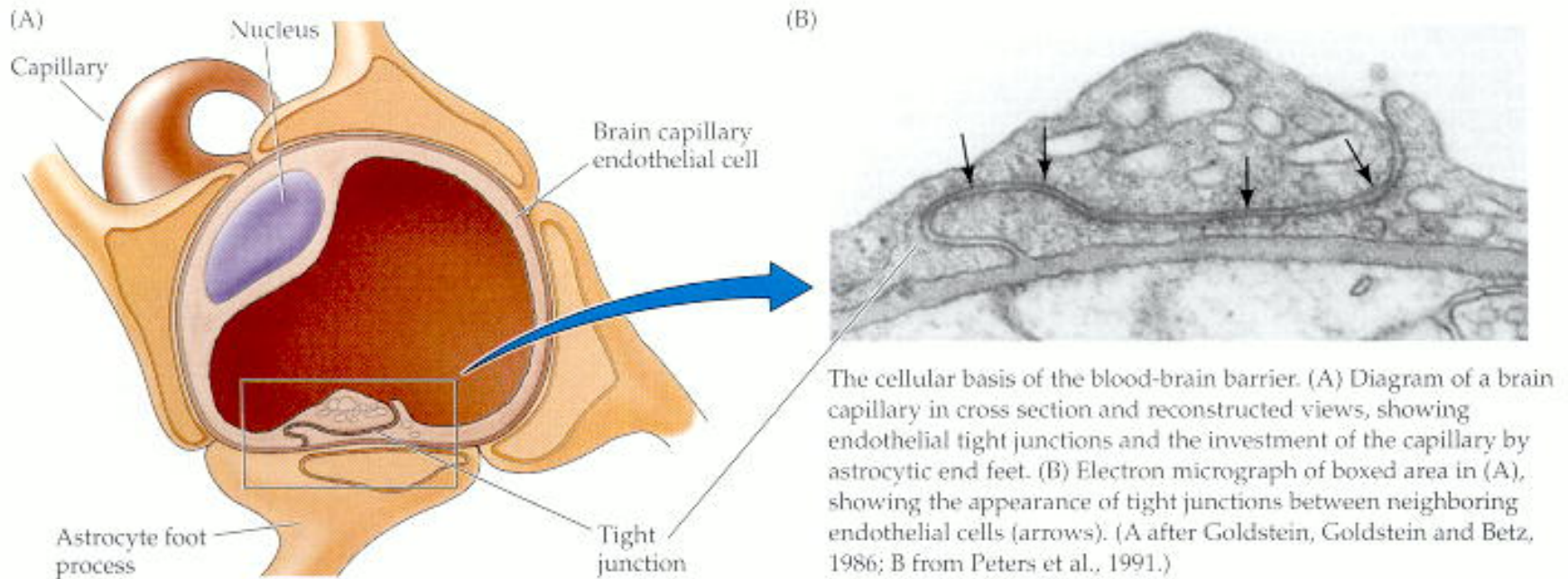# 4. Bone as Storage Depot

1. Compounds such as fluoride, lead, and strontium may be incorporated and stored in bone matrix.

2. 90% of lead in the body is eventually found in the skeleton.

3. The mechanism of storage is through exchange of bone components for the toxicant (e.g. F^- may displace ^-OH; Pb^{2+} and Sr^{2+} may substitute for Ca^{2+} in the hydroxyapatite lattice matrix).

Effects of Storage on Toxicity

1. Reduces toxicity of some substances by taking toxic substances out of the sites of action.

2. Increases toxicity if: a)toxicity at storage site, b) displacement of one substance by another (e.g. bilirubin), loss of storage site.

3. Can produce chronic toxicity from prolonged exposure.

Blood-Brain Barrier

The cellular basis of the blood-brain barrier. (A) Diagram of a brain capillary in cross section and reconstructed views, showing endothelial tight junctions and the investment of the capillary by astrocytic end feet. (B) Electron micrograph of boxed area in (A), showing the appearance of tight junctions between neighboring endothelial cells (arrows). (A after Goldstein, Goldstein and Betz, 1986; B from Peters et al., 1991.)

The blood-brain barrier serves to restrict access to many toxicants. It is not an absolute barrier.

It is a site that is less permeable to more hydrophilic substances than are most other areas of the body.

There are four major anatomic and physiologic reasons why some toxicants do not readily enter the CNS.

1. Capillary endothelial cells of the CNS are **tightly joined**, leaving few or no pores between cells.

2. Brain capillary endothelial cells contain an ATP-dependent transporter, the **multi-drug-resistant (mdr)** protein that transports some chemicals back into the blood.

3. Capillaries in the CNS are **surrounded by glial cells** (**astrocytes**) to further restrict access.

4. The **protein concentration in the interstitial fluid** of the CNS is much lower than in other body fluids.

Blood Brain Barrier

•For water-soluble molecules, the tighter junctions of the capillary endothelium and the lipid membranes of the glial cells represent the major barrier.

•Many lipid soluble compounds are restricted due to the many lipid membranes to be crossed (capillary and glial cell membranes) and low protein content.

•The blood-brain barrier is **more effective against water soluble substances.**

Methyl Mercury Transport Across the Blood-Brain Barrier

cysteine

Methyl mercury

Methyl Mercuric cysteine
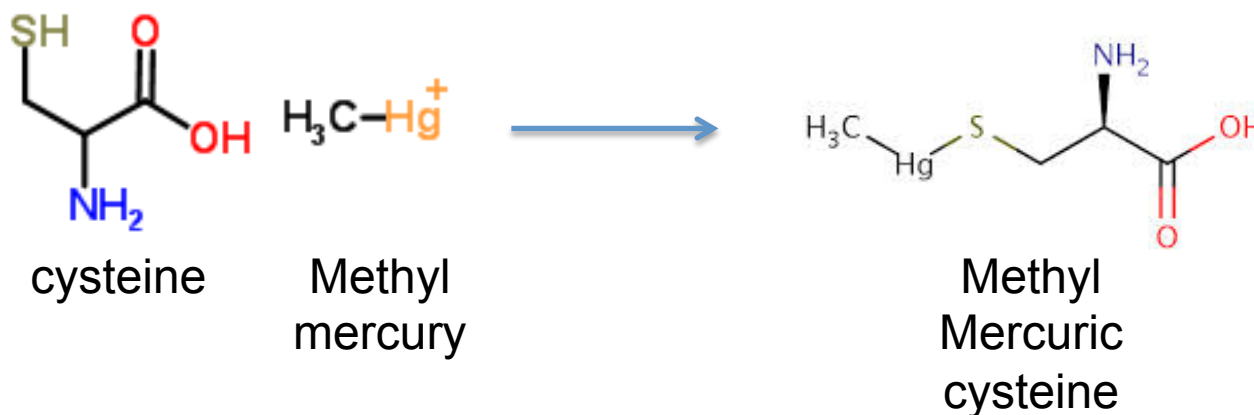
Methylmercury combines with cysteine, forming a structure similar to methionine, which is transported across the blood brain barrier through the methionine transporter in endothelial cells

Once in the brain, methyl mercuric cysteine can react with reactive cysteines on proteins and cause neurotoxicity

Children are more susceptible to neurotoxicants

•The blood-brain barrier is not fully developed at birth, and this is one reason why some chemicals are more toxic in newborns than adults.

•Morphine is 3-10 times more toxic to newborns than adult rats because of higher permeability into the brain.

•Lead produces toxicity in the brain and spinal cord (encephalomyelopathy) in newborn rats but not in adults, because of differences in the stages of development of the blood brain barrier.

Family of ATP Binding Cassette (ABC) Proteins

The ATP-binding cassette (ABC) transporters form a large family of membrane proteins that transport a variety of compounds through the membrane against a concentration gradient at the cost of ATP hydrolysis.
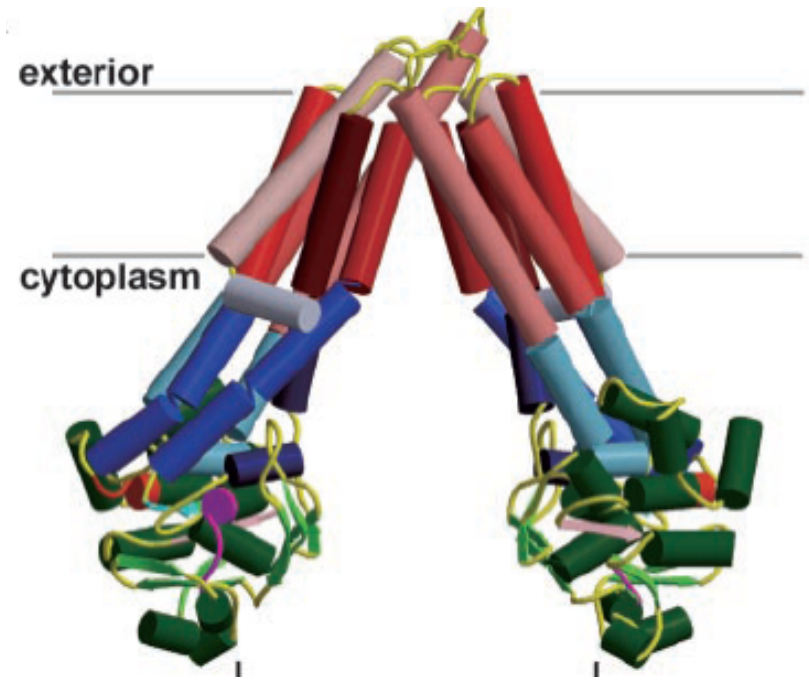
Substrates include lipids, bile acids, xenobiotics, and peptides for antigen presentation. As they transport exogenous and endogenous compounds, they reduce the body load of toxicants.

One by-product of such protective function is that they also eliminate various useful drugs from the body, causing drug resistance. Many types of cancer cells can up-regulate MDR (multidrug resistant).

MRP1 (multi-resistant protein) was originally cloned from a lung tumor cell.

<u>Three subfamilies of the human ABC family based on motifs in ATP binding domains:</u>

1. ABCB1 (MDR1/P-glycoprotein of subfamily (hydrophobic and cationic compounds)

2. ABCC (MRPs) (phase II conjugate metabolites)

3. ABCG2 (phase II conjugates)

<u>Xenobiotic substrates:</u>

1. Alkaloids (bases)

2. Metals—arsenic, oxidized GSH (GSSG)

3. Conjugates of glutathione, glucuronic acid, and sulfates

4. Neutral compounds (e.g. PAH)

A partial list of drug substrates transported by human P-gp[a]

Anticancer
- Actinomycin D
- Daunorubicin
- Doxorubicin
- Etoposide
- Teniposide
- Imatinib
- Mitomycin C
- Mitoxantrone
- Paclitaxel
- Irinotecan
- Topotecan
- Vinblastine
- Vincristine

Antihypertensive
- Celiprolol
- Losartan
- Nicardipine
- Reserpine
- Talinolol

Cholesterol lowering
- Atorvastatin
- Lovastatin

Antibiotics
- Clarithromycin
- Erythromycin
- Levofloxacin
- Rifampin
- Sparfloxacin
- Tetracycline

Antimycotics
- Itraconazole
- Ketoconazole

Antiepileptics
- Phenobarbital
- Phenytoin

Immuno suppressants
- Cyclosporine
- Sirolimus
- Tacrolimus
- Valspodar

Antiacids
- Cimetidine
- Ranitidine

Glucocorticoids
- Aldosterone
- Cortisol
- Dexamethasone

Antiviral
- Amprenavir
- Indinavir
- Nelfinavir
- Ritonavir
- Saquinavir

Antidepressants
- Amitriptyline
- Fluoxetine
- Paroxetine
- Sertraline
- St John's wort

Antiemetics
- Domperidon
- Ondansetron

Antihistamine
- Fexofenadine
- Terfenadine

Opioids
- Methadone
- Morphine
- Pentazocine

Antiarrhythmics
- Amiodarone
- Digoxin
- Propafenone
- Quinidine
- Verapamil

Others
- Bromocriptine
- Colchicine
- Dipyridamole
- Emetine
- Ivermectin
- Loperamide
- Mefloquine
- Progesterone
- Retinoic acid
- Rhodamine 123
- Spironolactone

[a]*Source*: Dantzig, de Alwis, and Burgess (2003), Dietrich, Geier, and Oude Elferink (2003), Fromm (2004), and Marzolini et al. (2004). The primary references are available in these reviews.