



Biotransformation and Elimination of Toxicants

Principles of Environmental Toxicology
Instructor: Gregory Möller, Ph.D.
University of Idaho

Principles of Environmental Toxicology

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.

2

Principles of Environmental Toxicology

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.

3

Principles of Environmental Toxicology

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.

4

Principles of Environmental Toxicology

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.

5

Principles of Environmental Toxicology

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.

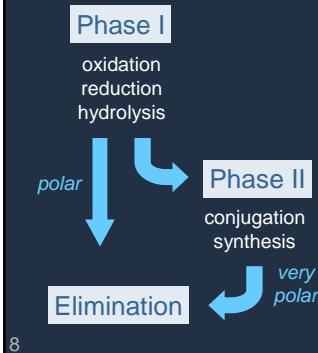
6

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.

7

Major Categories/Reactions



8

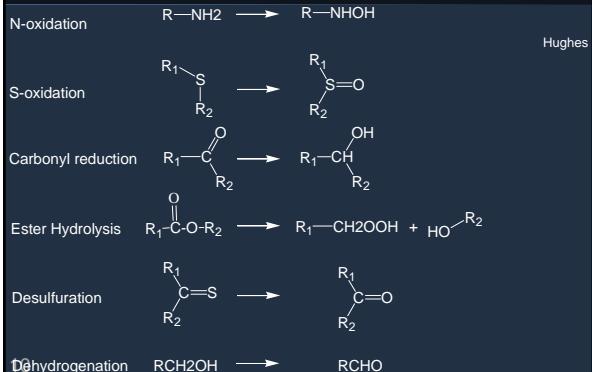
Enzymes of Biotransformation

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.

9

Phase I Reactions



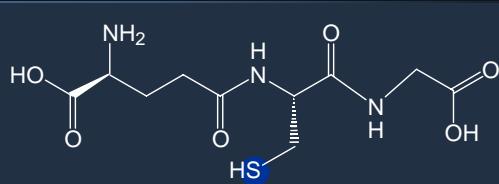
Enzymes of Biotransformation, 2

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.

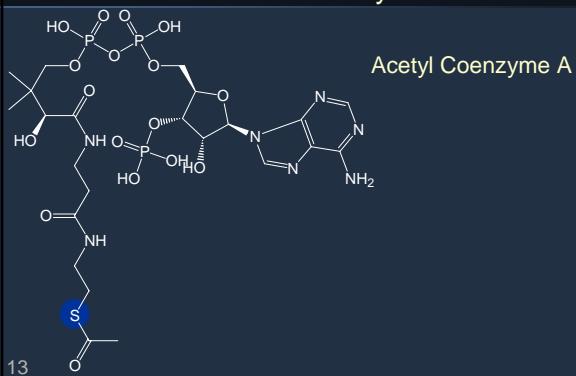
11

PII Cofactors: GSH



Glutathione

12

PII Cofactors: Acetyl-CoA

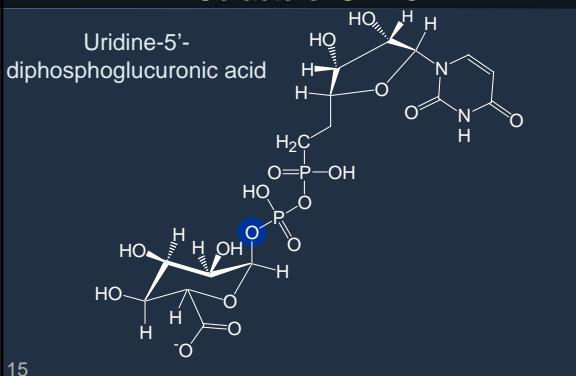
13

Acetyl Coenzyme A

PII Cofactors: PAPS

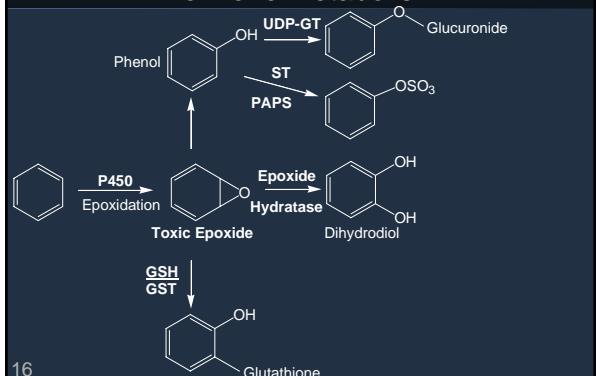
14

3'-Phosphoadenosine 5''-phosphosulfate

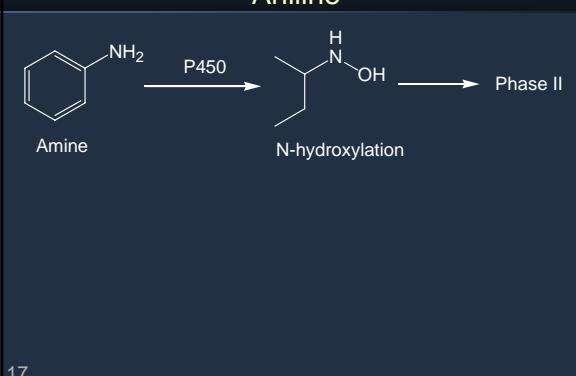
PII Cofactors: UDPGA

15

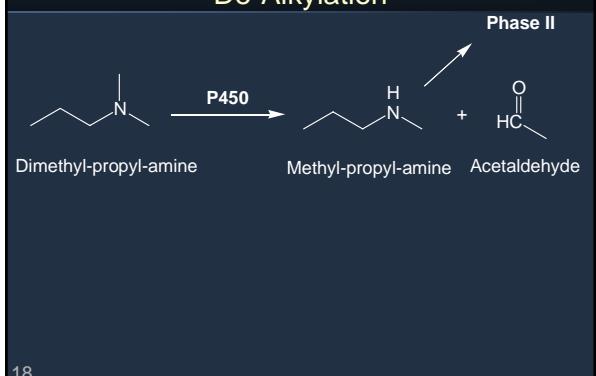
Uridine-5'-diphosphoglucuronic acid

Benzene Metabolism

16

Aniline

17

De-Alkylation

18

Principles of Environmental Toxicology Free Radical Generation



19

Principles of Environmental Toxicology 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

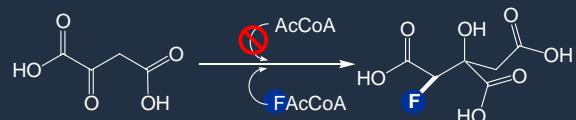
Principles of Environmental Toxicology Rodenticide: Fluoroacetic Acid



Sodium Fluoroacetate
Compound 1080
rodenticide
predator control

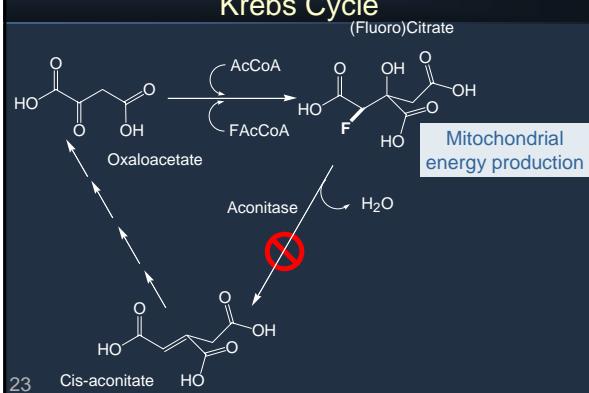
21

Principles of Environmental Toxicology Fluorocitrate Metabolite



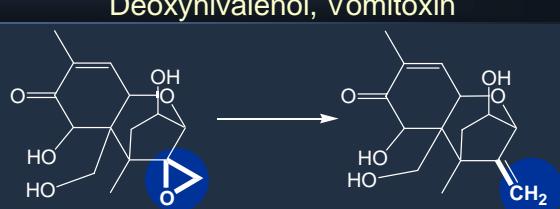
22

Principles of Environmental Toxicology Krebs Cycle



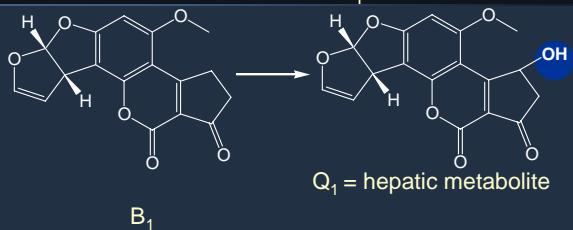
23

Principles of Environmental Toxicology Deoxynivalenol, Vomitoxin



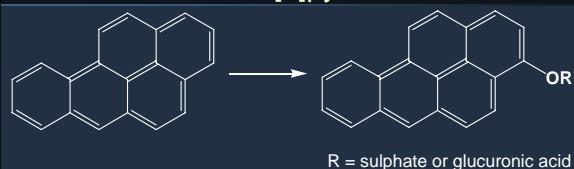
Fusarium trichothecene
mycotoxin found on
corn and barley

24

Aflatoxin B₁

Aspergillus mycotoxin
found on corn, peanuts
and cottonseed

25

Benzo[a]pyrene

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

26

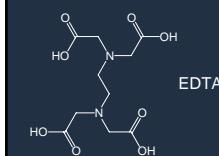
Heavy Metal Toxicity - Pb

- 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 sulphhydryl groups, as well as amino, phosphate, imidazole, and hydroxyl groups of enzymes and essential proteins.

27

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.



28

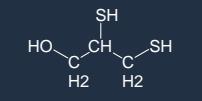
Heavy Metal Toxicity - Pb, 3

- 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.

29

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).



30

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

Principles of Environmental Toxicology

- 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

Principles of Environmental Toxicology

- 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.

32

Elimination of Toxicants

Principles of Environmental Toxicology

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

33 Hughes

