

Biotransformation and Elimination of Toxicants

Principles of Environmental Toxicology
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Learning Objectives

- Explain the role of biotransformation in toxicokinetics.
- Describe how biotransformation facilitates elimination of toxicants.
- Distinguish between Phase I and Phase II reactions.
- Define bioactivation or toxication.

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Learning Objectives, 2

- Identify tissues and factors involved in biotransformation.
- Summarize the role of elimination in toxicokinetics.
- Describe processes occurring in the kidney, liver and lung related to the elimination of toxicants.

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Metabolism

- Sum of biochemical rxns occurring to a molecule within the body.
 - Anabolism - "build-up"
 - Catabolism - "break-down"
- Occurs in the cytoplasm or at specific organelles within the cell.
- Storage affects the body's ability to biotransform and eliminate.
 - Bone, lipid.

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Biotransformation

- Process that changes substances from hydrophobic to hydrophilic to aid in elimination (grease to salt).
 - Hydrophilic molecules are less able to cross cellular membranes, hence fluid filterable (kidneys).
 - Major elimination routes are feces (biliary) and urine.
 - Biological half-life, $T_{1/2}$, allows comparison of rates of removal.

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Biotransformation Reactions

- Grouped as Phase I (functional group modification) and Phase II (conjugation).
- Goals
 - Produce water soluble metabolites.
 - Activate natural/endogenous compounds for normal function.
- Some compounds undergo bioactivation.
 - The biotransformed metabolite is more toxic than the original compound.

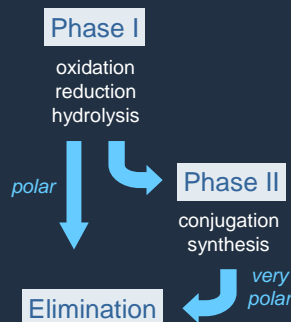
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Results of Biotransformation

- Increase toxicity via a toxic metabolite.
- Decrease toxicity via metabolism of a toxic parent compound.
- No effect on toxicity.
- Present to metabolize endogenous compounds.

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Major Categories/Reactions



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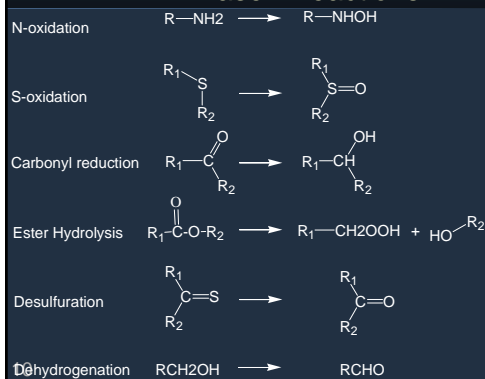
Enzymes of Biotransformation

Phase I Enzymes

- Oxidation (most important).
 - Add O, remove H, increase valence.
 - Cytochrome P-450, MFO, alcohol dehydrogenase, oxidases, others.
- Reduction (less important).
 - Remove O, add H, decrease valence.
 - Reductases.
- Hydrolysis.
 - Add water.
 - Esterases, phosphatases, others.

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Phase I Reactions



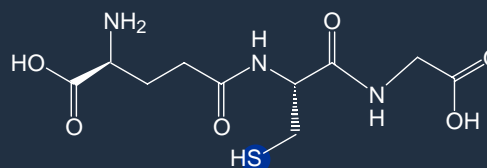
Enzymes of Biotransformation, 2

Phase II Enzymes

- Conjugation reactions.
- Enzymes (transferases) + cofactor.
 - Enzyme catalyzes.
 - Cofactor donates group.
 - Glucuronic acid, glutathione, sulfate, acetyl group, methyl group.
 - Tends to increase molecular size and polarity for excretion.

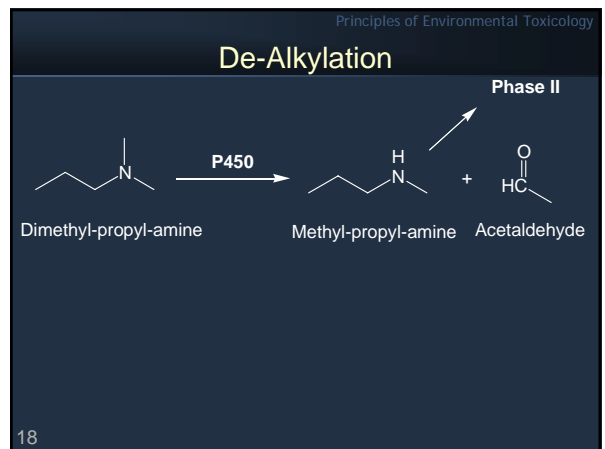
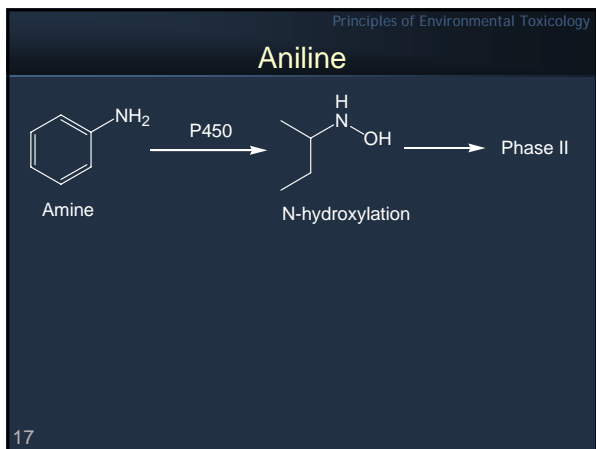
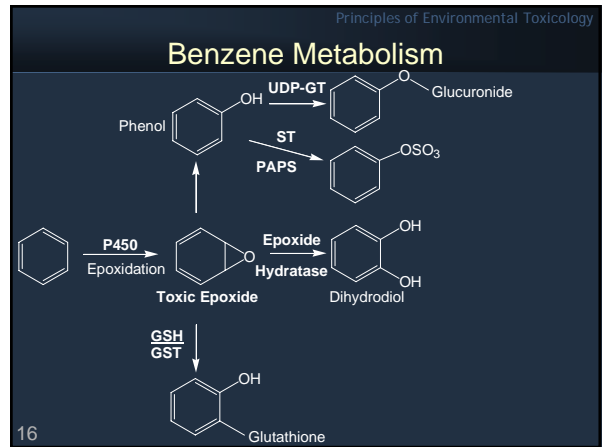
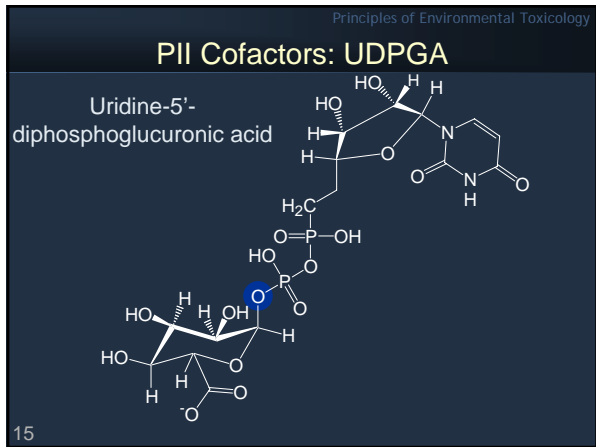
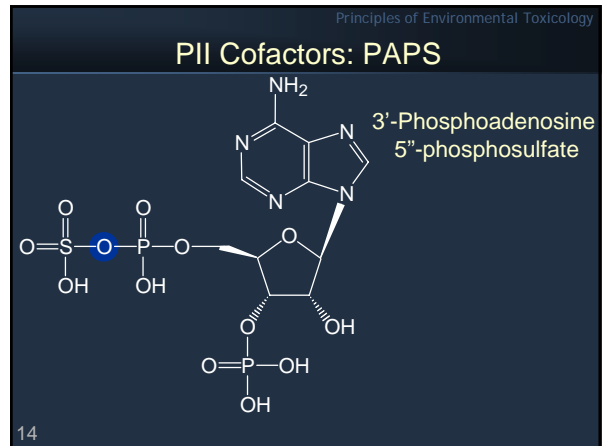
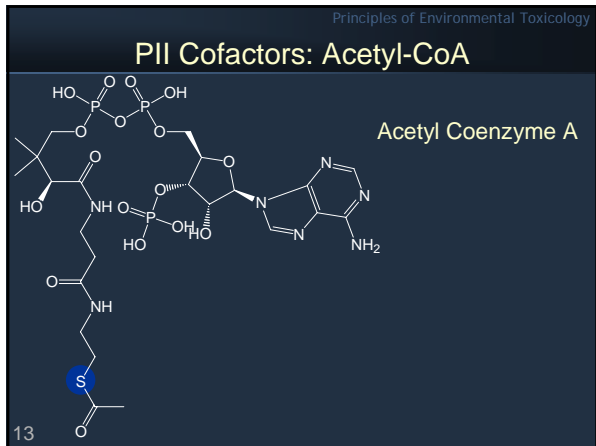
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PII Cofactors: GSH



Glutathione

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Free Radical Generation

$$\begin{array}{ccc}
 \begin{array}{c} \text{Cl} \\ | \\ \text{Cl}-\text{C}-\text{Cl} \\ | \\ \text{Cl} \end{array} & \xrightarrow[\text{Reductase}]{\text{NADH P450}} & \begin{array}{c} \text{Cl} \\ | \\ \text{Cl}-\text{C} \\ | \\ \text{Cl} \end{array} \longrightarrow \text{GSH}
 \end{array}$$


Tetrachloro-methane Toxic Free Radical

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Case Study: Fluorocitrate and Kangaroos

- Fluorocitrate found in legume pasture plants of Western Australia.
 - *Gastrolobium* and *Oxylobium*.
- Highly lethal (TD 1 mg/1080 kg).
 - Leaf concentrations can be 2.6 g/kg.
- The rat and gray kangaroo of Western Australia have evolved resistance.
 - *In vivo* defluorination w/ glutathione.
 - Other kangaroos from areas w/o these plants are not tolerant.



20 Harborne

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Rodenticide: Fluoroacetic Acid

$$\begin{array}{ccc}
 \begin{array}{c} \text{O} \\ || \\ \text{F}-\text{CH}_2-\text{C}-\text{OH} \end{array} & \xrightarrow{\text{CoASH}} & \begin{array}{c} \text{H} \\ | \\ \text{F}-\text{C}-\text{COSCoA} \\ | \\ \text{H} \end{array}
 \end{array}$$

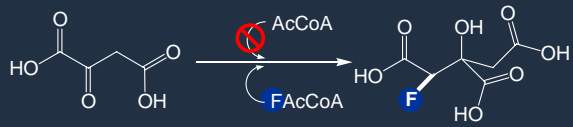
Fluoroacetate Fluoroacetyl CoA

Sodium Fluoroacetate
Compound 1080
rodenticide
predator control

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Fluorocitrate Metabolite

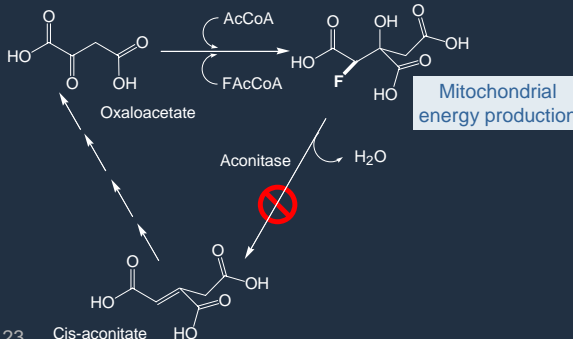


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Krebs Cycle

(Fluoro)Citrate

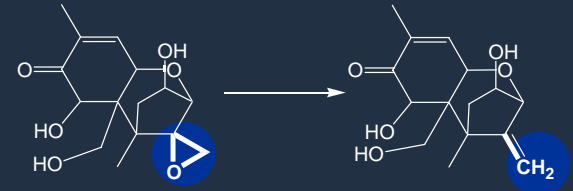


Oxaloacetate (Fluoro)Citrate Cis-aconitate

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Deoxynivalenol, Vomitoxin



Fusarium tricothecene mycotoxin found on corn and barley

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Aflatoxin B₁

B₁ → **Q₁ = hepatic metabolite**

Aspergillus mycotoxin found on corn, peanuts and cottonseed

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Benzo[a]pyrene

R = sulphate or glucuronic acid

- Polycyclic aromatic hydrocarbon.
- Environmental carcinogen.
- Cell cultures from rodents, fish and humans

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Heavy Metal Toxicity - Pb

- Absorbed via Ca channels as divalent ion.
- Capable of reacting with a variety of binding sites.
 - Protein precipitation.
- Specific toxic effect depends on rxns with ligands that are essential for the living system.
- Metal ligands are formed with sulfhydryl groups, as well as amino, phosphate, imidazole, and hydroxyl groups of enzymes and essential proteins.

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Heavy Metal Toxicity - Pb, 2

- Sensitivity of a system and degree of interference determines clinical effects.
 - Digestion/respiration → absorption.
 - Liver → detoxication.
 - Kidney → excretion.
- Antidotes are competing ligands.

EDTA

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Heavy Metal Toxicity - Pb, 3

- Metallic lead absorbed most efficiently by the respiratory tract.
- 10% of ingested lead is absorbed.
 - Small intestine.
 - Lead salts are soluble in gastric juices; absorbed.
- Plasma to blood cells – erythrocytes.
- After oral ingestion:
 - 60% bone (also hair, teeth).
 - 25% liver (hepatocytes).
 - 4% kidney (renal tubules).
 - 3% intestinal wall.

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Heavy Metal Toxicity - Pb, 4

- Some endpoints.
 - Sulfhydryl enzyme inhibition.
 - K transport in RBC inhibited
 - Anemia.
 - Porphyrinuria.
- Excreted chiefly in feces and urine.
- Chelating agents:
 - Ca - EDTA.
 - Penicillamine.
 - Dimercaptol (BAL).

2,3-Dimercapto-propan-1-ol

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Case Study: Elevated PbB Associated with Illicitly Distilled Alcohol, Alabama 1991

- The use of automobile radiators containing lead-soldered parts in the illicit distillation of alcohol (i.e., "moonshine") is an important source of lead poisoning among persons in some rural Alabama counties.
- In 1991, eight persons were diagnosed with elevated blood lead levels (BLLs) at a local hospital.
- 9 patients had been evaluated for alcohol-related medical conditions at the hospital. Manifestations included generalized tonic-clonic seizures (six), microcytic anemia (five) (hematocrit mean: 32.1%), encephalopathy (two), upper extremity weakness (one), and abdominal colic (one). BLLs ranged from 16 ug/dL to 259 ug/dL (median: 67 ug/dL).



31 MMWR (1992) 41(17):294-295

Case Study: "Moonshine" Lead Toxicity

- Seven patients required hospitalization for 48 hours or longer (range: 2-18 days). Three of these received chelation therapy; initial BLLs were 67, 228, and 259 ug/dL. One patient, whose BLL was 67 ug/dL, died during hospitalization from alcohol-withdrawal syndrome complicated by aspiration pneumonia.
- Patients reported moonshine ingestion ranging from 0.2 L per day to 1.5 L per day.
- The lead contents of specimens of moonshine confiscated from two radiator-containing stills in the county in 1991 were 7400 ug/L and 9700 ug/L, compared with nondetectable amounts (less than 1.0 ug/L) in municipal water from the county.
- Consumption of 0.5 L per day of moonshine containing 9700 ug/L lead would result in a steady state BLL of approximately 190 ug/dL.

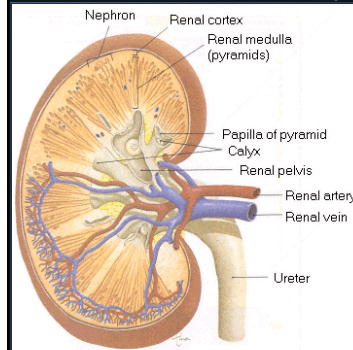
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Elimination of Toxicants

- Urinary.
- Fecal.
- Respiratory.
- Other:
 - Saliva.
 - Sweat.
 - Milk (transfer to child).
 - Nails, Hair, Skin.
 - Cerebrospinal fluid.

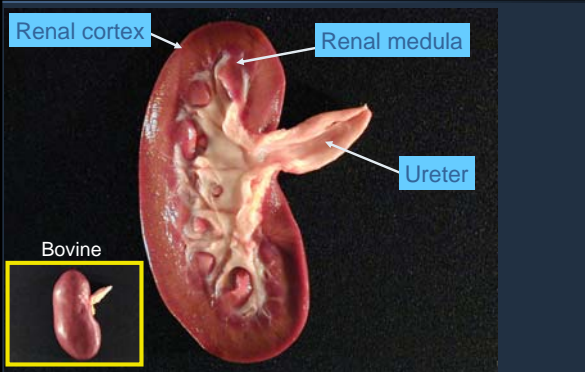
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Kidney



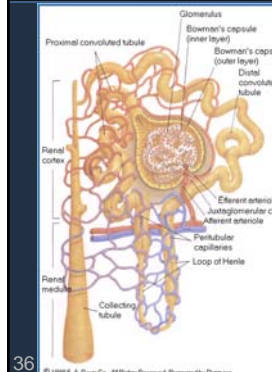
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Renal Macrostructure



Bovine

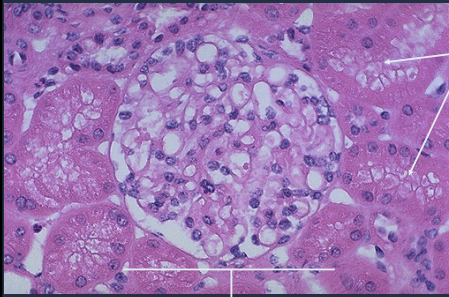
Renal Filtration Microstructure



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Renal Histology



Tubules

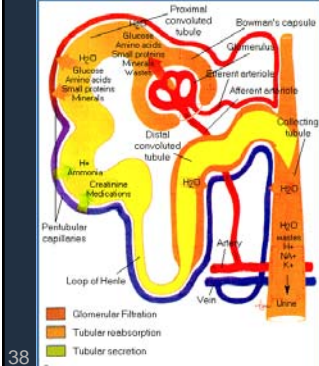
Glomerulus

Microscopic

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Urinary Excretion



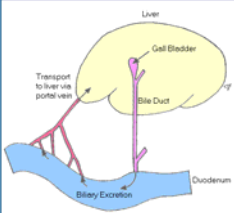
- Glomerular filtration
- Tubular secretion
- Tubular reabsorption

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Fecal Excretion

- Excretion in bile to intestine.
 - Active transport of toxicant parent and metabolites.
 - Highly soluble Phase II metabolites (large, ionized)
- Excretion into the lumen of the GI tract.
 - Direct diffusion from capillaries.

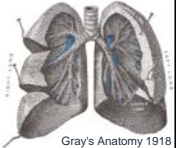


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Exhaled Air

- Gas phase xenobiotics.
- Passive diffusion from blood to alveolus via concentration gradient.
 - The total alveolar epithelial surface area within an average adult human lung has been estimated to be as large as 100-140 m².



Gray's Anatomy 1918

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