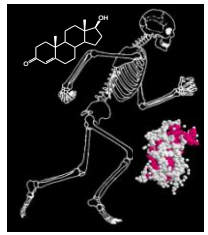
Chimica e Tecnologia Farmaceutica (sostanze dopanti e d'abuso): introduzione

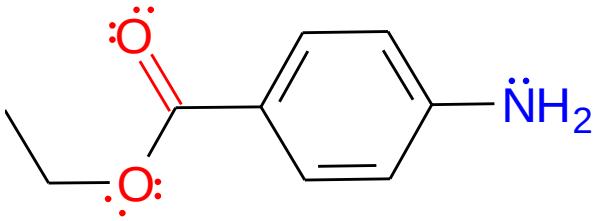


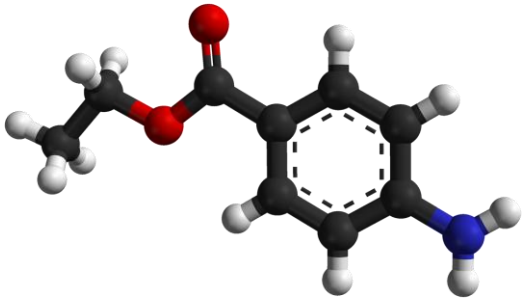
Pharmacodynamics

Chemical structure of drugs and biomolecules

bonds

functional groups



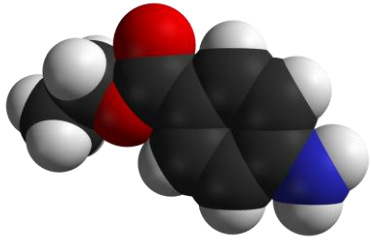


synthesis

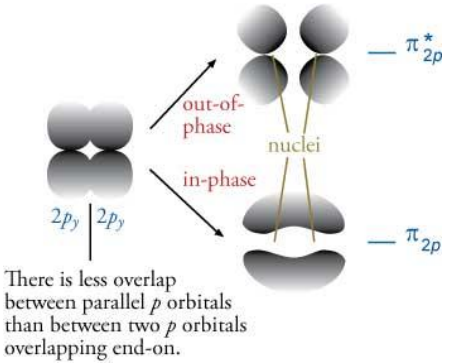
biological interactions / reactions

extraction / analysis

computational chemistry



Chemical interactions in biology



There is less overlap between parallel *p* orbitals than between two *p* orbitals overlapping end-on.

Bond type and bond strenght

Covalent bonds A-B

not usually involved
In drug action

electrons sharing

reactions as movement of electrons

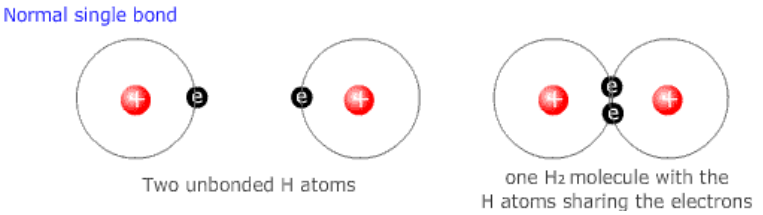
Table 1.2 The energy of some covalent bonds

Single bonds	Energy kJ mol $^{-1}$	Dipole →	Double bonds	Energy kJ/mol $^{-1}$	Dipole →
H–H	431				
H–O	455	1.51			
H–N	385				
H–S	367	0.68			
C–H	410	0.4			
C–O	330	0.74	C=O	170	2.3
C–C	330		C=C	146	
C–Cl	325				
C–N	275	0.22	C=N	147	3.5
C–S	235	0.9			
N–O	182				
P–O			P=O	120	

Electronegativity X:

$$[X_A - X_B] = \sqrt{D_{AB} - (D_{A_2}\, D_{B_2})^{0.5}}$$

D: bond dissociation energy



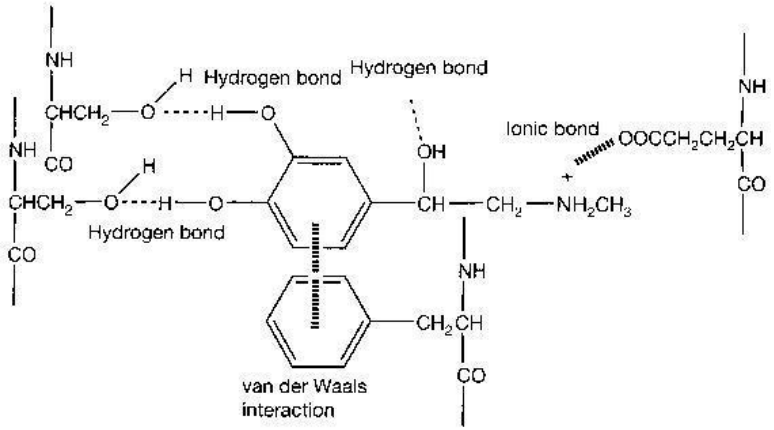
Chemical interactions in biology

The **action of drugs** on biological molecules involve **intermolecular forces** in water

Table 1.3 The effect of different intermolecular forces on melting point and boiling point

Substance	Mol. Wt.	M. P.	B. P.	Intermolecular forces
Argon (Ar)	40		−186°C	Dispersion forces
Carbon dioxide (CO_2)	44	−78.5°C sublimes		Increased dispersion forces due to larger number of bonds
Propane	42		−42°C	Further increase in dispersion forces due to more bonds
Methyl chloride CH_3Cl	50.5	−97°C	−23.7°C	Dispersion forces + weak dipole–dipole interaction
Nitrogen dioxide (NO_2)	42		21.2°C	Dispersion forces + dipole–dipole interaction
Ethanol C_2H_5OH	46	114°C	78.5°C	Dispersion forces + hydrogen bonding
Sodium fluoride	42	993°C	1704°C	Ionic bonding

Figure 1.1 Interaction of adrenaline with amino acids within its receptor protein.



Chemical interactions in biology

Ionic bonds $A^+ B^-$

broken by **water** as a solvent

electrons on one atom

solubility function of dielectric constant:
NaCl in water, 1 g / 2.8 mL
NaCl in glycerol, 1 g / 10 mL
NaCl in ethanol, almost insoluble

Force of attraction between two ions:

$F = Q_1 Q_2 / \varepsilon r^2$

ε: dielectric constant; Q: charge; r: distance

Table 1.4 Dielectric constants of some common solvents

SOLVENT	DIELECTRIC CONSTANT ε
Water	78.5
Glycerol $C_3H_5(OH)_3$	42.5
Acetonitrile CH_3CN	36.2
Methanol CH_3OH	32.6
Ethanol $CH_3 CH_2OH$	24.3
Benzene C_6H_6	4.6

Chemical interactions in biology

Ionisation

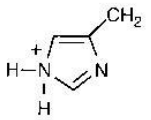
$$\text{ACIDS: \% ion.} = \frac{10^{pH-pKa}}{1 + 10^{pH-pKa}} \times 100$$

$$\text{BASES: \% ion.} = \frac{10^{pKa-pH}}{1 + 10^{pKa-pH}} \times 100$$

Charged groups within proteins:
Sites for binding of ionic drugs

Table 1.5 Ionised groups found on proteins

Acidic groups	pKa	% Ionisation at pH 7.4
Terminal carboxyl ($-COO^-$)	1.8–2.4	100
Aspartic acid side chain ($-CH_2CH_2COO^-$)	3.7	99.98
Glutamic acid side chain ($-CH_2CH_2CH_2COO^-$)	4.3	99.9
Basic Groups		
Terminal ammonium ($-NH_3^+$)	7.5–10.3	55.7–99.9
Arginine ($-NH-(NH_2)C-NH_2^+$)	12.5	100
Lysine ($-CH_2CH_2CH_2CH_2NH_3^+$)	10.5	99.9
Histidine	6.0	4



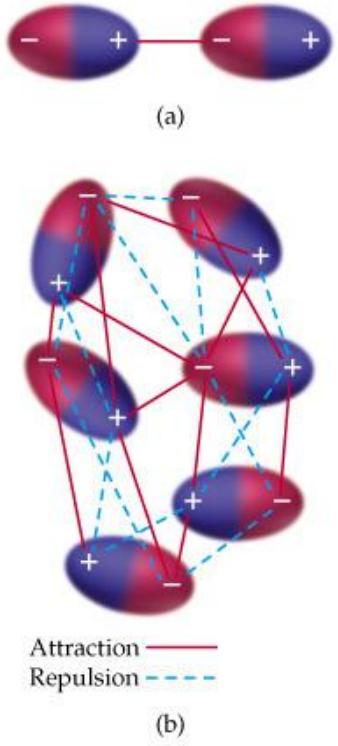
Interactions in solvents

Dipole-dipole $A^{+-}\ B^{+-}$

Force of attraction between dipoles:

$F = 2\ \mu_A\ \mu_B / \varepsilon\ r^4$ (linear) $\qquad F = 2\ \mu_A \cos\Theta\ \mu_B \cos\Theta' / \varepsilon\ r^4$ (angular)

ε: dielectric constant; μ: dipole moment; r: distance



Ion-dipole $A^{+-}\ B^{+-}$

Force of attraction between ion and dipole:

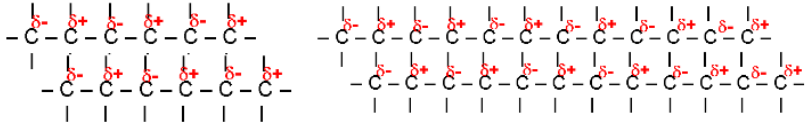
$F = Q\ \mu \cos\Theta / \varepsilon\ r^3$

ε: dielectric constant; μ: dipole moment; r: distance

Interactions in solvents

Van der Waals forces (transient dipoles)

Force of attraction between chains



$F = 3\ I\ \alpha^2 / 4\ r^7$

I: first ionisation potential; α: polarisability

Charge transfer

Force of attraction between π-bases and π-acids:

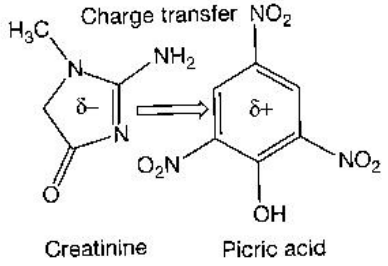


Figure 1.10 Charge transfer complex between creatinine and picric acid.

Chemical interactions in biology

Classes of organic compounds and properties

Hydrocarbons

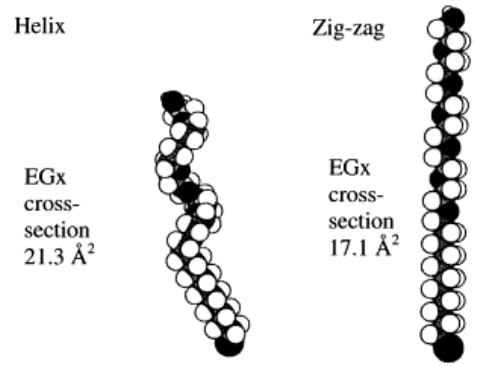
Lipophilicity (devoid of polarity): physical properties governed by Van der Waals interactions

LogP positive value: interaction with membranes and hydrophobic pockets within receptor proteins. Alkyl, aryl and alkylhalides

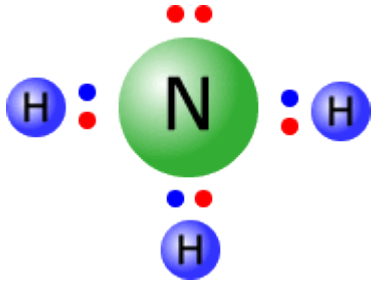
Importance of stereochemistry (low temperature: zigzag form: thinner membranes)

Optical isomerism

Double bonds, lipids oxidation



Classes of organic compounds and properties



Amines

Positive charge

pKa and factors affecting it: alkyl groups, steric factors, electron-withdrawing groups

Aromatic amines and heterocyclic amines

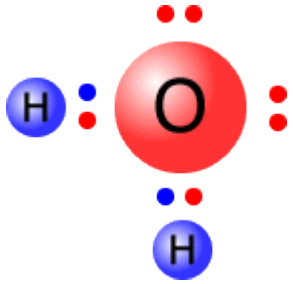
Guanidines and quaternary amines

Neutral and acidic nitrogen compounds

Amides, barbiturates, sulphonamides, xanthines

Chemical interactions in biology

Classes of organic compounds and properties

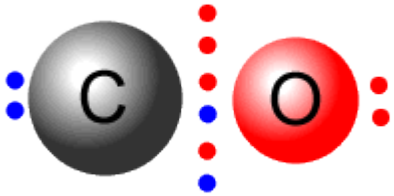


Oxygen and sulphur containing functional groups

Loss of water

Oxidation

Phenols



Carbonyls

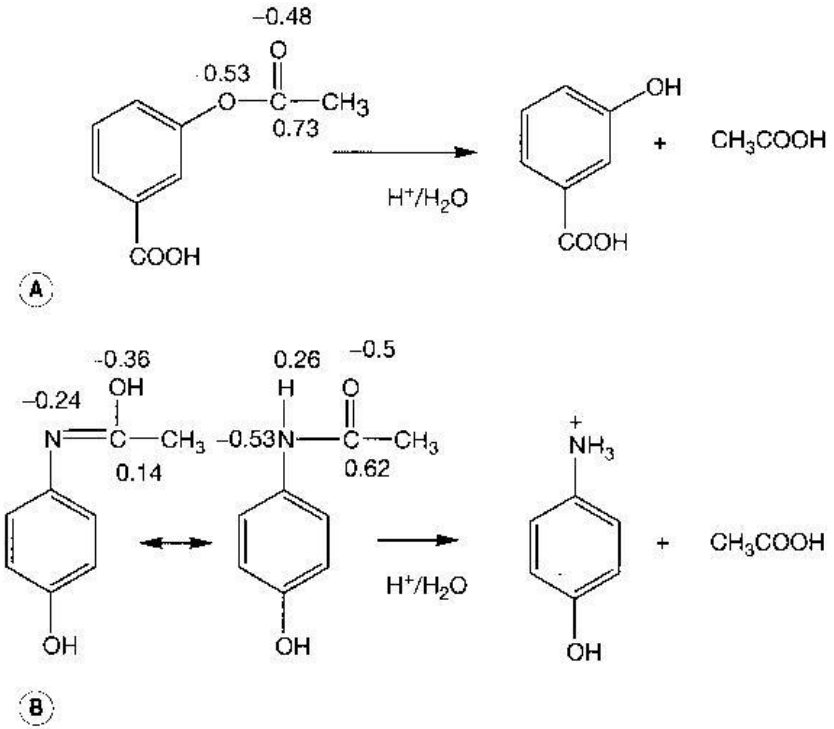
Esters, amides and hydrolysis; aldehydes and ketones; carboxylic acids

Proteins and nucleic acid chemistry

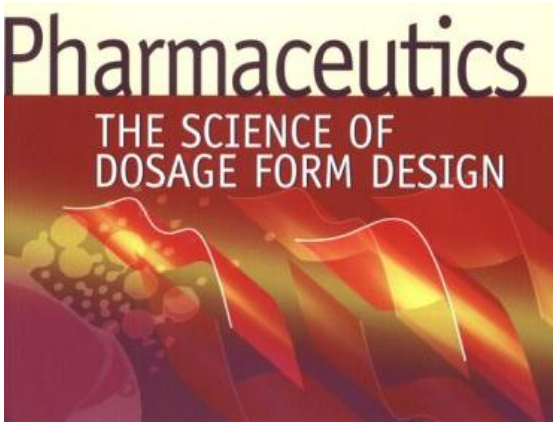
Classes of organic compounds and properties

Carbonyls

Esters hydrolysis



Pharmaceutics



Turning a chemical entity to a medication

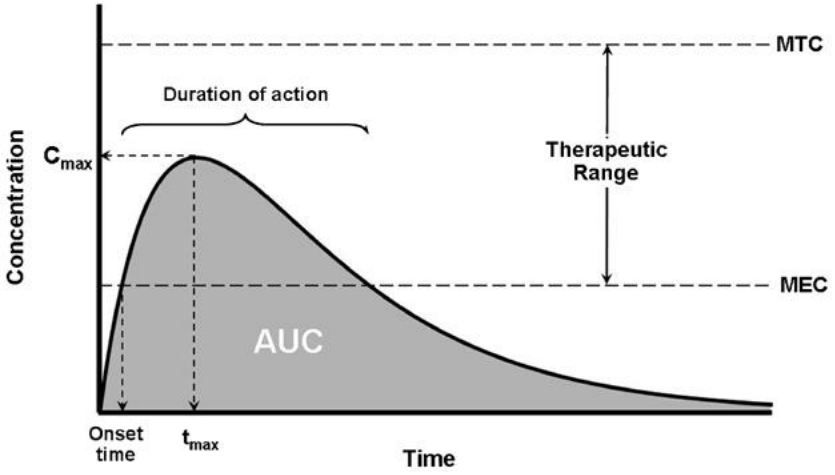
Pharmaceutical formulation


Routes of administration:
p.o. - i.v. - s.c. - i.p. …


Pharmaceutical manufacturing: synthesis, scaling-up, industrial installations

Pharmacokinetics

What the body does to a drug



L*iberation:* the process of release of a drug from the pharmaceutical formulation; *in vivo - in vitro* correlation

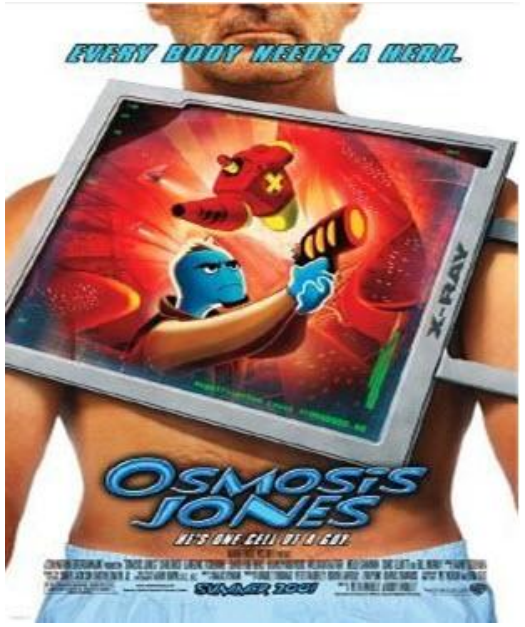
A*bsorption*

D*istribution*

M*etabolism*

E*xcretion*

*[**T**oxicity]*



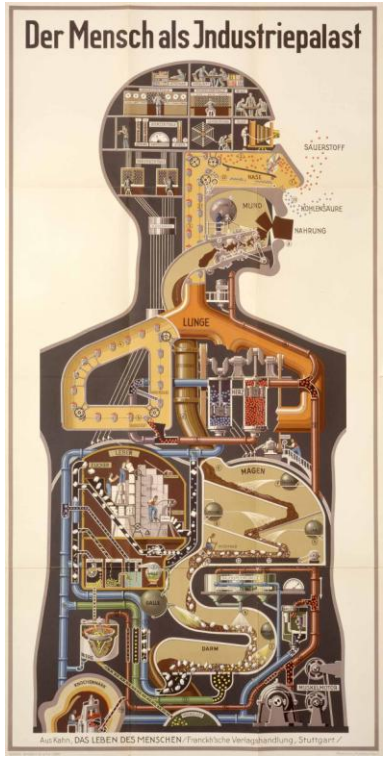
A D M E

What the body does to a drug

L*iberation:*

A*bsorption*
D*istribution*
M*etabolism*
E*xcretion*

*[****T****oxicity]*



Partitioning/Dissociation of different species

Drug stability:
Chemical and enzymatic hydrolysis
Pro-drugs

Pharmacokinetic response of the body to the drug:

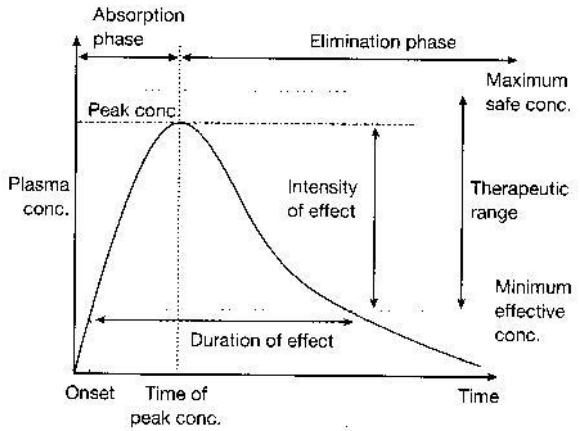


Figure 8.1 Drug dose response profile for a hypothetical drug, showing the absorption and elimination phases following administration.

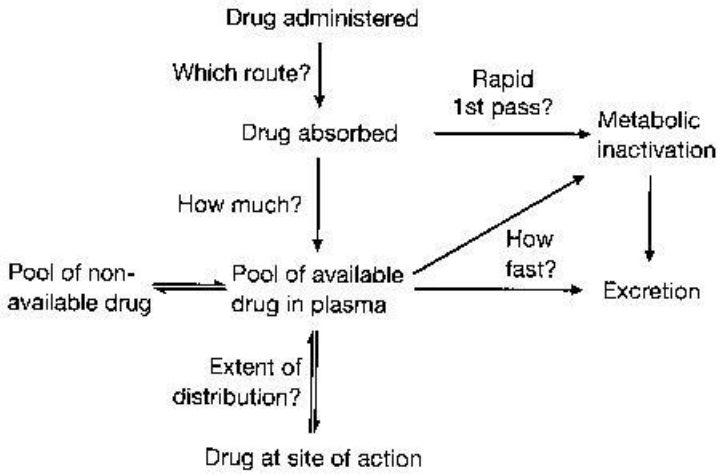


Figure 8.2 The route of a drug into the body.

Partition coefficient (logP)

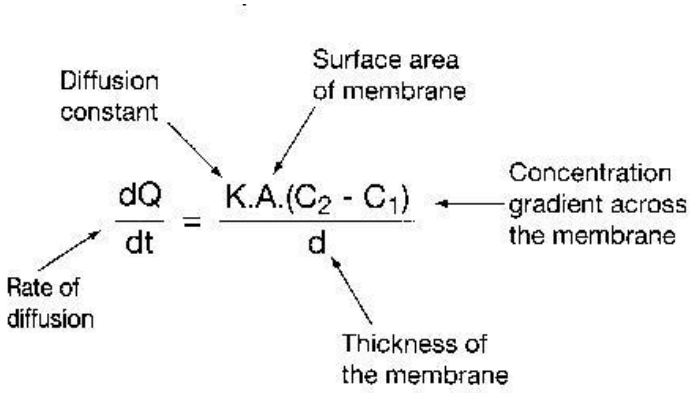
Dissociation constant (ionisation state, Ka, logD)

Solubility

Chemical / enzymatic stability

Transport through biological membranes:

✓ *Diffusion*: transport of molecules in the gas or liquid phase (solution) due to their continuous and rapid movement (2500 Km h^{-1} for water at 37° C). Collisions. Diffusion depends on ***difference in concentration*** and on ***permeability*** of membrane.



Transport through biological membranes:

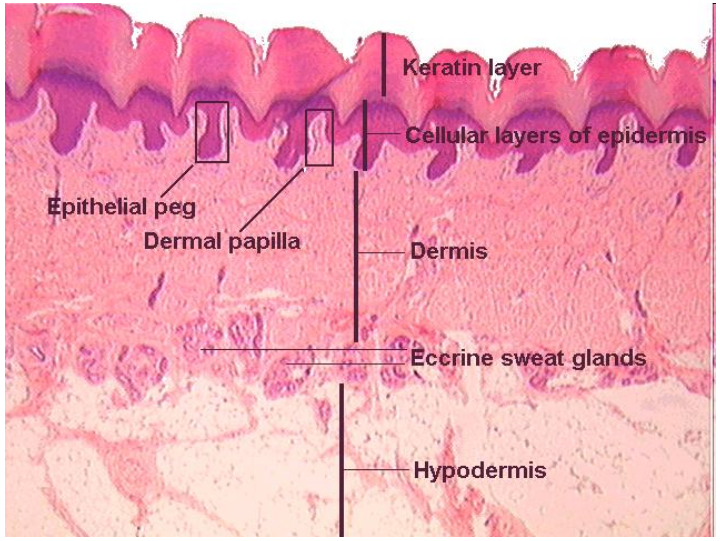
✓ *Passive (protein-assisted) transport:* the ***specificity*** is characteristic and important. The limited ***capacity*** may cause saturation. Change of conformation occurs. Solute concentration determines the flow sense. Ion channels are transmembrane pores.

✓ *Active (protein-assisted) transport:* requires energy in the form of ATP (***primary active transport***) or an ion gradient (***secondary a. t.***) The plasma membrane Na^+/K^+ pump generates sodium and potassium gradient.

✓ *Exocytosis and Endocytosis*: involve the formation of ***vesicles*** surrounded by membranes. Pino- and phago- (particles) –cytosis. Macrophages.

Absorption of chemicals:

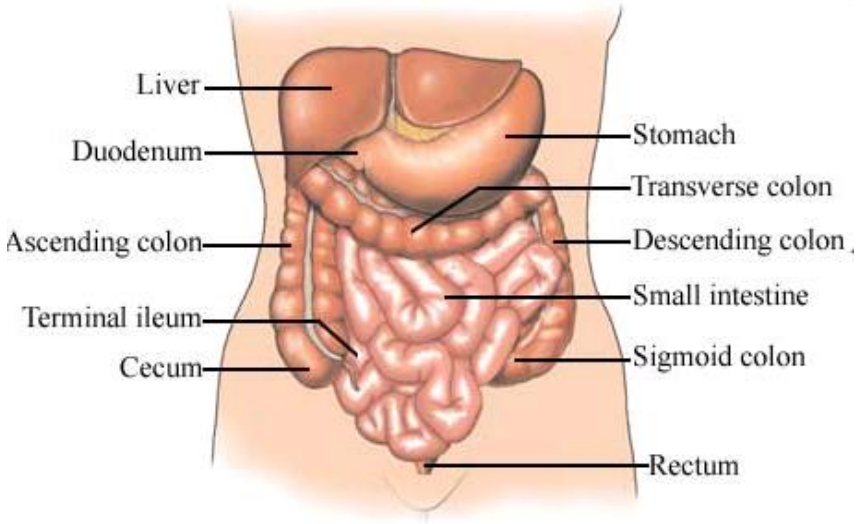
✓ *via the skin*: not for nutrients → diffusion only. Epidermis is the external layer. Dermis is the internal layer, rich in blood vessels. Epidermis is relatively dry: water content may increase absorption. DMSO more than H_2O

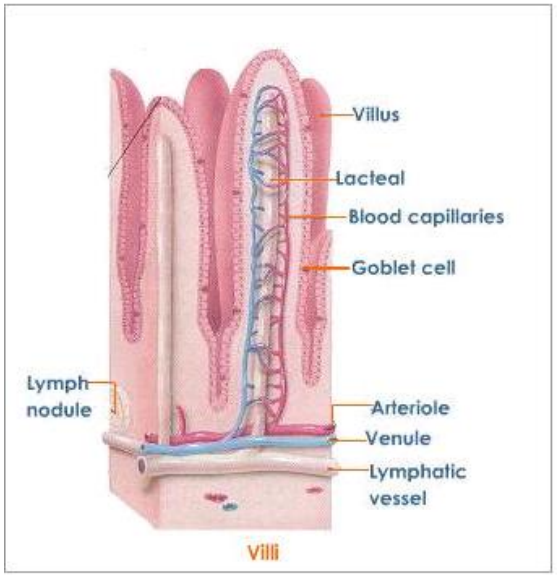


Absorption of chemicals:

✓ *by the gastrointestinal tract:* 8 m long. 300 m^2 of surface.

- ***stomach***: pH 2 (HCl). Enzymatic hydrolysis of proteins: pepsin.
- ***small intestine***: pH 7-8 (with HCO_3^- from pancreas/liver). Enzymatic hydrolysis of proteins, polysaccharides, fats, nucleic acids. Daily small intestine absorption: 8.5 L. Functional unit: **villus**





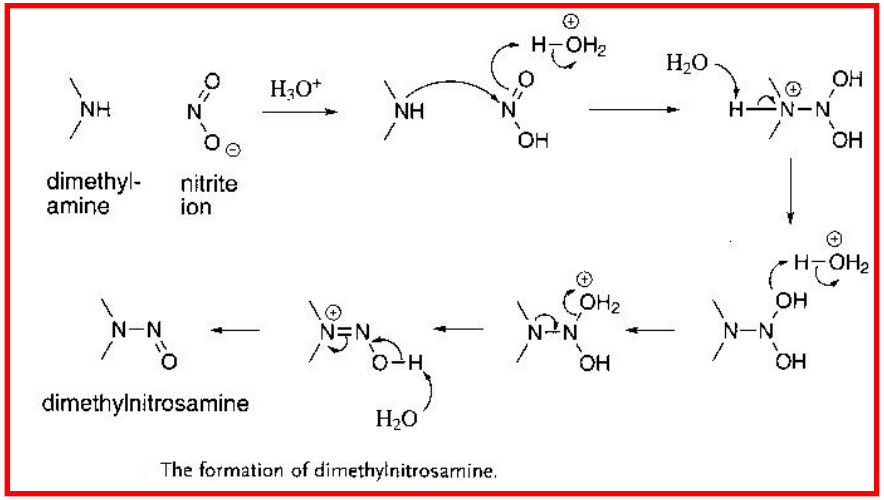
Absorption of chemicals:

✓ *by the gastrointestinal tract*

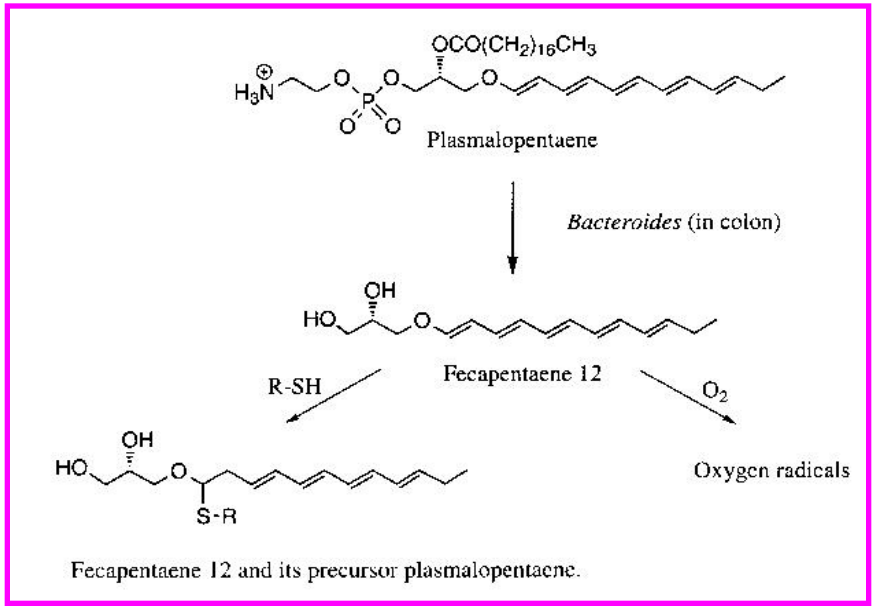
Some (toxic) elements use membrane ***transport carriers*** of physiological ones: Ta, Co, Mn of Fe; Pb of Ca.

Stomach: unique ***acid*** environment.

Intestine: bacterial flora as ***reductive*** enclave.



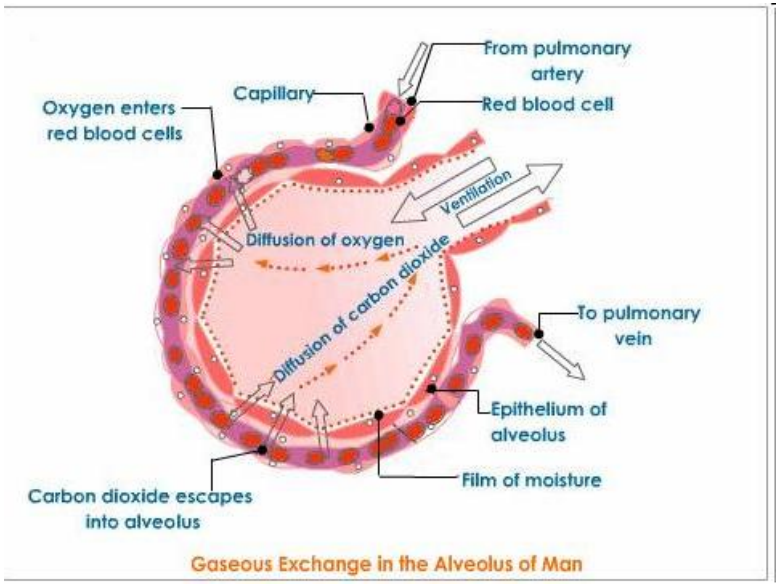
The formation of dimethylnitrosamine.

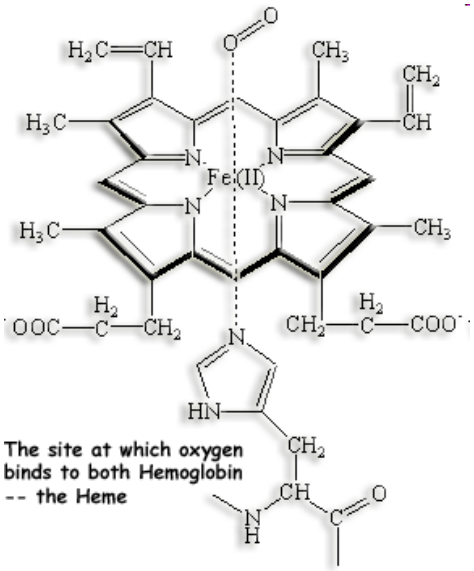


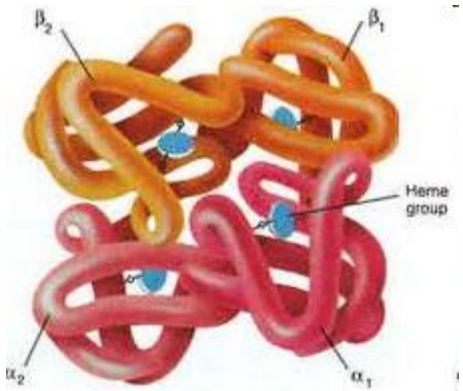
Fecapentaene 12 and its precursor plasmalopentaene.

Absorption of chemicals:

✓ *via the lungs:* 300 m^2 of surface. Functional unit: **alveolus**. Air/blood distance: 1 µm. Inhalation at rest: 5 L min^{-1}. Inhalation at work: 20 L min^{-1} and more. Site for oxygen complexation by hemoglobin.



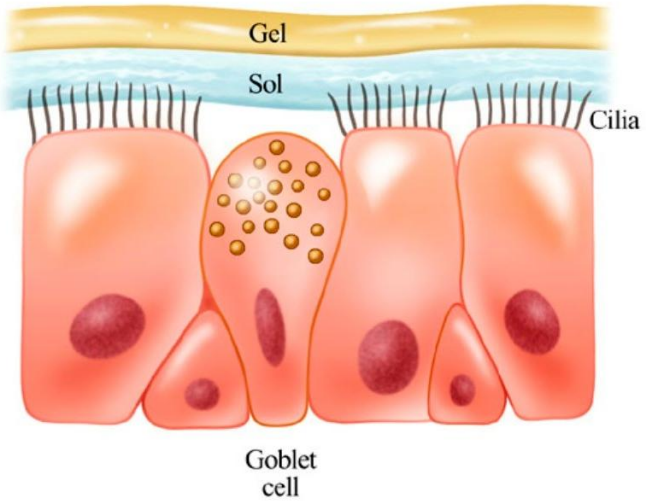




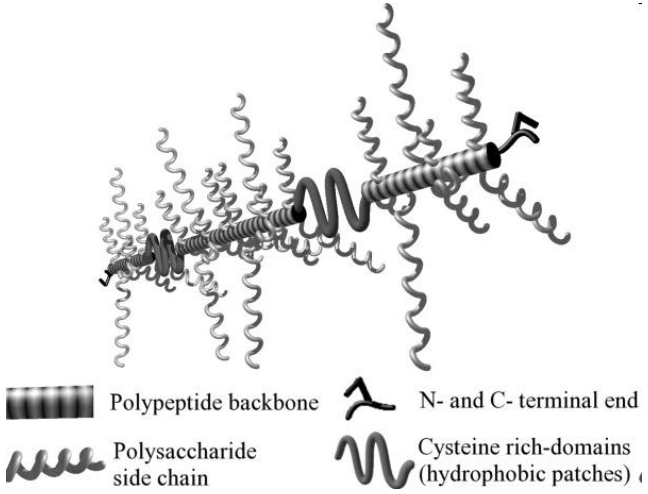
Absorption of chemicals:

✓ *via the lungs:*

- ***aerosols:*** dust (solid particles), fume (combustion products), smoke (organic combustion products), fog and mist (liquid droplets), smog (particles and gas)
- ***gases and vapors:*** highly reactive (HCl, NH_3, SO_2), intermediate reactive ($COCl_2$, O_3, Cl_2, NO, NO_2, etc.), less reactive but toxic.



Mucociliary escalator



Mucin

Distribution of chemicals in organisms:

ability to pass through biological membranes

blood flow in various tissues and organs: binding to plasma proteins (hydrophilic compounds) / accumulation in the adipose tissue (lipophilic c.)

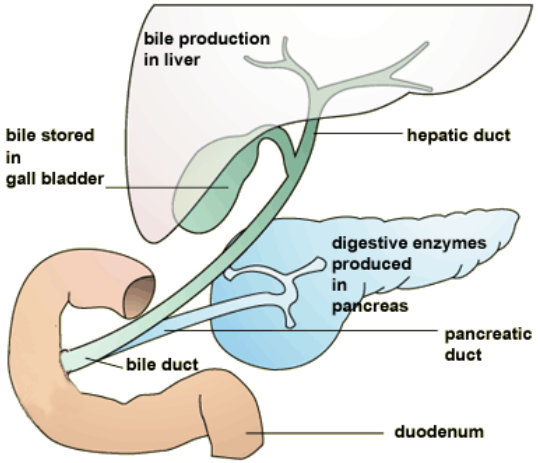
✓ *biological barriers*: "resistance" to passage between the two compartments. Blood-brain barrier protect the brain from many chemicals but it may also act as a cage (Hg / Hg^{2+})

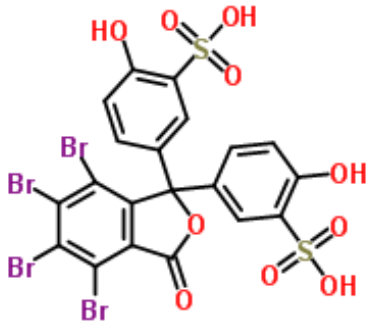
✓ *partition coefficients*: blood/air; blood/brain; blood/body fat; blood/oil (different from water/oil because of the presence of proteins). Saturation (in the case of low blood/oil coefficient)

Excretion of chemicals from organisms:

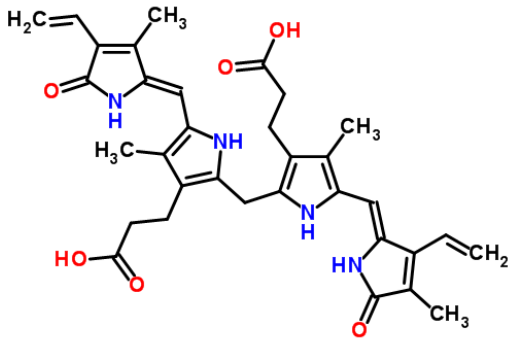
✓ *via the lungs*: volatile compounds.

✓ *via the liver (bile)*: Active transport. Metals (Pb^{2+}, Mn^{2+}, Hg^{2+}) and high molecular weight (>500) compounds. Sulfobromophthalein* is used to test liver function. Yellow bilirubin** is normally excreted through the liver. Enterohepatic circulation.





*$C_{20}H_{10}Br_4O_{10}S_2$ MW 838

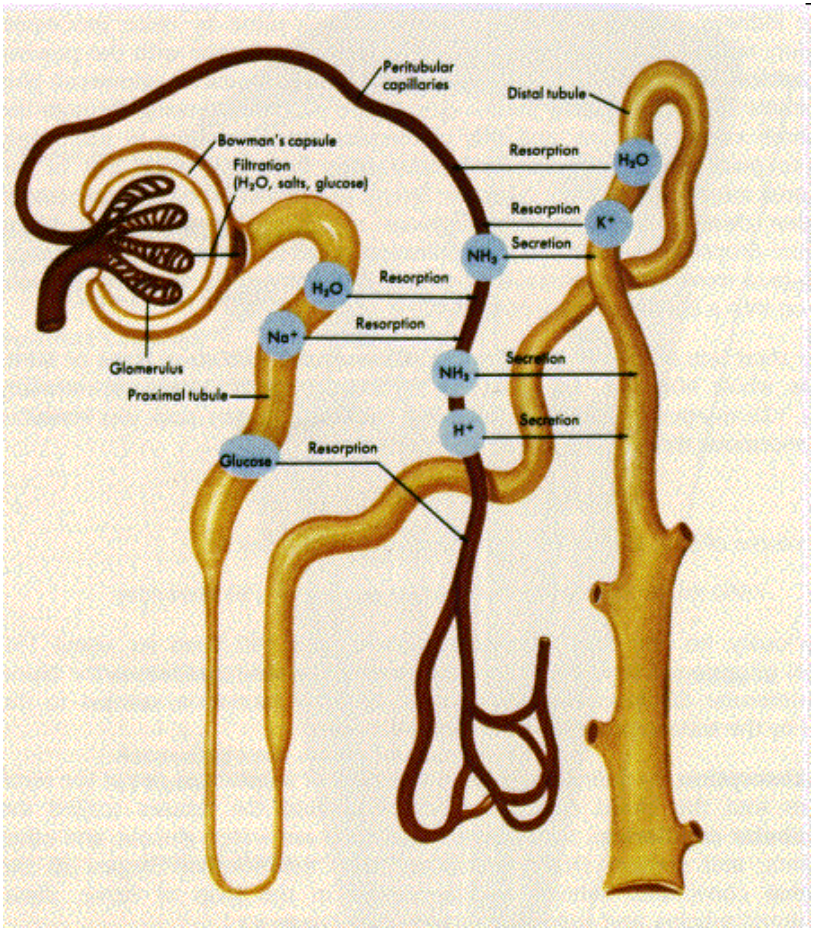


**$C_{33}H_{36}N_4O_6$ MW 585

Excretion of chemicals:

✓ *via the kidneys:* Functional unit: **nephron**. Primary urine: 200 L/die. After water, nutrients and minerals reabsorption: secondary urine, 1.5 L/die.

✓ *via minor ways (sweat, hair, nails, teeth, saliva, pancreatic secretion, milk)*



Metabolism of xenobiotics:

Enzymatic systems that exclude / degrade /detoxify / expel exogenous chemicals have evolved.

CHEMICAL CONVERSION

- ✓ *to increase volatility:* excretion with the exhaled air
- ✓ *to increase the molecular weight:* excretion with the bile
- ✓ *to increase the water solubility:* excretion with the urine

- ✓ *by breaking bonds*
- ✓ *by changing functional groups*
- ✓ *by combining the exogenous with an endogenous compound*

Metabolism of xenobiotics

(by enzymes belonging to both the primary and the secondary metabolism)

✓ *Phase I* (functional groups introduction or modification)

✓ *Phase II* (conjugation)

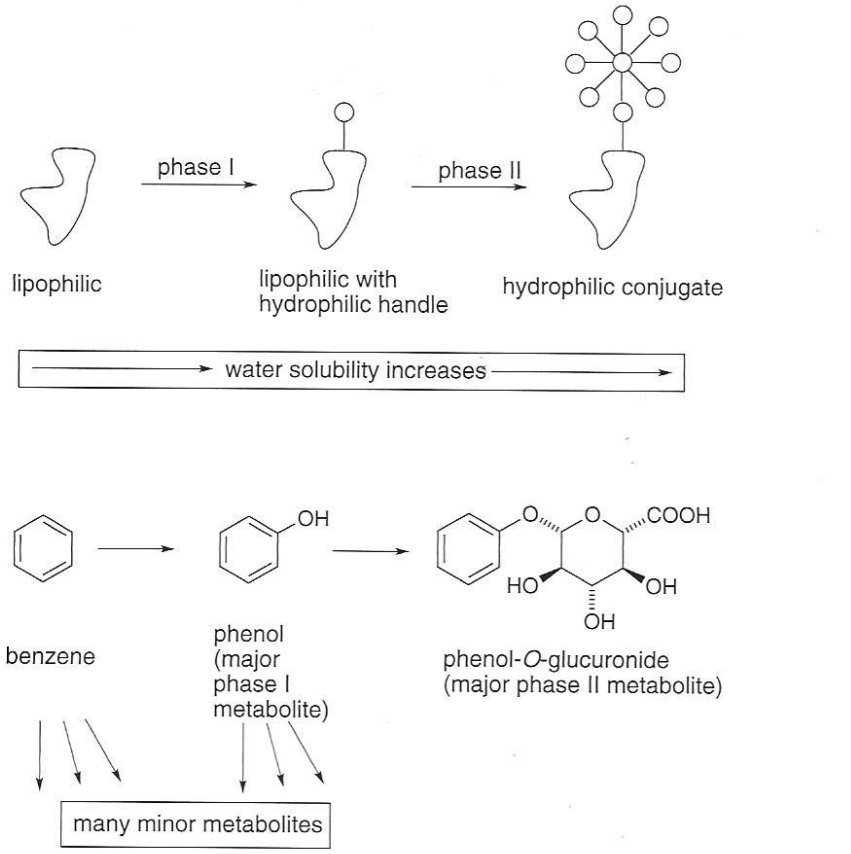
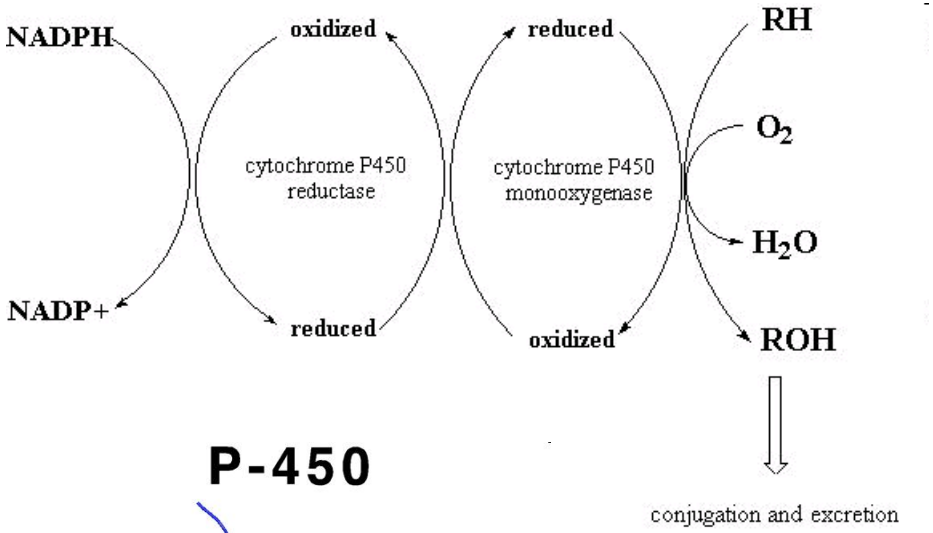
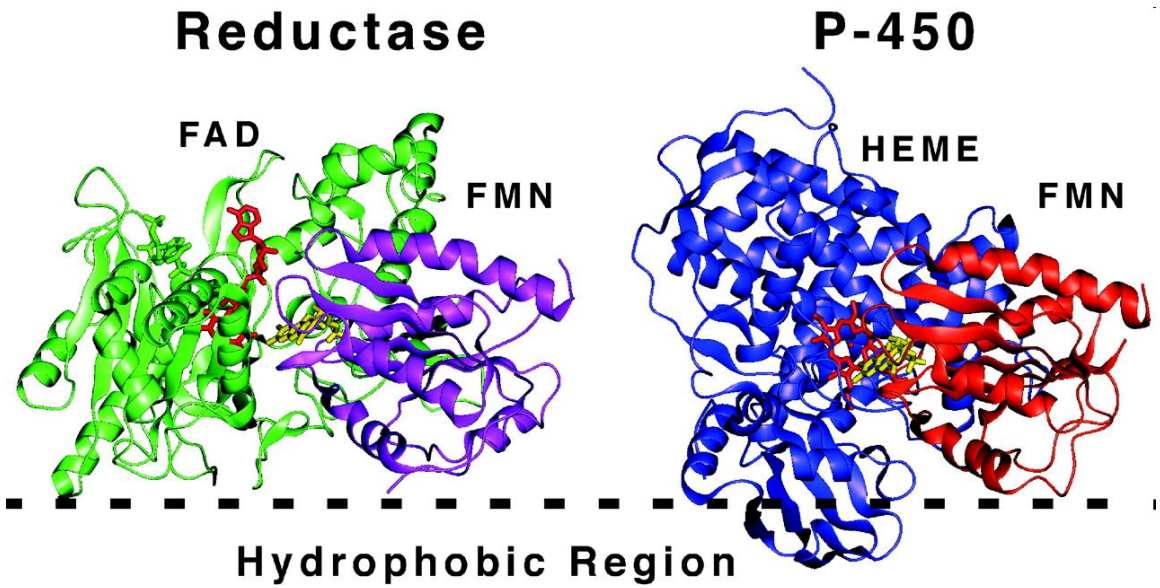


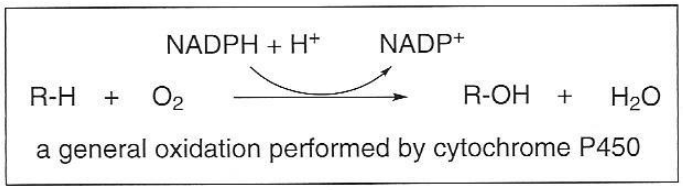
Figure 5.1 The two phases of the metabolism of exogenous compounds, exemplified by the major conversion of benzene.

Metabolism of xenobiotics: cytochrome P450





Metabolism of xenobiotics: cytochrome P450



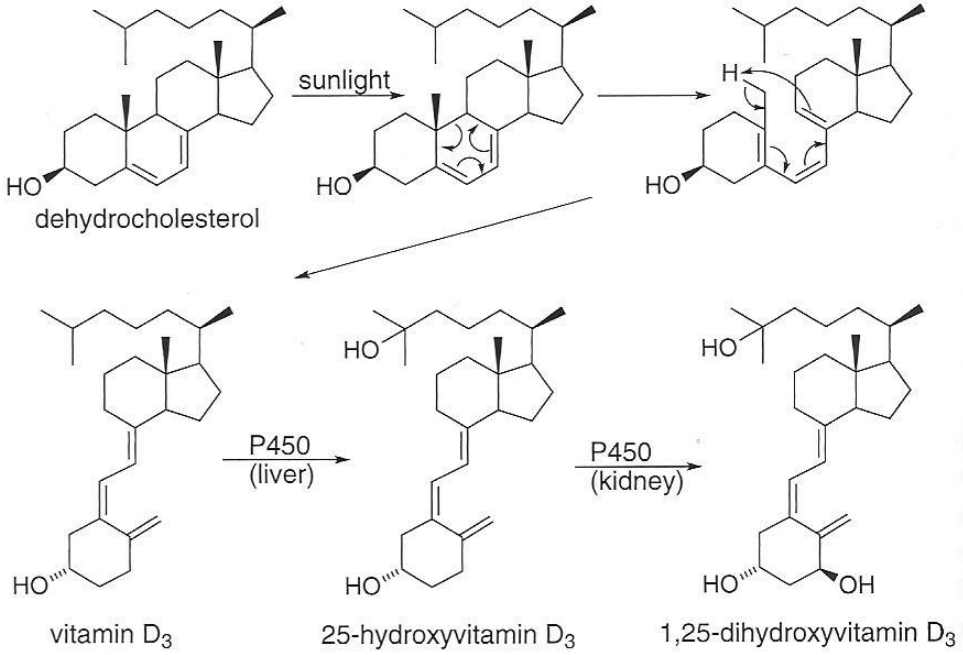
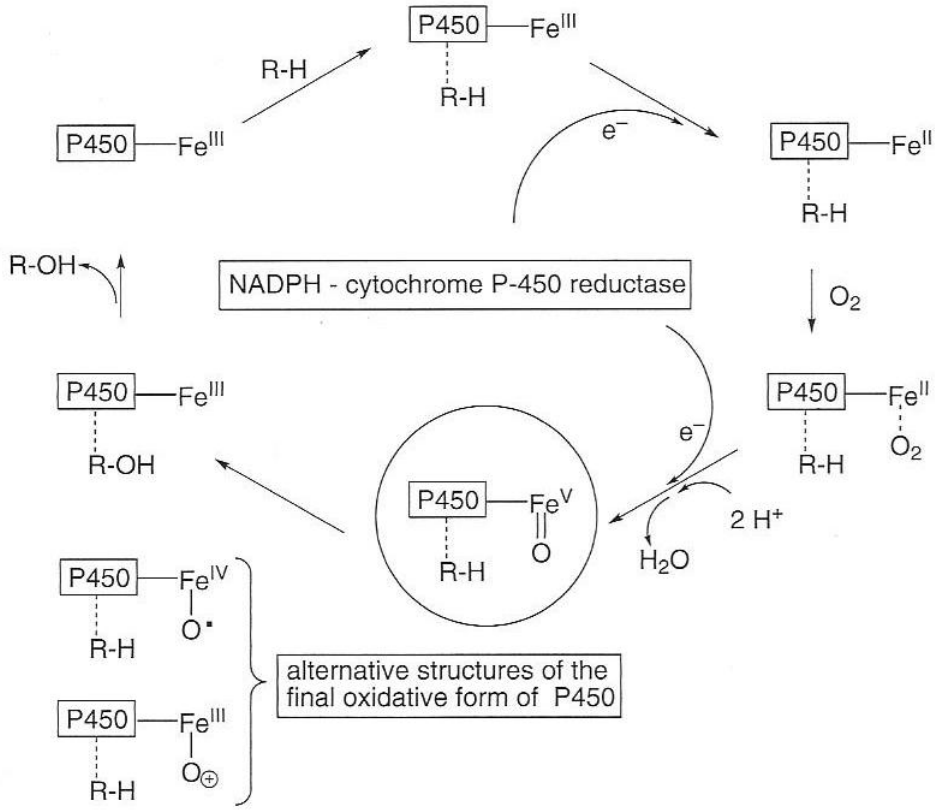


Figure 5.2 The oxidation of vitamin D_3 by cytochrome P450.

A D M E

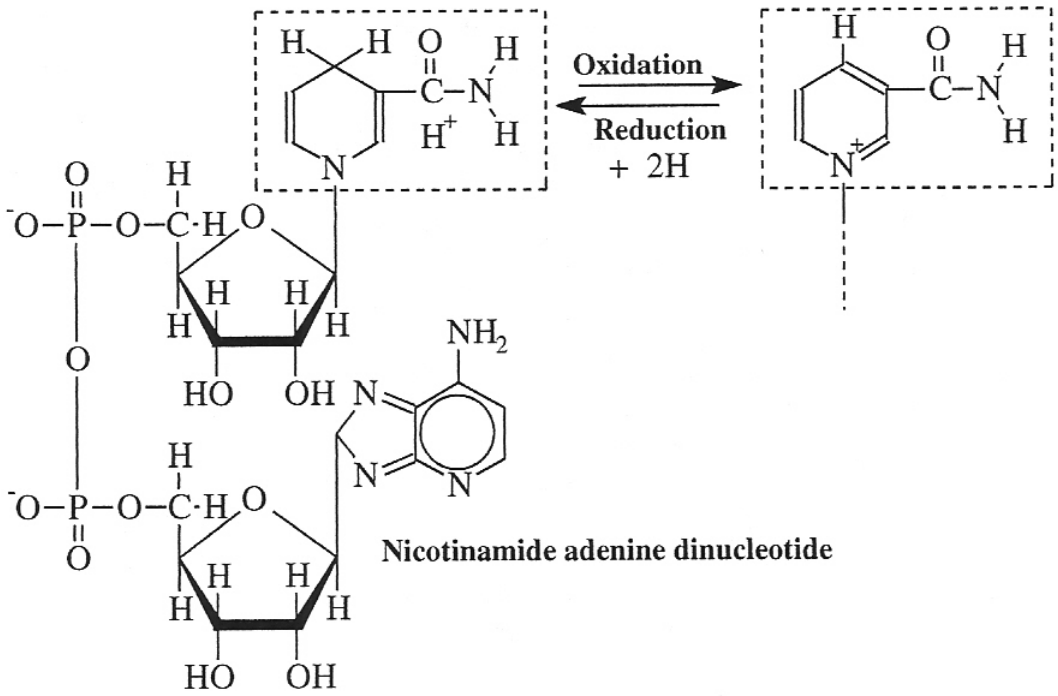
Metabolism of xenobiotics: cytochrome P450



The oxidation cycle of cytochrome P450.

Metabolism of xenobiotics:

NADH / NAD^+



Metabolism of xenobiotics: cytochrome P450

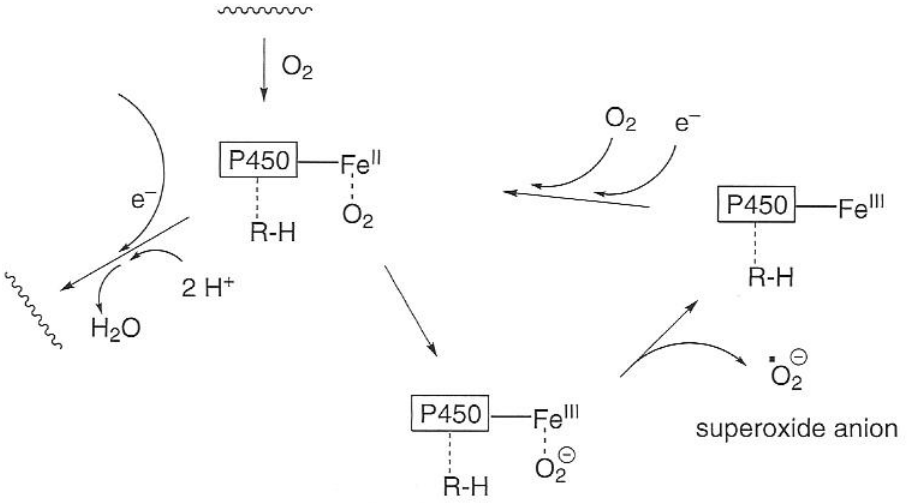
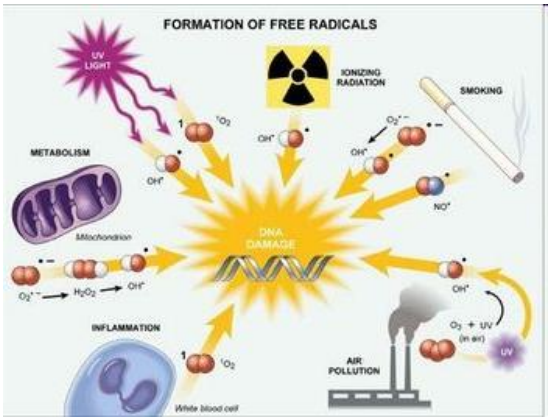
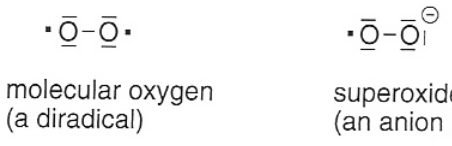


Figure 5.4 Reactive oxygen species are generated during cytochrome P450 oxidations.





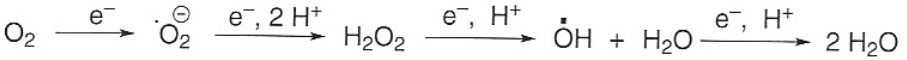


Figure 5.5 The reduction of O_2 to H_2O via reactive oxygen species.

Metabolism of xenobiotics:
superoxide inactivation
and deleterious reactions

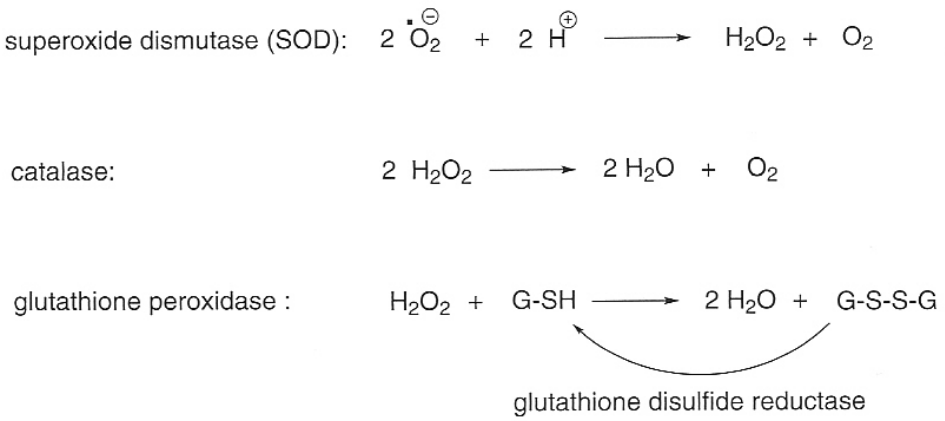
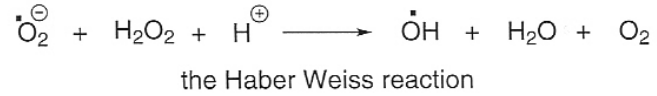
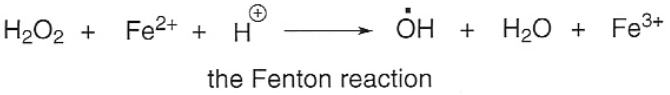


Figure 5.6 The enzymatic disarmament of superoxide and hydrogen peroxide.



the Haber Weiss reaction



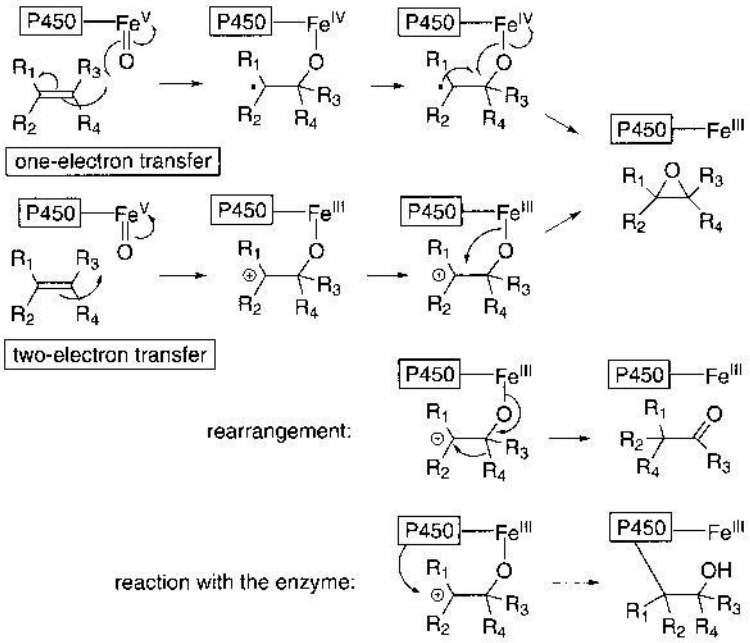
the Fenton reaction

Metabolism of xenobiotics: other (main) enzymes

- *dioxygenases* (insertion of two oxygen atoms from molecular O_2)
- *amine oxidases* (transform primary amines to aldehydes, secondary to ketones)
- *peroxidases* (could generate electrophilic compounds)
- *catalase* ($RH_2 + H_2O_2 \rightarrow R + H_2O$). Ethanol/acetaldehyde conversion
- *aldehyde dehydrogenase* ($RCHO \rightarrow RCOOH$).
- *acyl coenzyme A dehydrogenase* (fatty acids $\rightarrow$ acetyl units).

Phase I metabolism: OXIDATION

✓ *epoxidation of C-C multiple bonds*. Metabolic electrophilic activation possible.

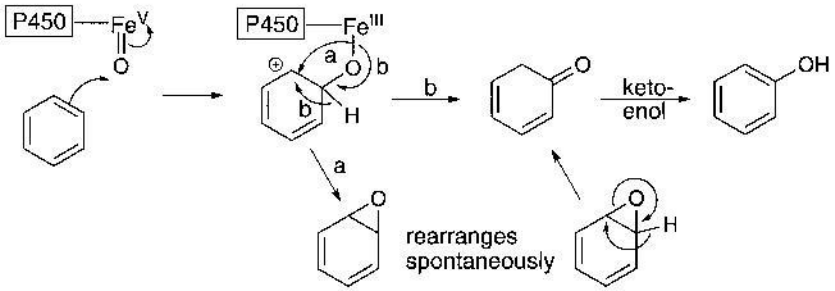


"suicide mechanism"

Figure 5.10 Possible mechanisms for the oxidation of alkenes.

Phase I metabolism: OXIDATION

✓ *epoxidation of C-C multiple bonds*.



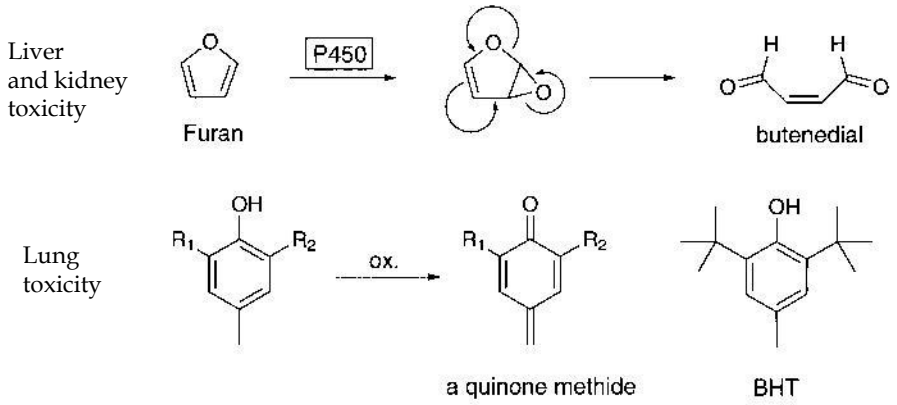


Figure 5.11 Oxidation of aromatics.

reactive ketene
(water or other Nu^{-})

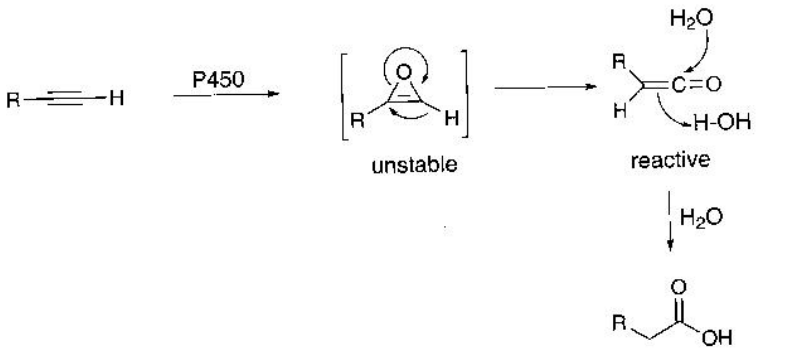


Figure 5.12 Oxidation of alkynes.

Phase I metabolism: OXIDATION

✓ *hydroxylation of saturated C.*

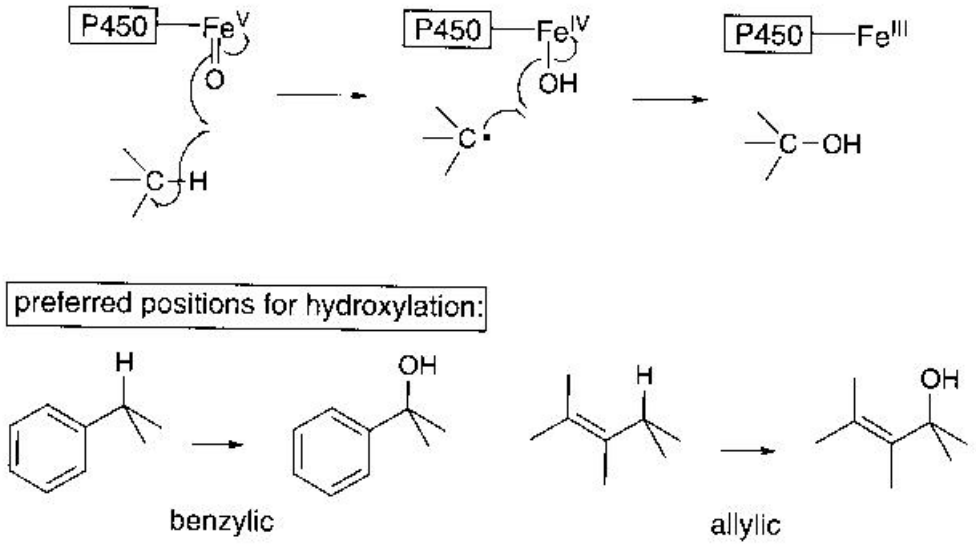
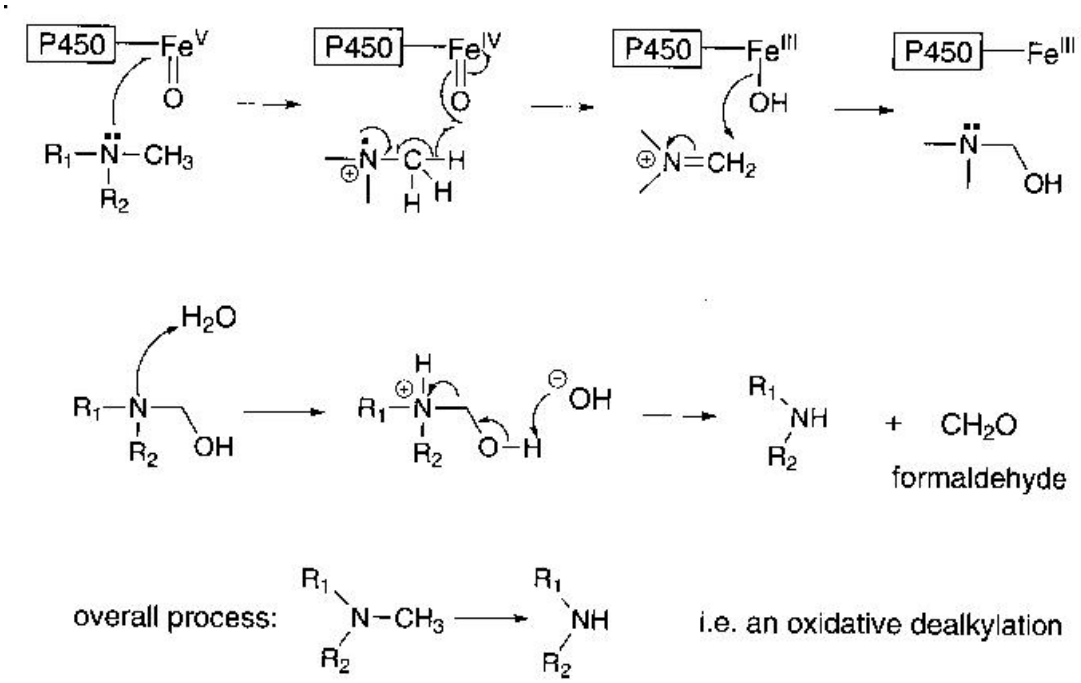


Figure 5.13 Hydroxylation of hydrocarbons.

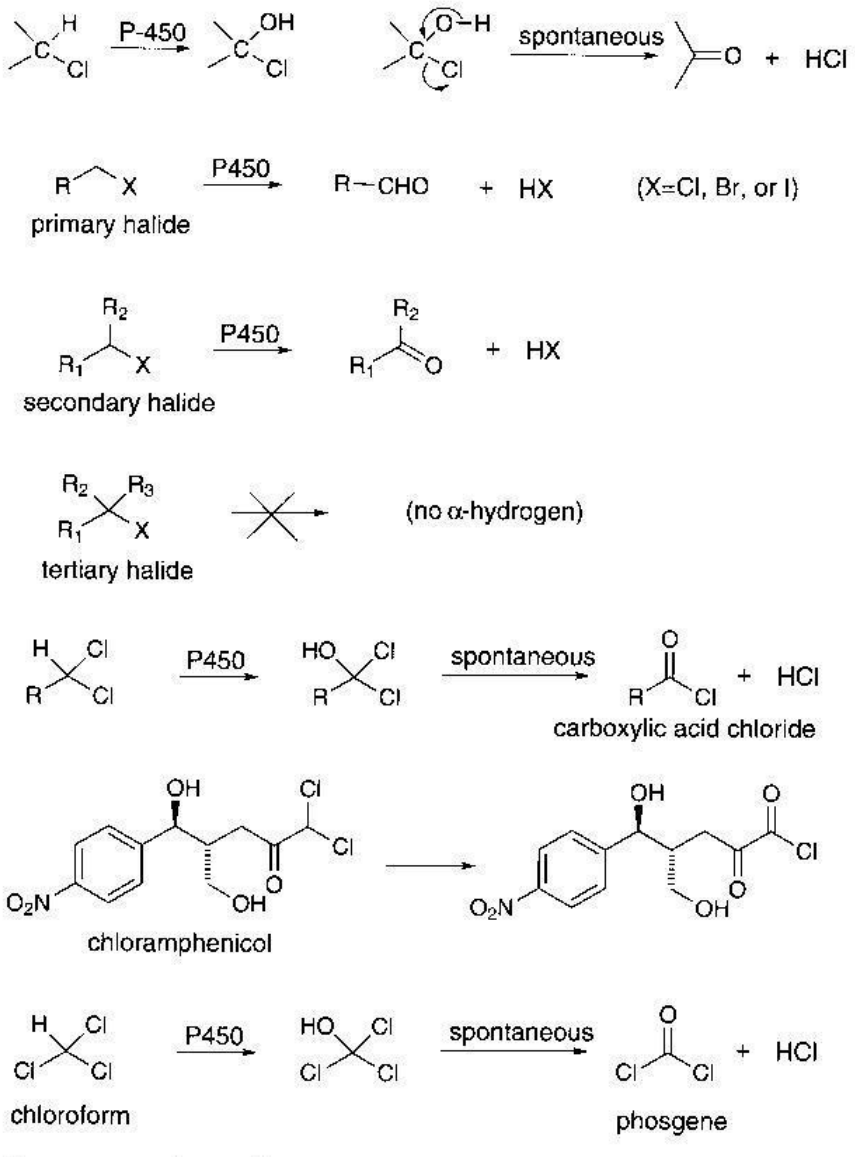
Phase I metabolism: OXIDATION

✓ *hydroxylation of amino groups.* α-hydroxylation (with N, O, S)



Phase I metabolism:
OXIDATION

✓ *hydroxylation of halides.*



Phase I metabolism: OXIDATION

✓ *hydroxylation of amino groups.* N-hydroxylation (benzylic)

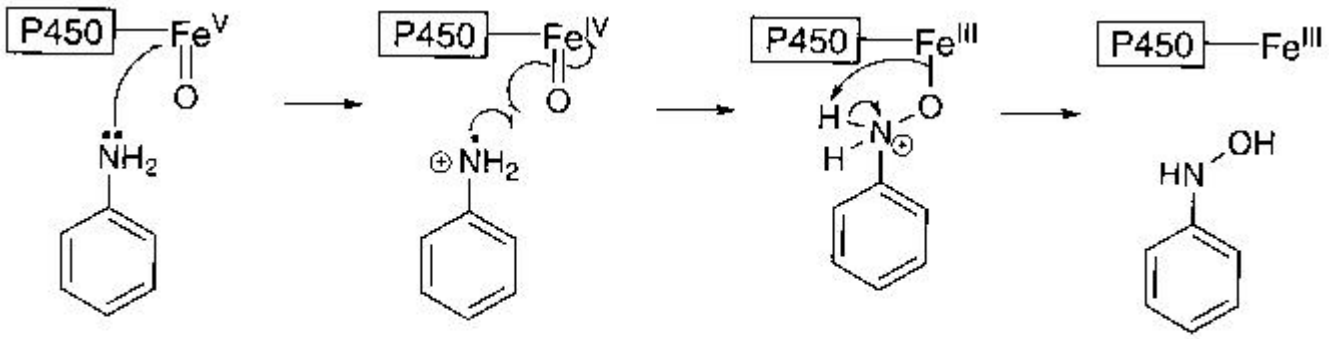


Figure 5.16 *N*-Hydroxylation of an aromatic amine.

Phase I metabolism: OXIDATION

✓ *oxidation of heteroatoms.* N-oxidation, S-oxidation

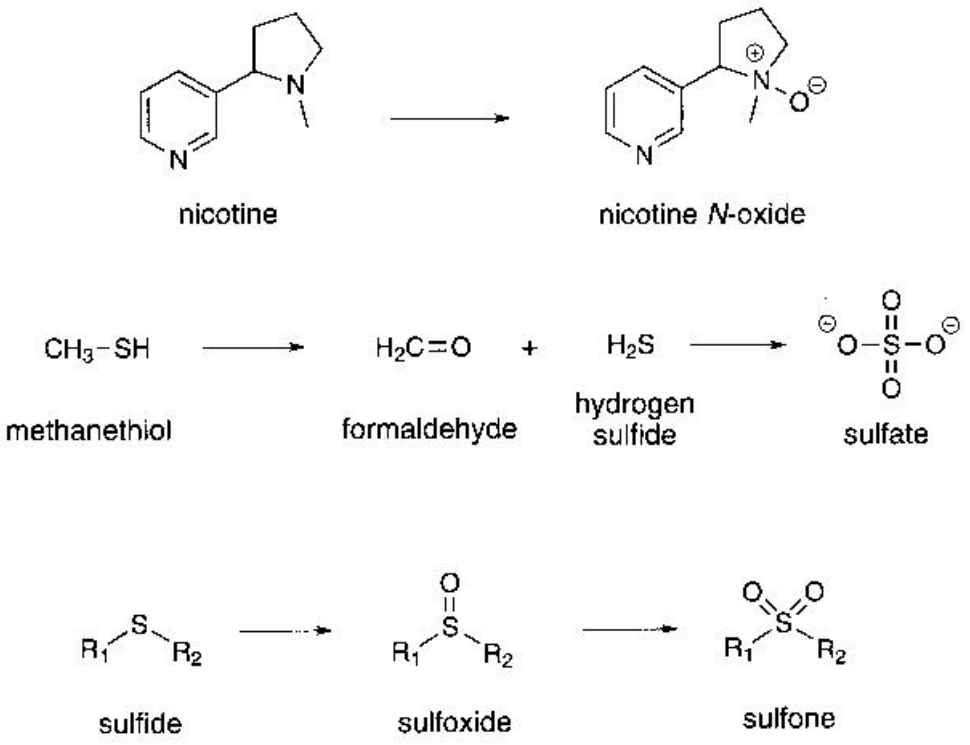


Figure 5.20 Oxidation of nitrogen (in tertiary amines) and sulfur.

Phase I metabolism: OXIDATION

✓ *oxidation of C-C to C=C*

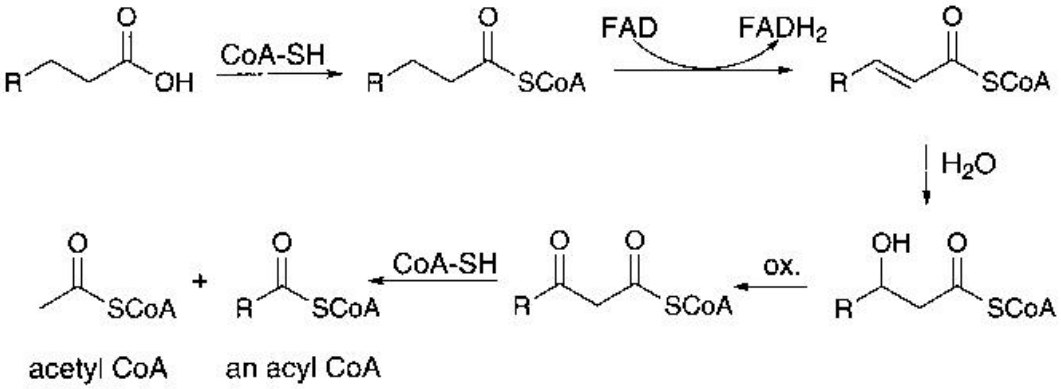


Figure 5.17 The oxidation of a single bond to a double bond during β-oxidation.

Liver toxicity

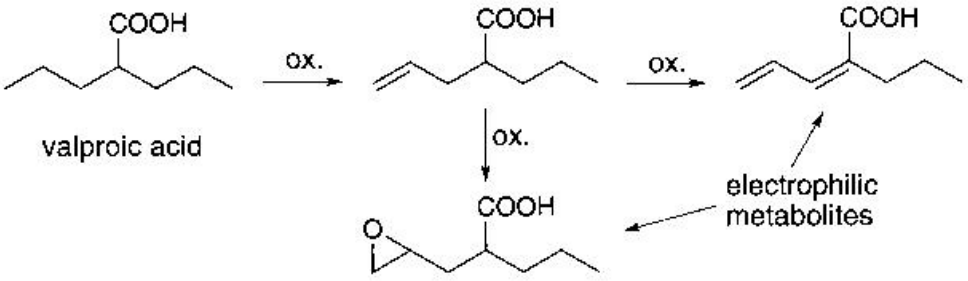


Figure 5.18 The metabolic activation of valproic acid.

Phase I metabolism: OXIDATION

✓ *oxidation of C-N to C=N to C=O.* Oxidative deamination

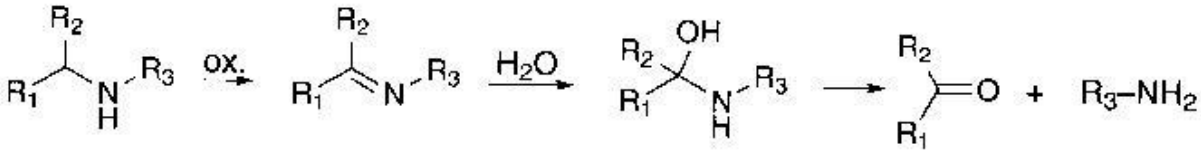


Figure 5.19 The oxidation of an amine to an imine, which can be hydrolyzed to a ketone.

Phase I metabolism: OXIDATION

✓ *oxidation of C-OH to CHO*

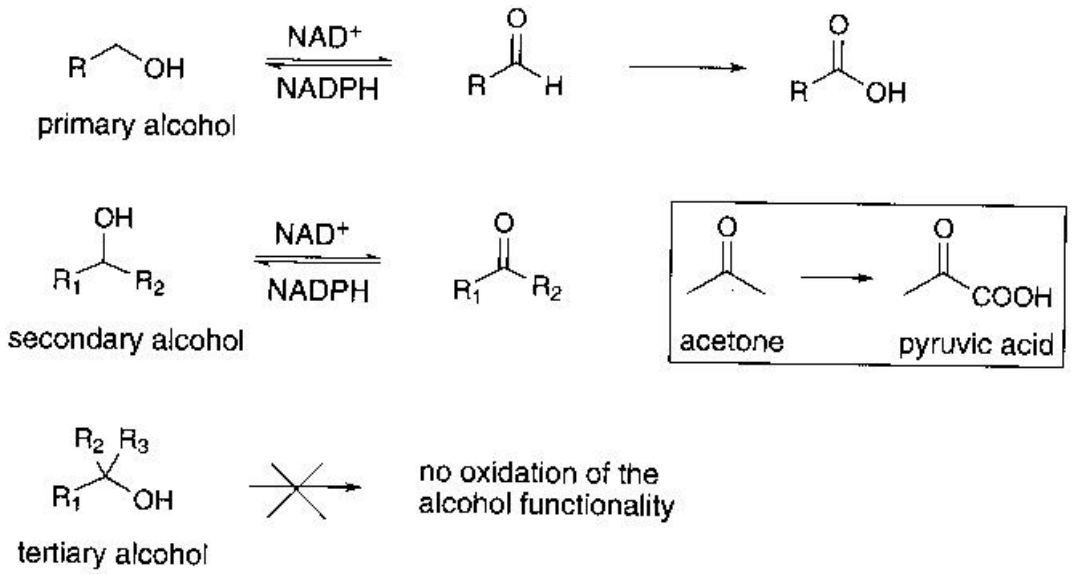


Figure 5.21 Oxidation of alcohols.

Phase I metabolism: REDUCTION

✓ *reduction of heteroatoms*

✓ *reductive dehalogenation*

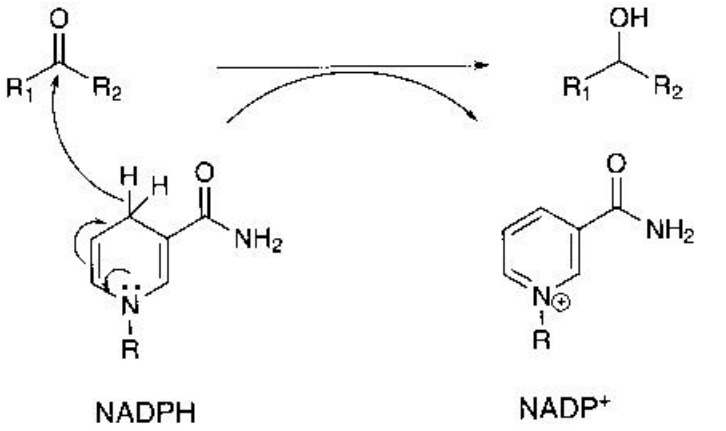


Figure 5.22 Reduction of a ketone with the coenzyme NADPH.

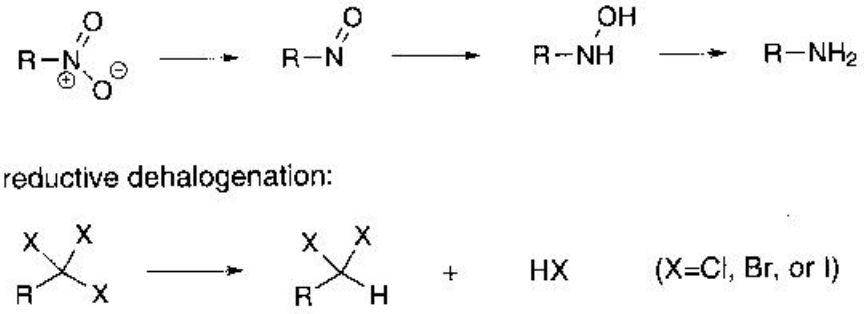


Figure 5.23 Examples of reductions that may take place in mammals.

Phase I metabolism: HYDROLYSES

✓ *hydrolyses of epoxides*

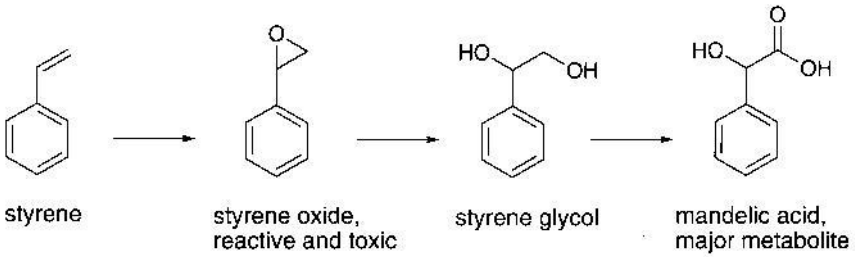


Figure 5.25 The metabolism of styrene.

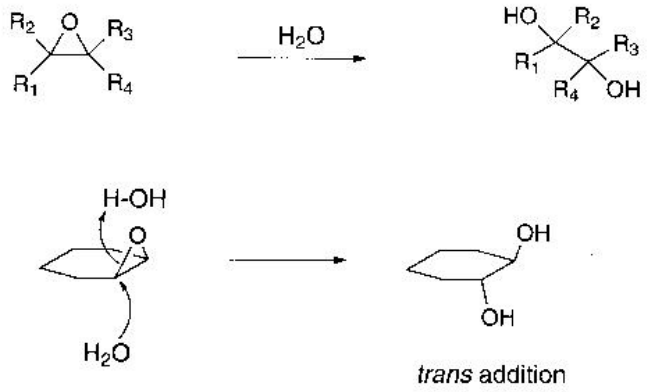


Figure 5.24 The hydrolysis of epoxide by epoxide hydrolase.

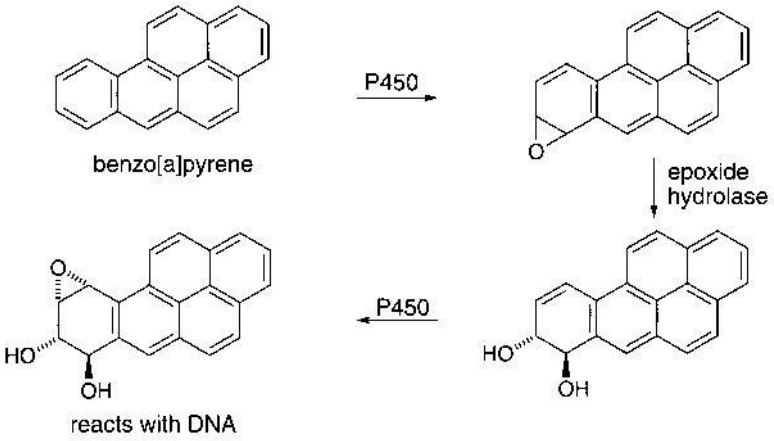
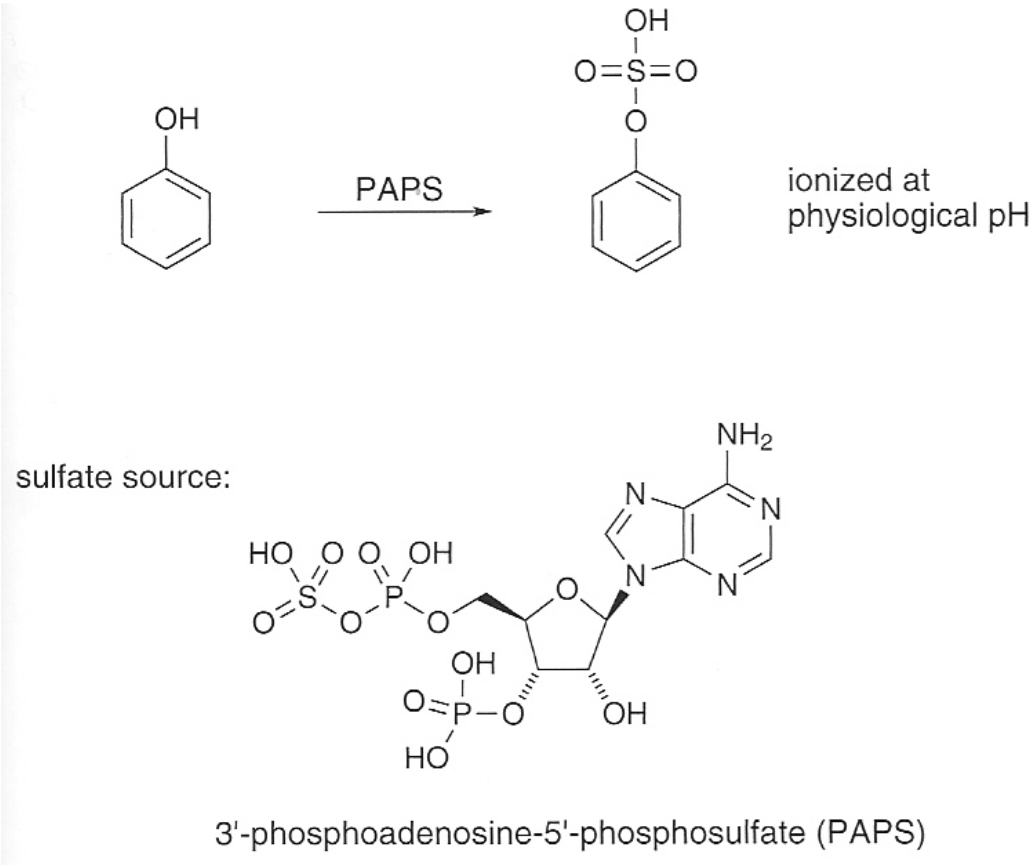


Figure 5.26 Metabolic activation of benzo[a]pyrene.

✓ *hydrolyses of esters and amides.* RCOOR' → RCOOH + HOR'

RCONR'R" → RCOOH + NR'R"

Phase II metabolism: CONJUGATIONS WITH SULPHATE



3'-phosphoadenosine-5'-phosphosulfate (PAPS)

Phase II metabolism: CONJUGATIONS WITH SULPHATE

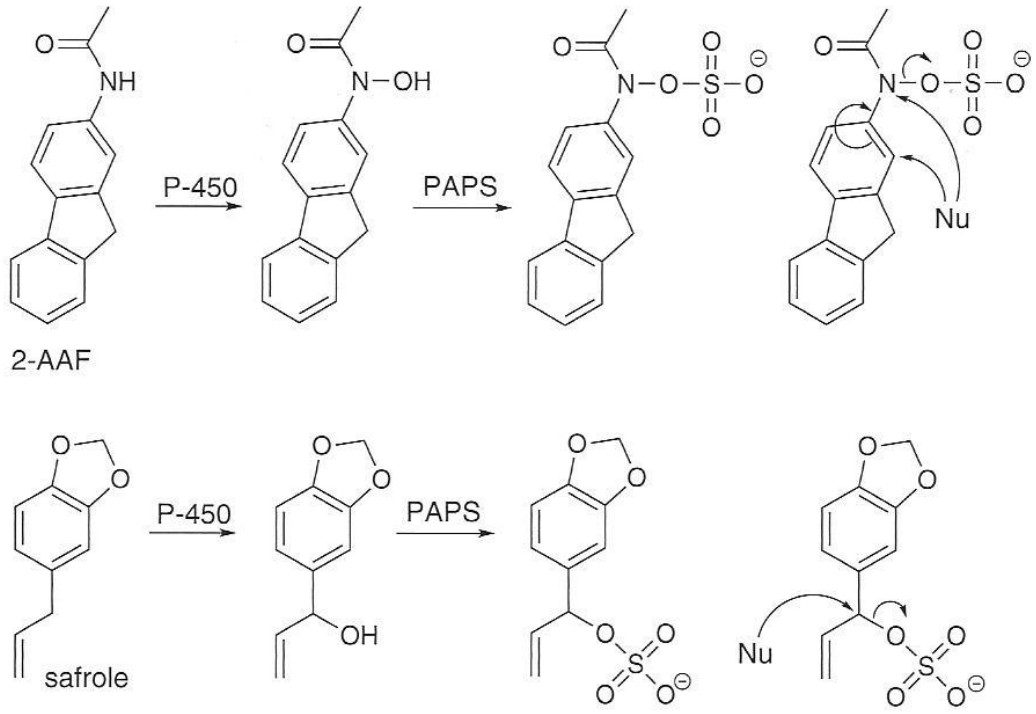
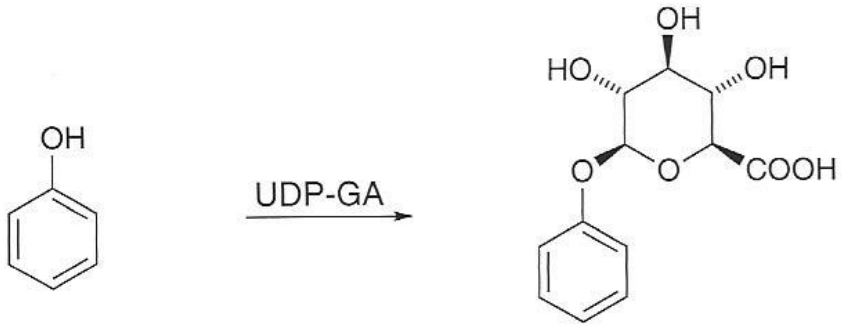
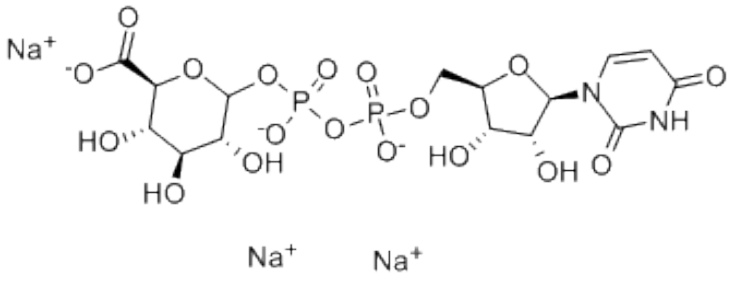


Figure 5.29 The sulfate group as a leaving group.

Phase II metabolism: CONJUGATIONS WITH GLUCURONIC ACID



glucuronic acid source:



uridine-5'-diphospho-a-D-glucuronic acid (UDP-GA)

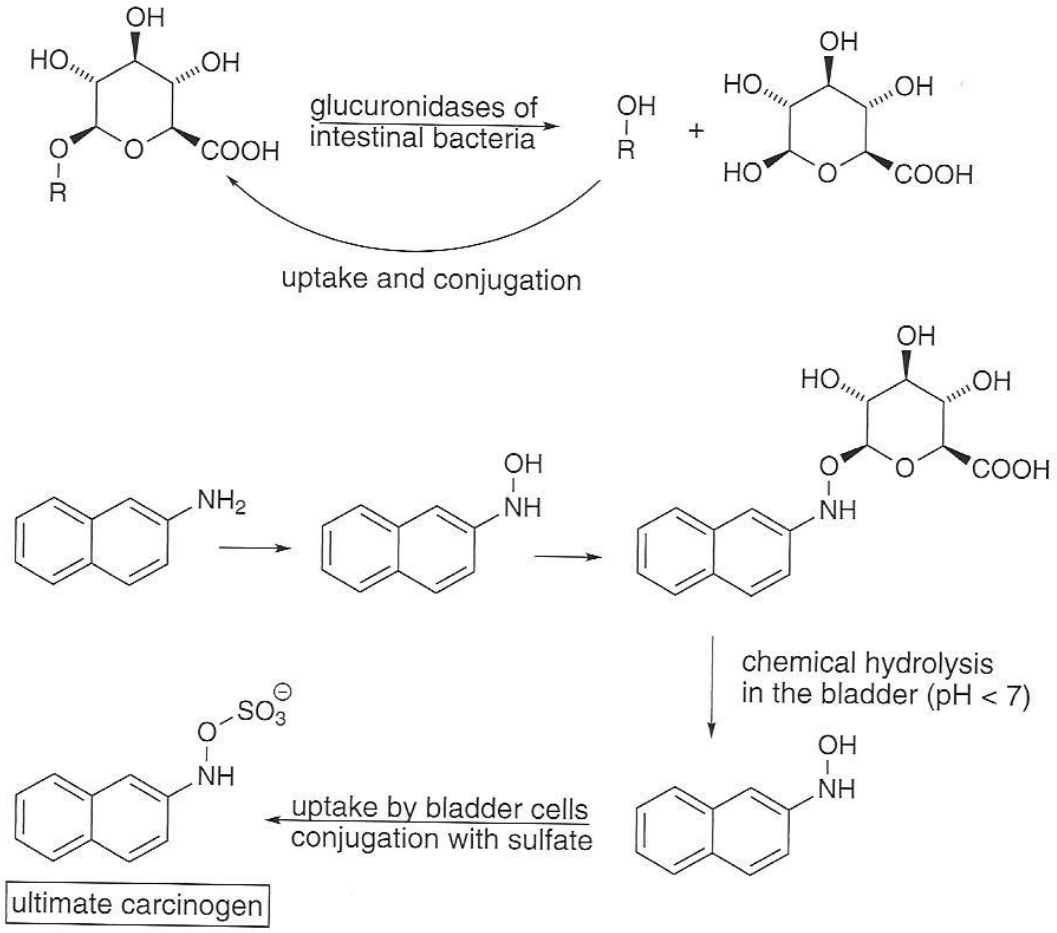


Figure 5.31 The hydrolysis of conjugates with glucuronic acid.

Phase II metabolism: CONJUGATIONS WITH AMINOACIDS

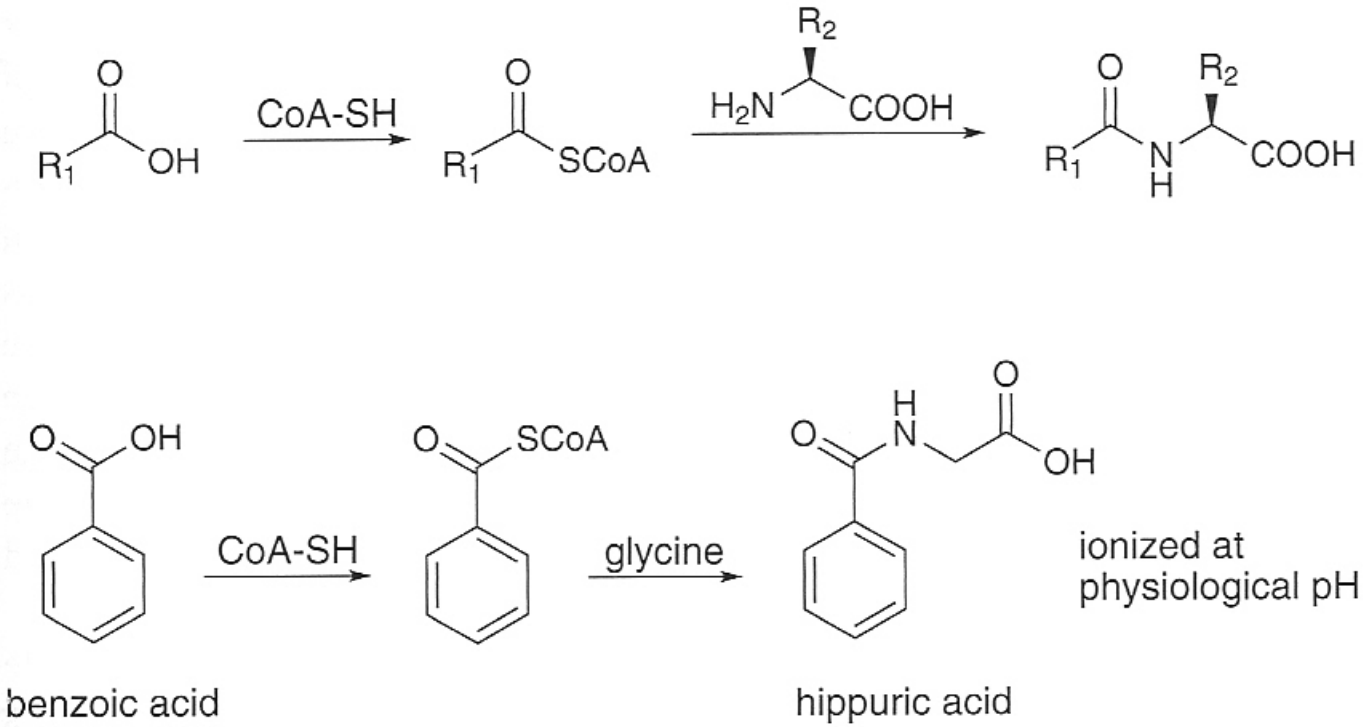


Figure 5.32 Conjugation with an amino acid.

Phase II metabolism: CONJUGATIONS WITH GLUTATHIONE

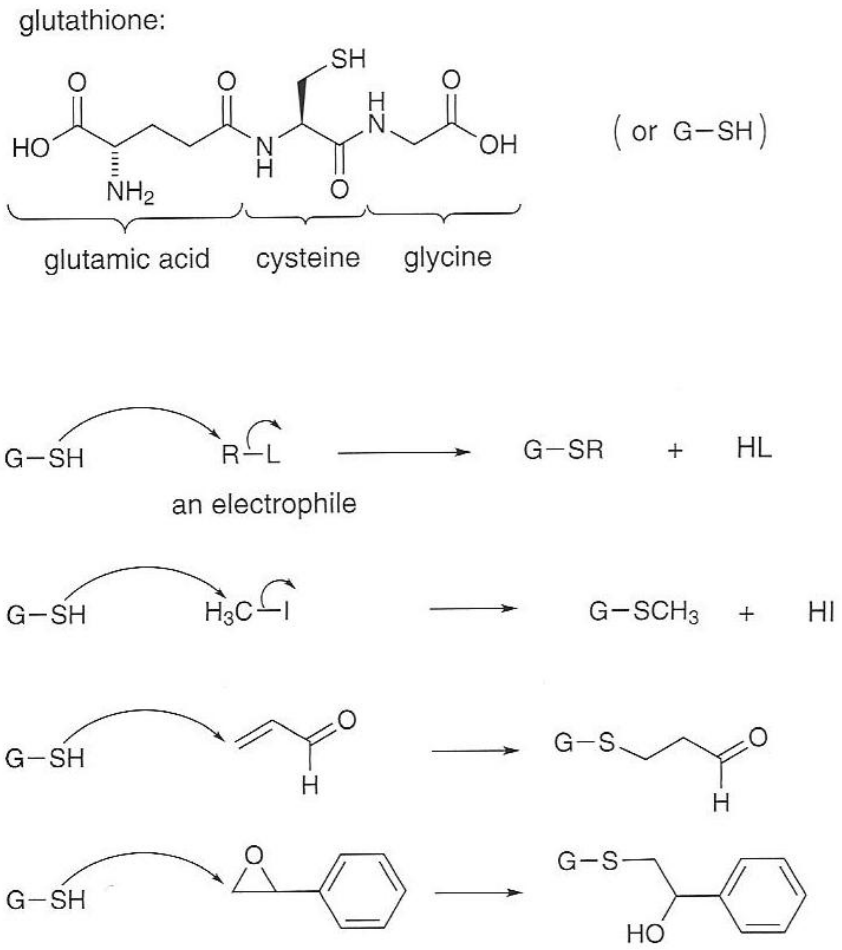
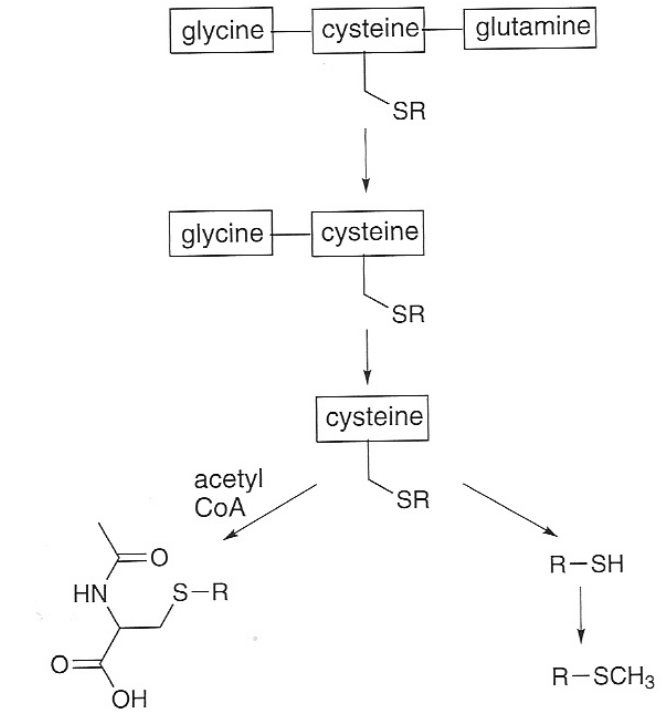


Figure 5.33 Conjugation of electrophiles with glutathione.



mercapturic acid derivative

Phase II metabolism:
CONJUGATIONS WITH GLUTATHIONE

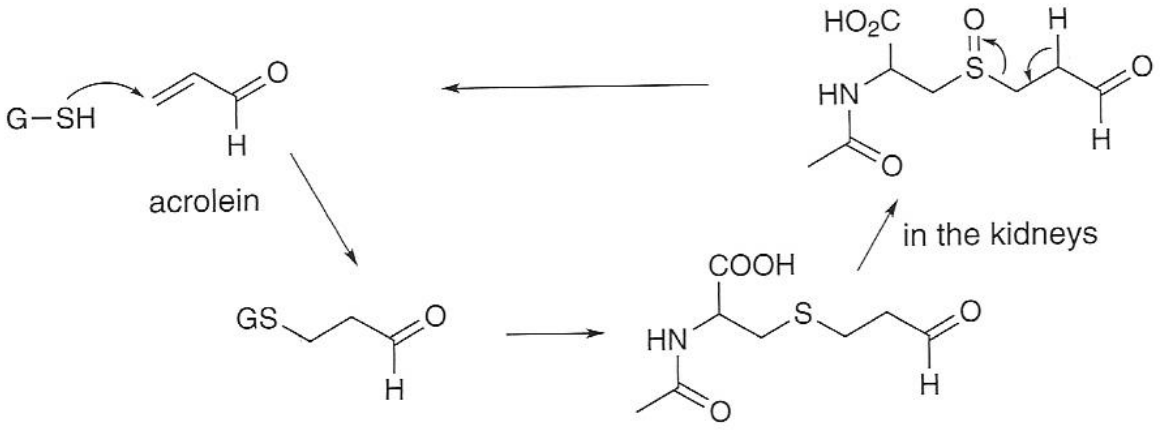


Figure 5.35 The conjugation of acrolein with glutathione.

Phase II metabolism: OTHER CONJUGATIONS

- ✓ *acylation*
- ✓ *methylation*

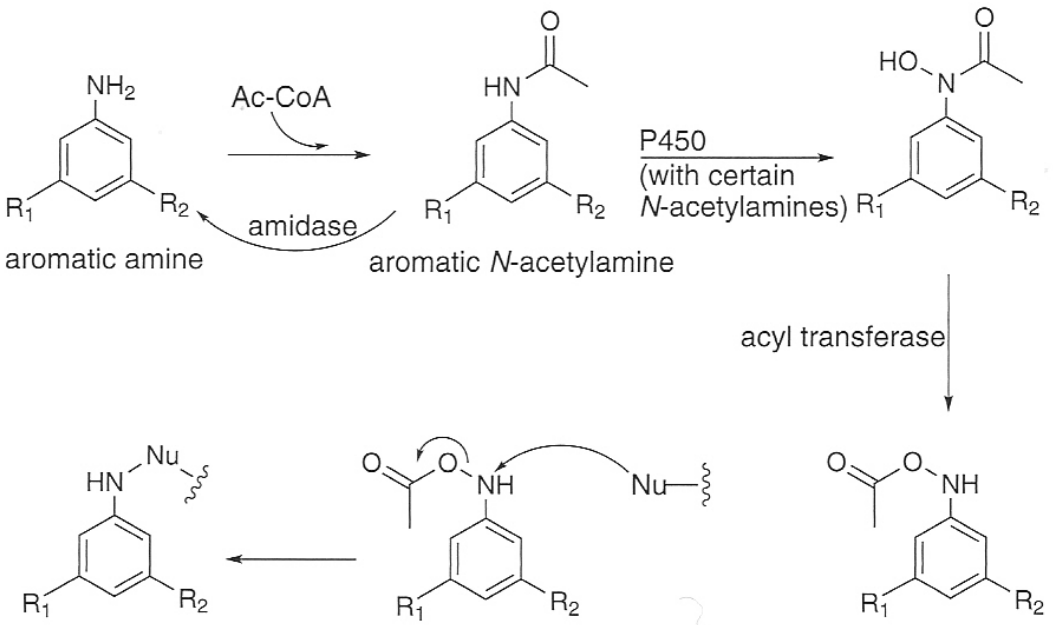


Figure 5.36 A possible way to activate aromatic amines.

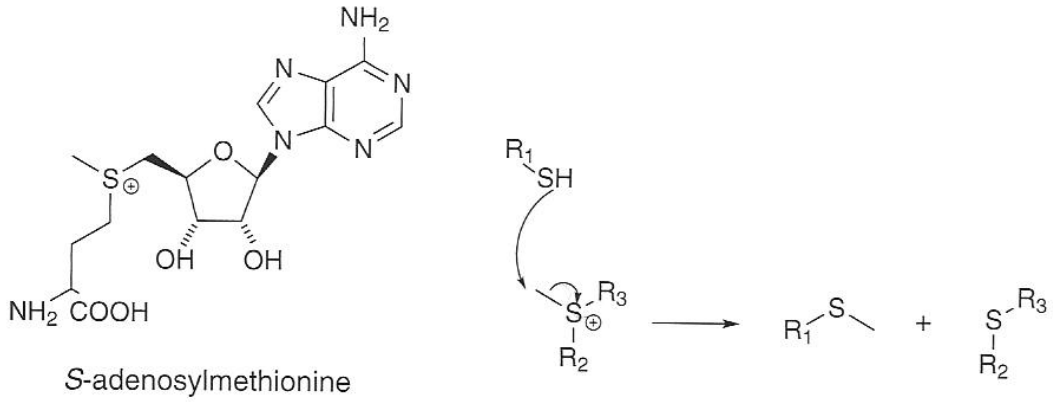


Figure 5.37 Methylation of thiols with SAM.

Toxicological effects

- **Acute and chronic effects :** single or repeated event (cumulative) . The same compound can have 2 different effects (acute and chronic) using 2 different mechanisms (eg Benzene SNC - leukemia). The effect can result from chronic and difficult to eliminate subsequent accumulation .
- **Reversible effects :** cease when exposure ceases and irreversible damage is not repairable. The same compound can have 2 different effects (reversible and irreversible)
- **Local effects :** first contact (eyes , skin) and systemic . Target Organs: for accumulation or selective action (enzymes , metabolism, receptors) . 1° : CNS circulatory system 2° , 3° Blood and blood-forming organs ; 4° parenchyma (liver , kidney, lungs). Muscles and bones are rarely target .
- **Independent effects :** no correlation to each other .
- **Additional Effects :** different compounds with the same effect = sum .
- **Synergistic Effects :** Sum effect > additive effects. eg. ethanol + CCl_4 on the liver .
- **Potentiating effect :** one of the two is not toxic but potentiates the effect of the other one.
- **Antagonistic effects :** functional or physiological / chemical / PK / receptor