Xenobiotic Metabolism

Overview of Key Concepts & Components

Xenobiotics
Drugs, Environmental Toxins

Modulation by:
- Induction
- Inhibition
- Disease
- Genetic Variability

Phase 1
Addition or unmasking of a functional polar group. Typically results in a relatively small increase in hydrophilicity. May cause metabolic activation

Cytochromes P450
Flavin monooxygenases
Epoxide Hydrolase
Hydrolases
Carboxyl Esterases
Alcohol Dehydrogenase
Aldehyde Dehydrogenase

Metabolic Activation

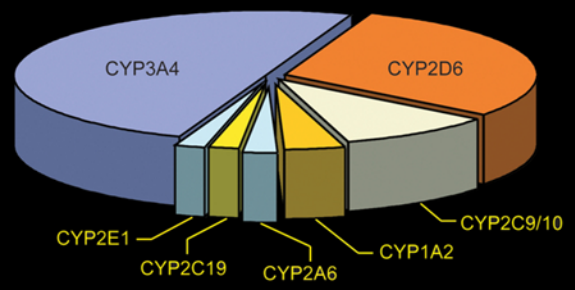
Free Radicals $O_2^{\cdot -}$

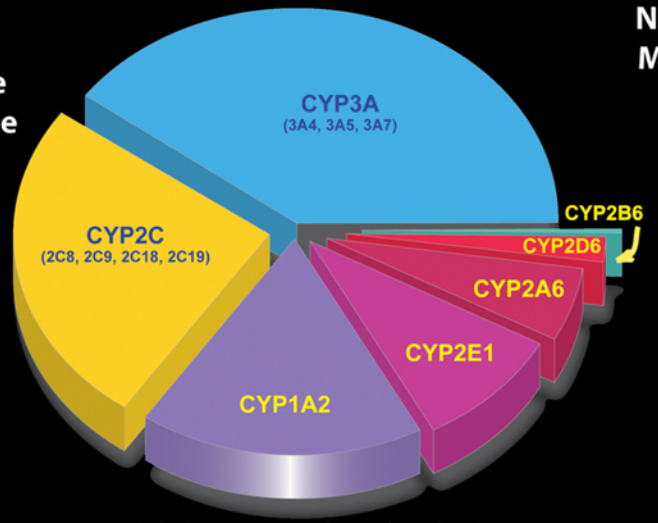
Phase 2
Conjugation with a small hydrophilic endogenous substance. Often to a functional group provided by a Phase I reaction, significantly increasing hydrophilicity.

UDP glucuronosyl transferases
Glutathione-S-transferases
Sulfotransferases
N-acetyltransferase
Methyltransferases

Excretion
Urine & Bile

Contribution of P450 Isoforms to Human Drug Metabolism





Relative concentrations of predominant CYP isoforms expressed in human liver.

Diagnostic substrates and inhibitors of human CYP isoforms

Form	Substrate	Inhibitor
CYP1A1	7-Ethoxyresorufin	7,8 Benzoflavonea
CYP1A2	Phenacetin Caffeine	Furafylline, fluvoxamine
CyP2A6	Coumarin	Diethyldithiocarbamate, 9-methoxpsoralen
CYP2B6	6-Aminochrysene Cyclophosphamide	Not known
CYP2C8	Taxol	Quercetin
CYP2C9	Tolbutamide	Sullfaphenazole
CYP2C19	S-Mephenytoin	Tenoposide?
CYP2D6	Debrisoquine Dextromethorphan	Quindine
CYP2E1	Chlorzoxazoneb	Diethyldithiocarbamatec
CYP3A4	Testosterone Nifedipine	Troleandomycin Gestodene

Adapted from Pelkonen and Raunio, Env Health Perspectives supp 4. 105:767-774 (1997)