Biotransformation and Elimination of Toxicants

Food 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.

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.

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.

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, $T_{½}$ allows comparison of rates of removal.

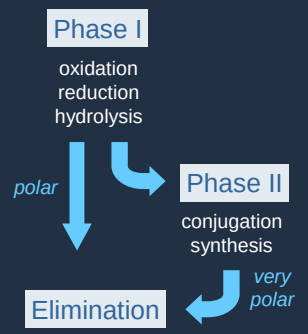
Biotransformation Reactions

- 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.

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.

Major Categories/Reactions

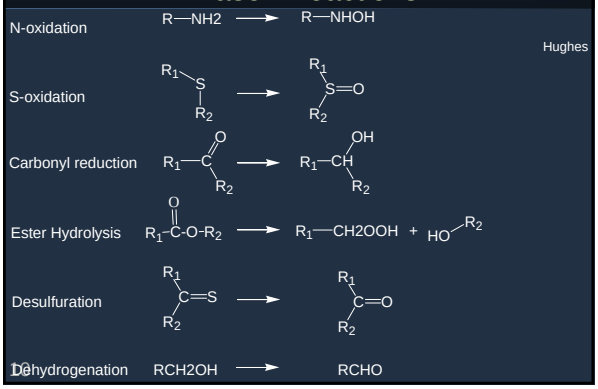


Enzymes of Biotransformation

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, phosphtases, others.

Phase I Reactions

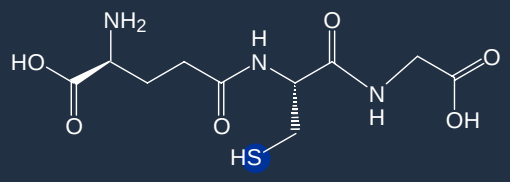


Enzymes of Biotransformation, 2

Phase II Enzymes

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

PII Cofactors: GSH



Glutathione

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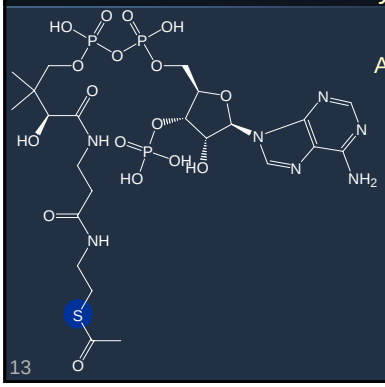
PII Cofactors: Acetyl-CoA



Acetyl Coenzyme A

13

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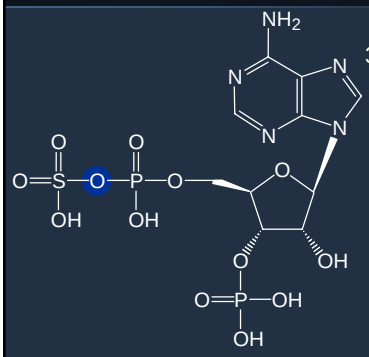
PII Cofactors: PAPS



3'-Phosphoadenosine
5"-phosphosulfate

14

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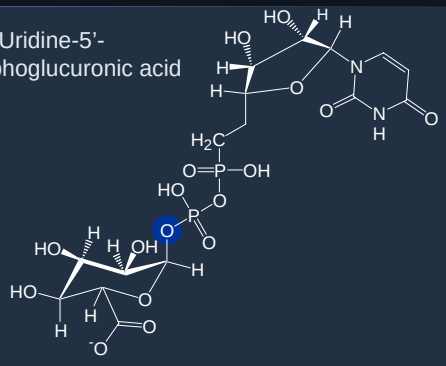
PII Cofactors: UDPGA

Uridine-5'-
diphosphoglucuronic acid



15

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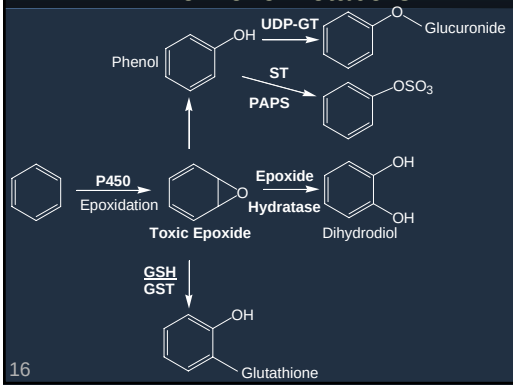
Benzene Metabolism



16

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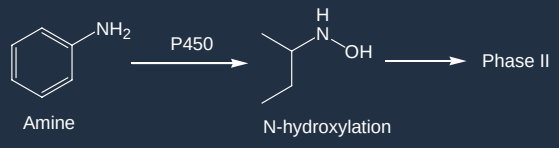
Aniline



17

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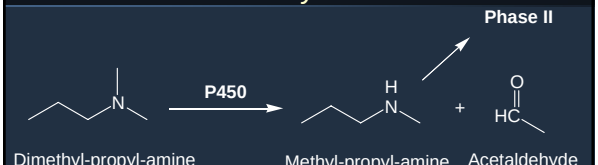
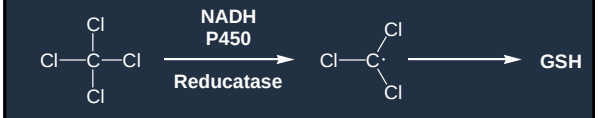
De-Alkylation



18

Free Radical Generation



Tetrachloro-methane Toxic Free Radical

19

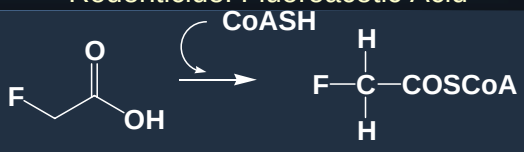
Case Study: Fluorocitrate and Kangaroos

- 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.

Harborne

20

Rodenticide: Fluoroacetic Acid



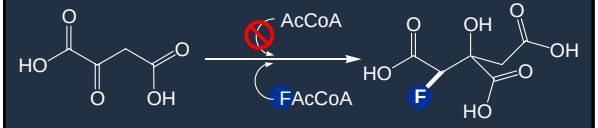
Fluoroacetate Fluoroacetyl CoA

Sodium Fluoroacetate
Compound 1080

rodenticide
predator control

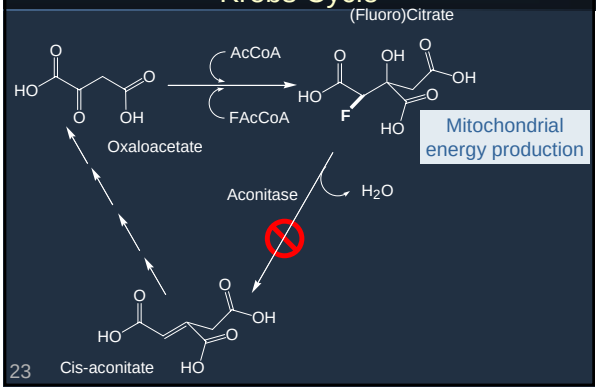
21

Fluorocitrate Metabolite



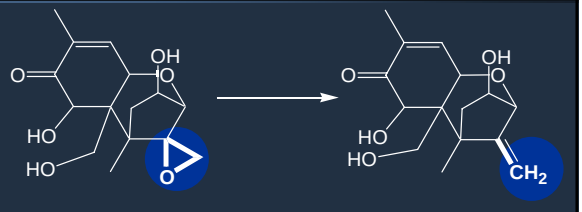
22

Krebs Cycle



23

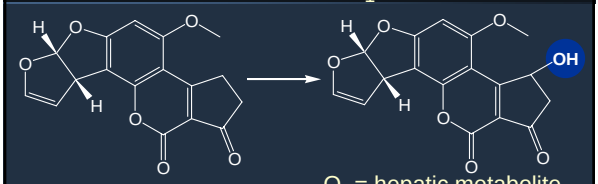
Deoxynivalenol, Vomitoxin



Fusarium trichothecene mycotoxin found on corn and barley

24

Aflatoxin B_1

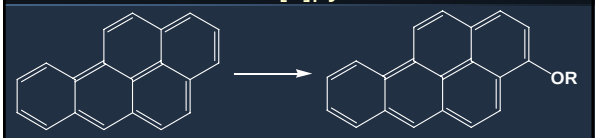


B_1

Q_1 = hepatic metabolite

Aspergillus mycotoxin found on corn, peanuts and cottonseed

Benzo[a]pyrene



R = sulphate or glucuronic acid

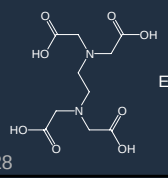
- Polycyclic aromatic hydrocarbon.
- Environmental carcinogen.
- Cell cultures from rodents, fish and humans

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.

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.



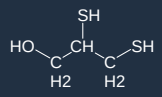
EDTA

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.

Heavy Metal Toxicity - Pb, 4

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



2,3-Dimercapto-propan-1-ol

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).

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

Case Study: "Moonshine" Lead Toxicity

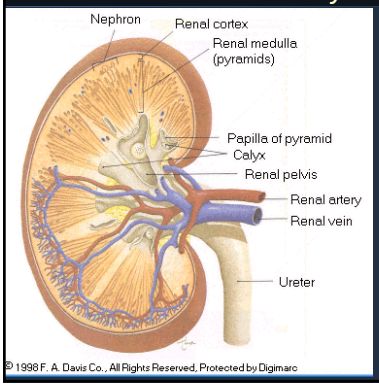
- Seven patients required hospitalization for 48 hours or longer (range: 2-18 days). Three of these received chelation therapy; initial BLLs were 67, 228, and 259 ug/dL. One patient, whose BLL was 67 ug/dL, died during hospitalization from alcohol-withdrawal syndrome complicated by aspiration pneumonia.
- 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.

Elimination of Toxicants

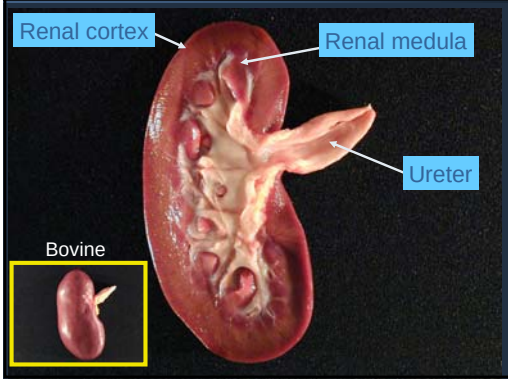
- Urinary.
- Fecal.
- Respiratory.
- Other:
  - Saliva.
  - Sweat.
  - Milk (transfer to child).
  - Nails, Hair, Skin.
  - Cerebrospinal fluid.

 Hughes

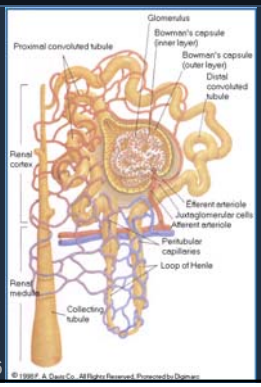
Kidney



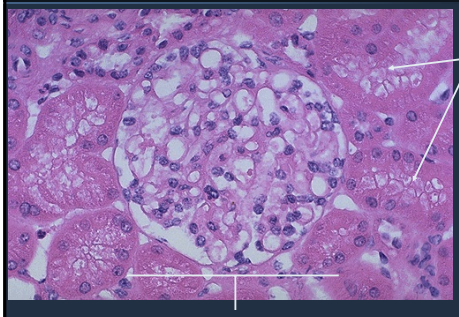
Renal Macrostructure



Renal Filtration Microstructure

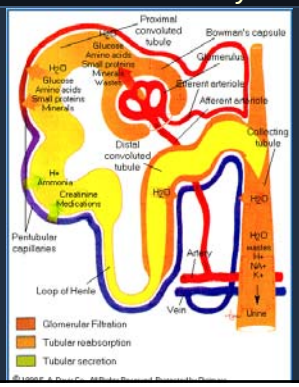


Renal Histology



Microscopic

Urinary Excretion

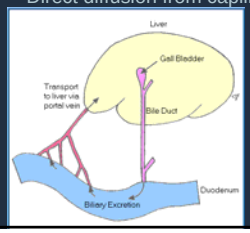


- Glomerular filtration
- Tubular secretion
- Tubular reabsorption

Fecal Excretion

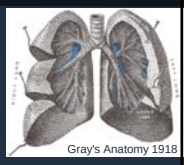
- Excretion in bile to intestine.
  - Active transport of toxicant parent and metabolites.
  - Highly soluble Phase II metabolites (large, ionized)
- Excretion into the lumen of the GI tract.
  - Direct diffusion from capillaries.

NLM



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 m^2.



Gray's Anatomy 1918