Metabolism: friend and foe? (De)Toxification processes in the liver

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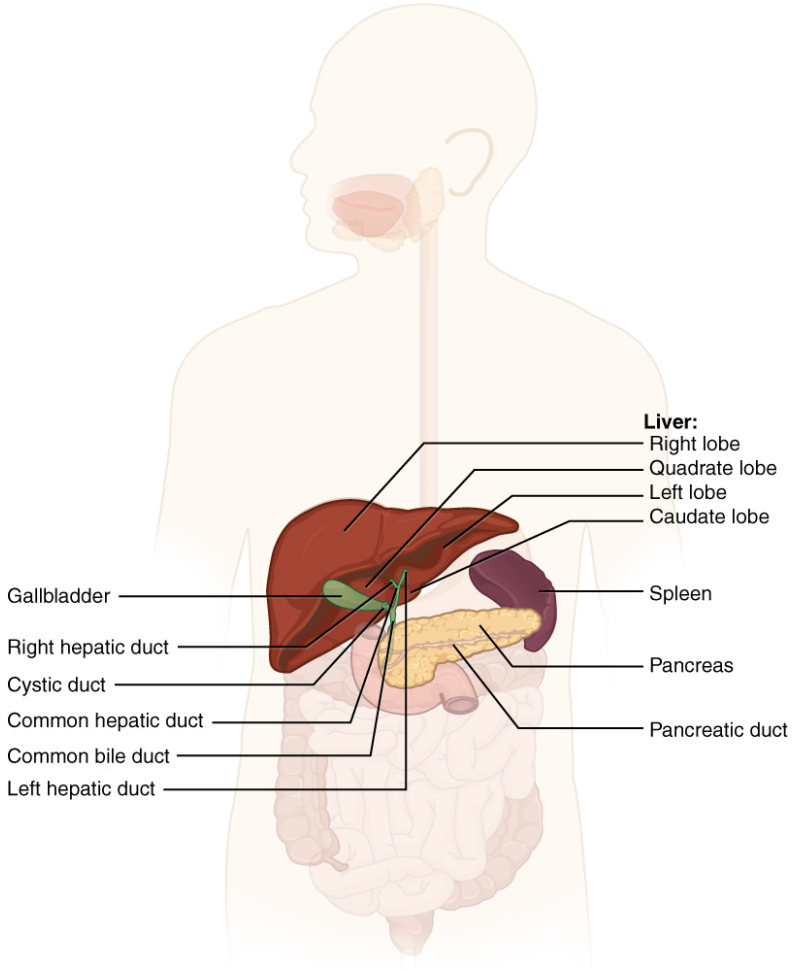
Targets in TOXICOLOGY
Research Training Group

Content

- Liver
- Metabolism
  - Phase I and Phase II
  - CYP450
  - First-Pass Effect
  - Enterohepatic Circulation
- Examples for Toxification Processes
- Take Home Message

Liver

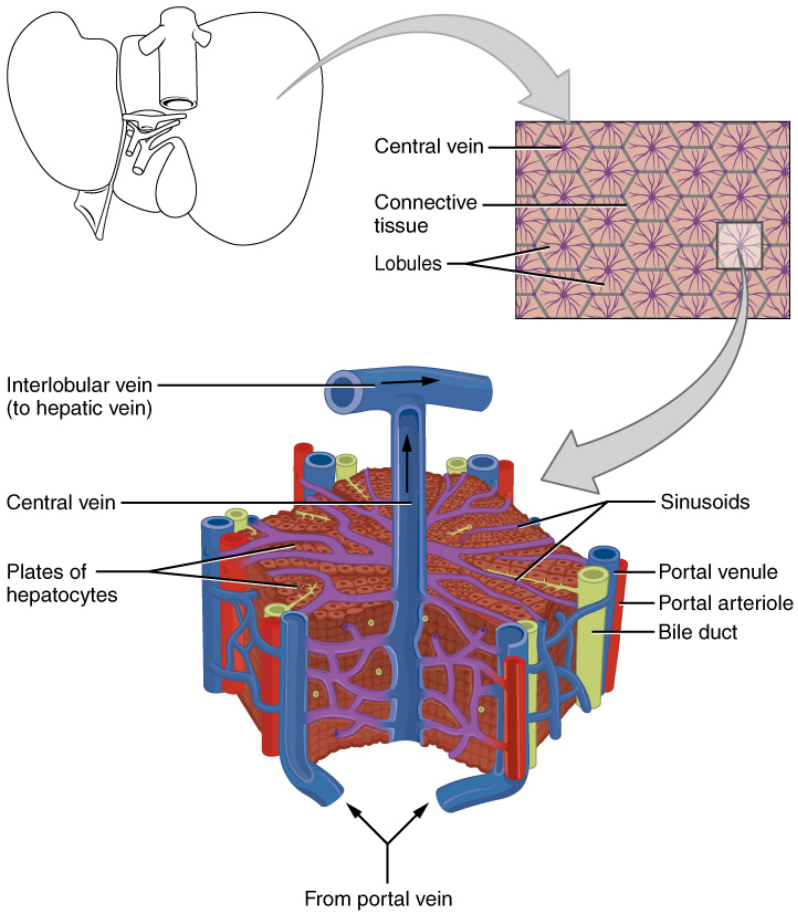
- located in right upper quadrant of abdomen
- heaviest internal organ (1.5 kg)
- functions:
  - bile production and excretion
  - metabolism of fats, proteins and carbohydrates
  - detoxification of xenobiotics
  - storage of glycogen, vitamins and minerals
  - blood detoxification and purification



Human Anatomy and Physiology, Book by: OpenStax

Liver

- made up of hepatic lobules which consist of hepatocytes
- portal triad:
  - hepatic artery, portal vein and bile duct as well as lymphatic vessels and branch of vagus nerve
- xenobiotics reach liver via portal vein (from gastrointestinal tract) or via hepatic artery (from systemic circulation)



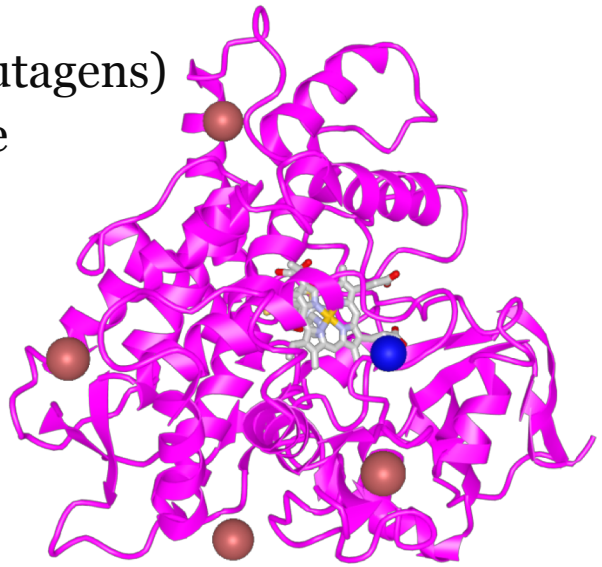
Human Anatomy and Physiology, Book by: OpenStax

Drug Metabolism

- biotransformation of a drug or toxin in the body
  - aim: detoxification of xenobiotic
- pathways of drug metabolism can be divided into
  - phase I (modification)
  - phase II (conjugation)
  - phase III (excretion)
- drugs can undergo one of four potential biotransformations:
  - active drug to inactive metabolite
  - active drug to active metabolite
  - inactive drug to active metabolite (prodrug)
  - active drug to toxic metabolite (biotoxification)

Phase I

- Phase I
  - oxidation, reduction or hydrolysis of xenobiotics
  - aim: modification/functionalization
  - drug becomes inactive
  - **BUT** also creating active compounds (e.g. mutagens)
  - only metabolites are pharmacologically active
    -> original substance is called prodrug
- important enzyme family: **cytochrome P450**



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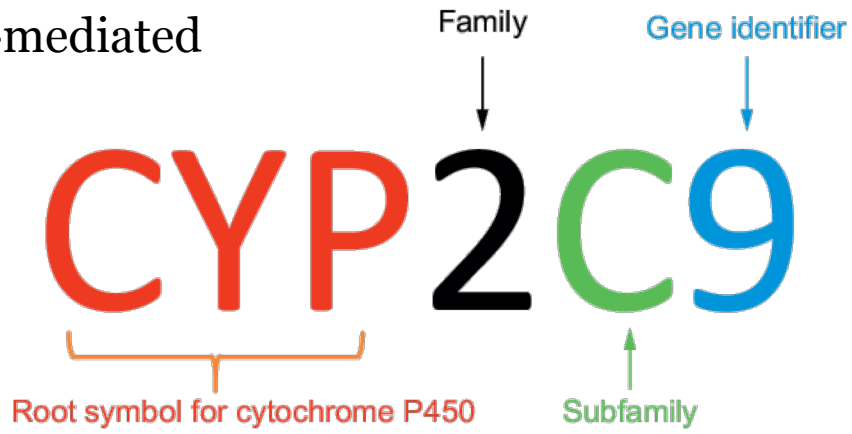
CYP450

- hemeproteins located in ER
  - P450 from the spectrophotometric peak
- major enzyme involved in drug metabolism
  - 90-95 % of all CYP are located in the liver
- drugs can also increase or decrease activity of various CYP enzymes
- grapefruit juice inhibits CYP 3A4-mediated metabolism
  - increased bioavailability

  -> overdosing



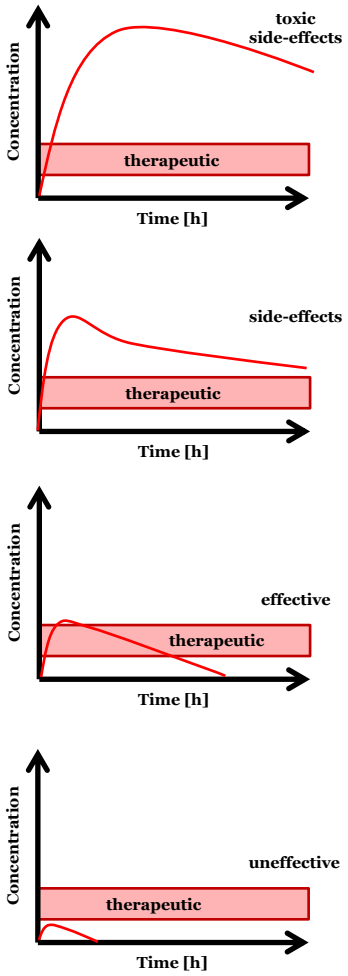
Mittal B. et al., Adv Clin Chem., 2015

CYP Polymorphism

- CYP polymorphism: primary cause of interindividual differences in therapeutic effects and adverse reactions to drugs

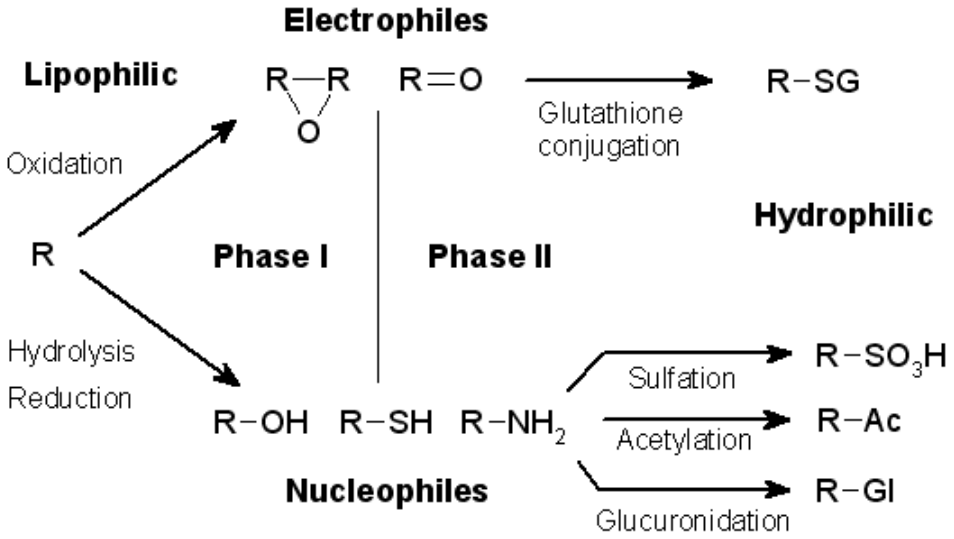
- CYP 2D6 (e.g. codein into morphine)
  - poor metabolizer – little or no CYP 2D6 function
  - intermediate metabolizer – slow CYP 2D6 function
  - extensive metabolizer – normal CYP 2D6 function
  - ultrarapid metabolizer – multiple copies of CYP 2D6 gene expressed

- CYP 2C19 (e.g. diazepam into nordazepam)
  - 3-5 % no or poor CYP 2C19 function



Phase II

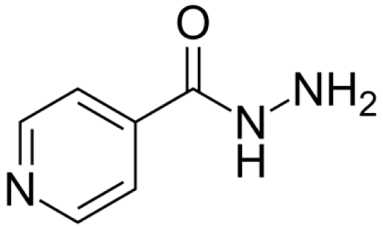
- Phase II (conjugation reaction)
  - aim: conjugation of water-soluble groups onto the molecule -> excretion
  - unlikely to be pharmacologically active
- important enzymes:
  - Glutathione-S-transferase (GST)
  - UDP-glucuronosyltransferase (UGT)
  - Sulfotransferase (ST)
  - N-acetyltransferase (NAT)



https://en.wikipedia.org/wiki/Drug_metabolism

Fast vs. Slow Acetylators

- rate of acetylation is genetically determined
  - 40-70 % of Americans and Caucasians are slow acetylaters
- slow acetylation may lead to higher blood levels of the drug
  -> increase in toxic reactions
- isoniazid
  - different elimination half-life (0.5-1.6 h vs. 2-5 h)
- slow acetylators: higher risk of bladder cancer
  - amino group is hydroxylated
  -> mutagenic nitrenium ion in bladder
- fast acetylators: higher risk of colon cancer



First-Pass Effect

- concentration of a drug is greatly reduced before it reaches the systemic circulation
  - example: morphine (oral), propranolol (oral)

  -> low bioavailability

- **BUT:** some drugs are enhanced in potency
  - example: THC (active metabolite is 11-hydroxy-THC)

https://de.wikipedia.org/wiki/Morphin

Morphine is metabolized into morphine-6-glucuronide (phase II) which is more potent than morphine

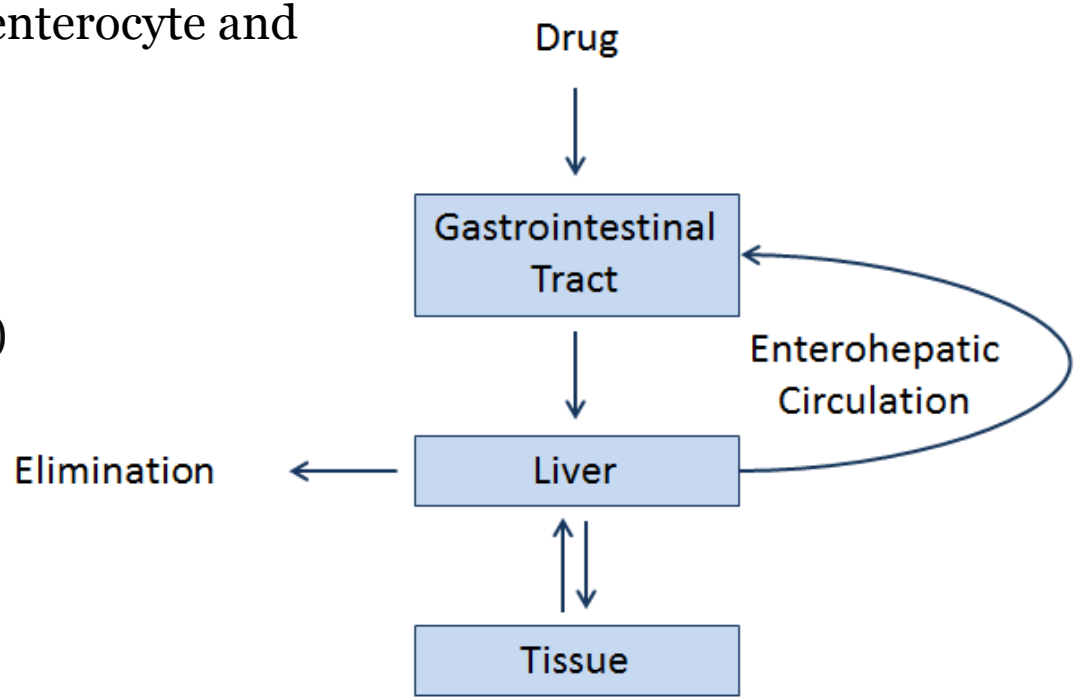
https://www.n-tv.de/wissen/THC-synthetisch-hergestellt-article1307781.html

Enterohepatic Circulation

- circulation of drugs from the liver to the bile followed by entry into the small intestine, absorption by the enterocyte and transport back to the liver
  - longer half-time of drugs
  - extension of intoxication
- example: α-Amanitin (inhibits RNA polymerase II)

A. phalloides

Gossauer A., Struktur und Reaktivität von Molekülen, 2006

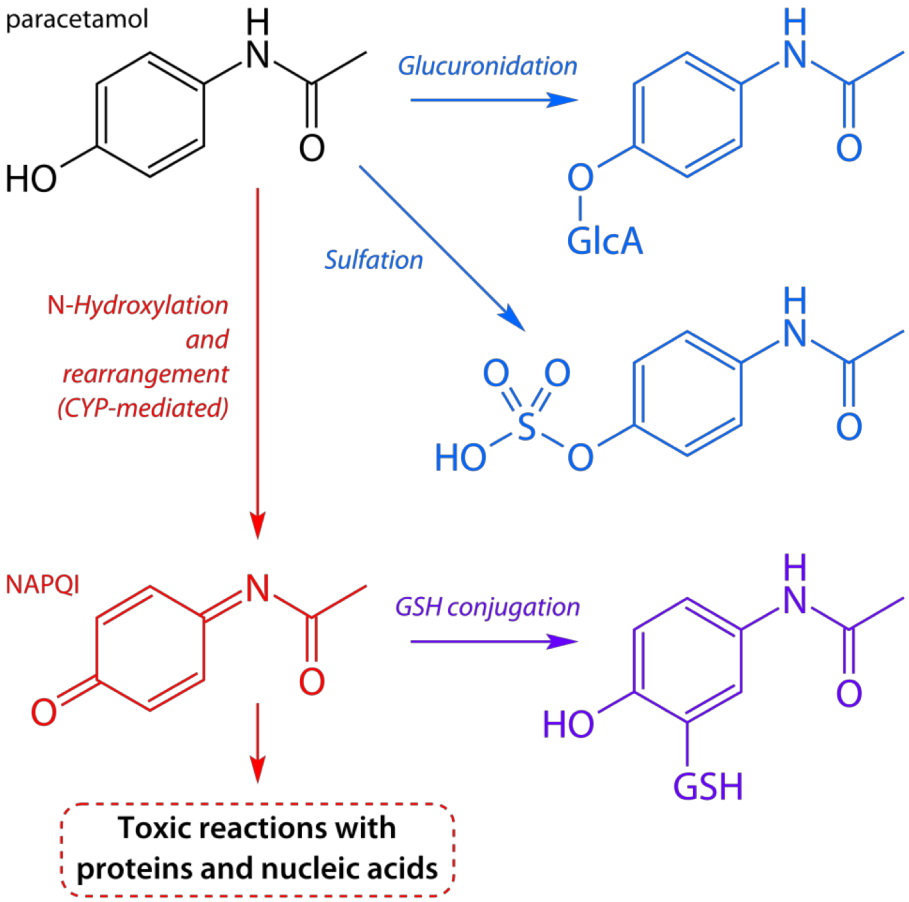


Examples for Toxification

Paracetamol

https://www.ratiopharm.de/produkte/praeparate-details/praeparate/praeparatedaten/detail/pzn-1126111.html

- converted into hepatotoxic metabolite NAPQI
  - CYP 2E1
- detoxification by glutathion (GSH)
- in case of overdose:
  - GSH storage ↓
    NAPQI binds to hepatic proteins resulting in acute liver injury
- antidote: N-acetylcysteine

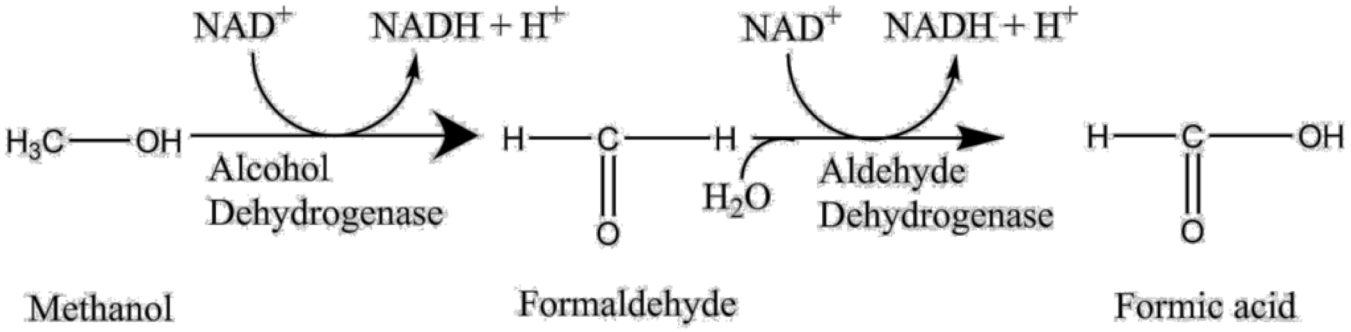


Lewis et al., Goldfrank's toxicologic emergencies, 2009

Methanol

- methanol shows low toxicity
  - damage optic nerve, CNS depression
- formate and formaldehyde significantly more toxic
  - hypoxia, metabolic acidosis
- treatment: ethanol
  - competitive inhibitor of alcohol dehydrogenase

https://www.fotocommunity.de/photo/methanol-alkohol-florianm/9154189

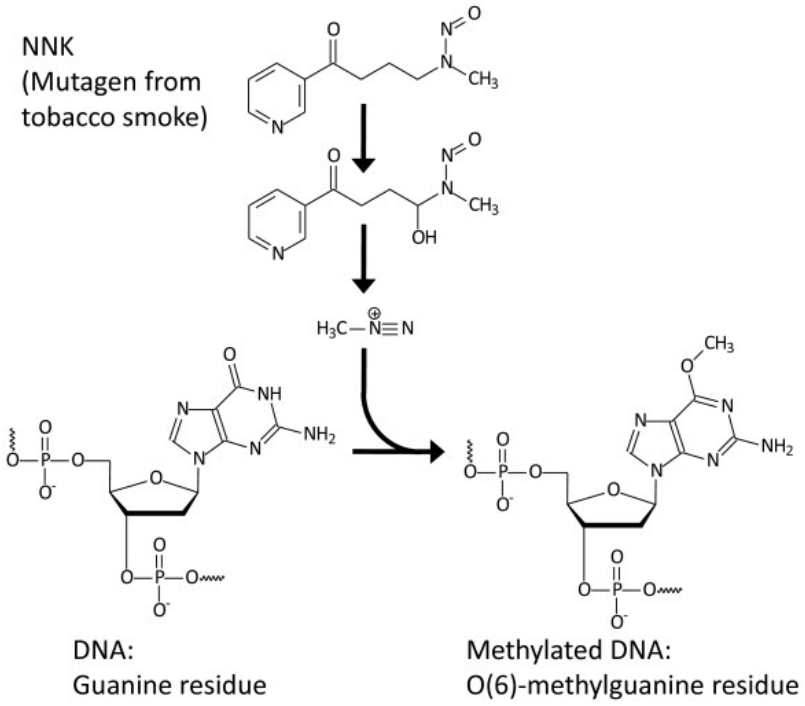


https://www.anaesthesiamcq.com/AcidBaseBook/ab8_6a.php

N-Nitrosamine

https://www.modernmom.com/2c620212-051f-11e2-9d62-404062497d7e.html

- nicotine-derived nitrosamine ketone (NNK)
  - tobacco-specific nitrosamines
- procarcinogen that needs activation to exert its effects
  - dimethylnitrosamine -> carbenium ion
  - ultimate carcinogen

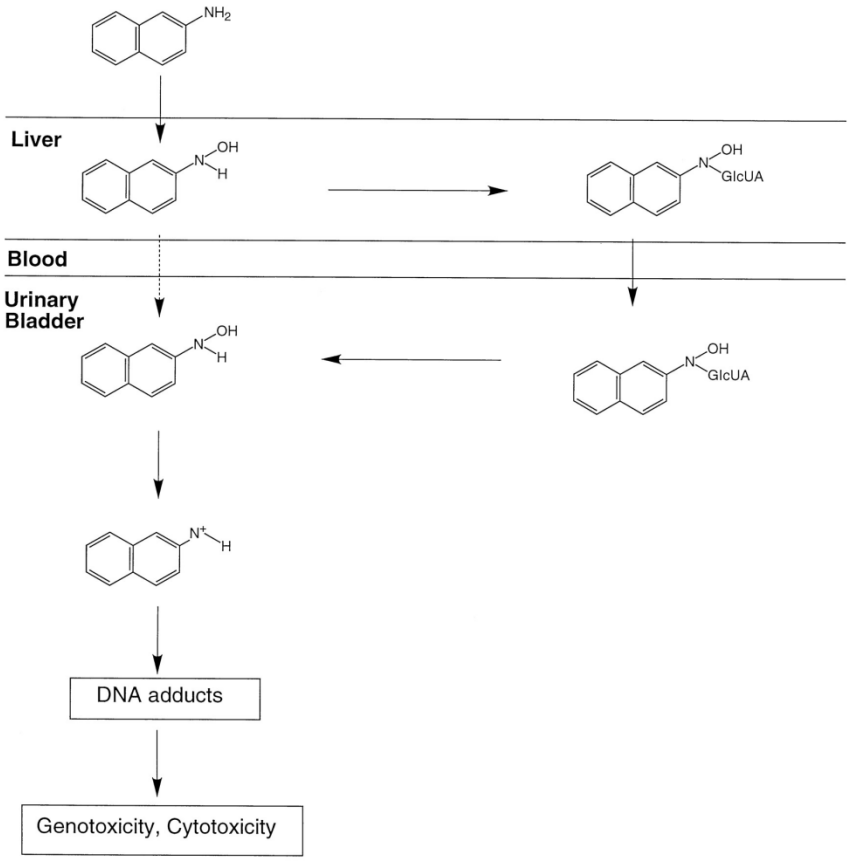


Gzman et al., Diagn Path, 2012

Aromatic Amines

https://www.modernmom.com/2c620212-051f-11e2-9d62-404062497d7e.html

- 2-naphthylamine
  - found in cigarette smoke and roasted/grilled meat
  - glucuronidation (detoxification) or N-hydroxylation by CYP450 (toxification)
  - bladder cancer due to formation of nitrenium ion which can react with proteins, DNA and RNA

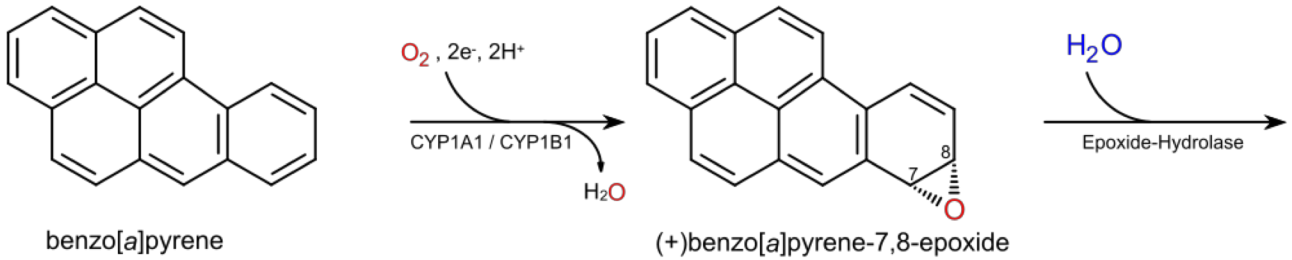


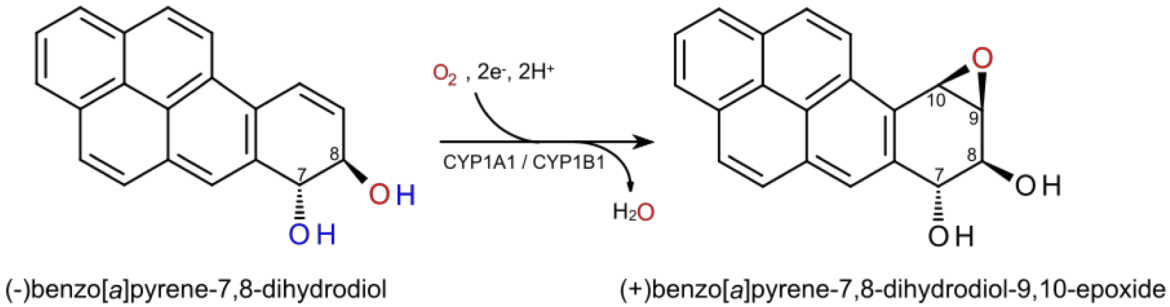
Lin & Lu, Pharm Review, 1997

Benzo[a]pyren

https://www.modernmom.com/2c620212-051f-11e2-9d62-404062497d7e.html

- polycyclic aromatic hydrocarbon
- found in automobile exhaust fumes, tobacco smoke and many foods (roasted/grilled meat)
- metabolites are mutagenic and carcinogenic



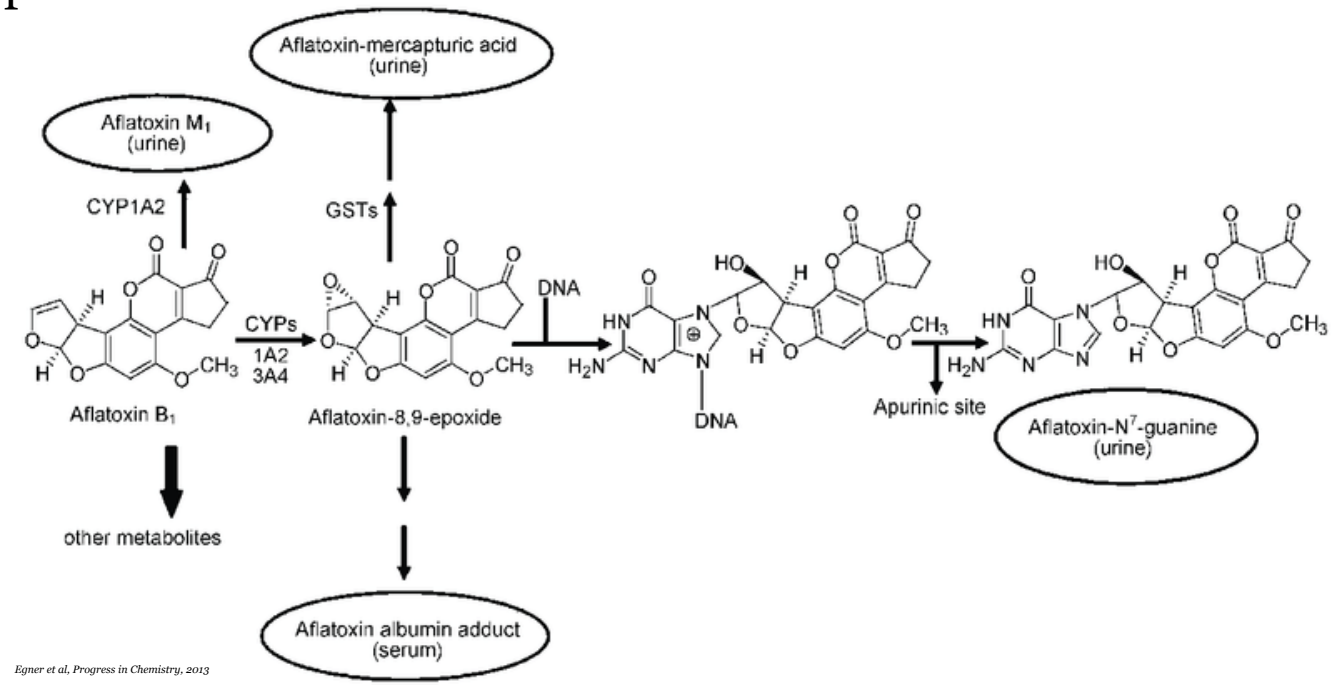


https://en.wikipedia.org/wiki/Benzo(a)pyrene

Aflatoxin

https://www.foodsafety-experts.com/food-safety/aflatoxin-detection/

- aflatoxins are produced by certain molds
  - found e.g. in nuts, rice, spices
- metabolic activation of Aflatoxin B1 to epoxide and binding to guanine but also proteins

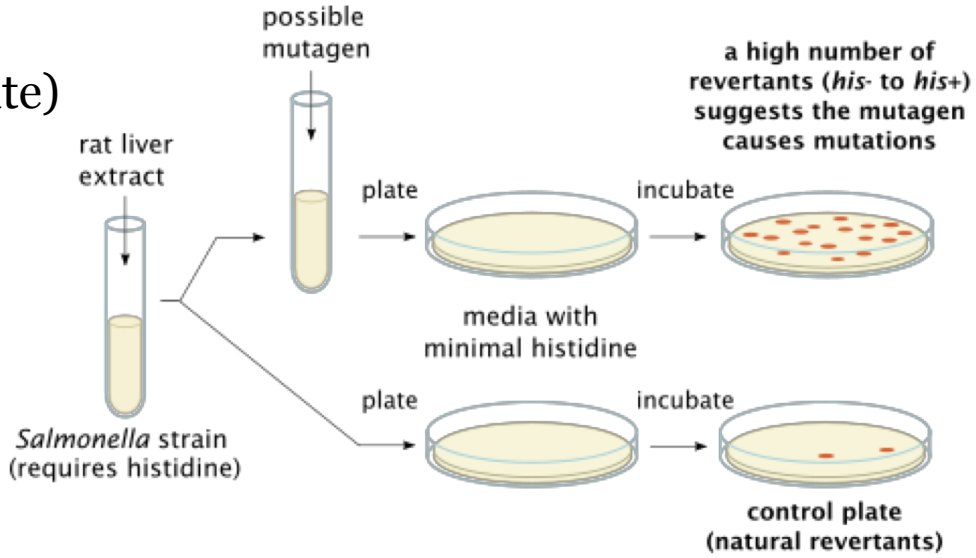


Egner et al, Progress in Chemistry, 2013

How to test for mutagens?

Ames Test

- identification of mutagens
- *Salmonella typhimurium*
  - carry mutations in genes involved in histidine synthesis
  - capability of tested substance to create mutation so that bacteria can grow on histidine-free medium
- mimic metabolic conditions
  - use of S9 mix
    (product of rat liver homogenate)



https://en.wikipedia.org/wiki/Ames_test

Take Home Message

- liver is one of the main organs for metabolism
  - phase I and phase II
- processes in the liver that have an effect on drug
  - CYP polymorphism
  - first-pass effect
  - enterohepatic circulation
- examples for toxification processes:
  - Paracetamol
  - Methanol
  - N-Nitrosamine
  - Aromatic amines
  - Benzo[a]pyren
  - Aflatoxin B1

Metabolic Activation!

- metabolism: **friend AND foe**

Thank You For Your Attention!

Questions?

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CYP Polymorphism

- if CYP converts drug that has a strong effect into a substance that has a weaker effect
  - → poor metabolizers will have an exaggerated response to the drug and stronger side-effects
- if CYP converts drug into a substance that has a greater effect
  - → ultrarapid metabolizers will have an exaggerated response to the drug and stronger side-effects