Biotransformation
Drug metabolism

Metabolism of Xenobiotics
Biotransformation is a process in which a foreign xenobiotic or an endogenous hormone, neurotransmitter, paracrine hormone is transformed to become more hydrophylic, consequently exretable. English name is drug metabolism or metabolism of xenobiotics, although there are endogenous substrates, too.

Sometimes molecules are converted to active, more often to inactive formes. It does not yield energy, but uses products of common metabolic reactions:

- UDP-glucose, NADPH, SAM, PAPS, glutathione, acetyl-CoA, glycine, taurine.

It is ancient mechanism (3.5 billion years) found in bacteria, fungi, plants, animals (each cells) to get rid of foreign, harmful or endogenous regulatory molecules.

It has 3 phases:

<table>
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<tr>
<th>Preparation</th>
<th>Conjugation</th>
<th>Excretion</th>
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<tr>
<td>Oxidation</td>
<td>Glucuronidation</td>
<td>Out of the organelles, out of the cells</td>
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<td>Reduction</td>
<td>Sulfation</td>
<td>a.) secreted to bile then not reabsorbed from gut</td>
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<tr>
<td>Hydrolysis</td>
<td>Glutathione conj.</td>
<td>b.) they are filtered in kidney and not reabsorbed from urine</td>
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<td>Free OH, SH, NH2, COOH</td>
<td>Acetylation</td>
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<td>Are formed</td>
<td>Glycine, taurin, Gln conj.</td>
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Cytochrome P450 enzyme system

main family: at least 40% amino acid sequence homology

CYP1A1

subfamily: at least 55% amino acid sequence homology

numbering of CYP and sources of enzymes:

1 - human, higher animals
51 – lower eucaryotic animals and fungi
71 – plants
101 – bacteria

11 gene family CYP proteins are found in humans and mammals
All CYP enzymes together can catalyze ~60 different kind of reactions.
In human and mammals CYP enzymes are membrane bound in ER and mitochondria.
1-4 gene family members have unimaginably broad and overlapping substrate specificity:

- several enzyme can transform the same substrate, possibly by different way
- and one enzyme accepts huge amount of substrates
- these enzymes transform plant poisons, medicines, chemicals, pollutants

5-51 gene family members are specific, they transform endogenous compounds

Main localization of CYP enzymes:
- liver, kidney, lung, intestine, skin

Genetic polymorphism often occurs: small alterations in amino acid sequence can affect
- enzyme activity, stability, substrate specificity, affinity for substrates
- leading to differences in medicine’s tolerance

Liver failure results toxicity of usual doses of drugs.

Regulation of CYP enzymes is done by regulation of amount of enzymes:
- induction-repression, mRNA stability, protein stability. Regulators are chemicals, hormons etc.
The same molecule: originating from food or spicy plant, food preservatives, hormone, pesticides and herbicides, soil pollutants, water pollutants, air pollutants and smoke, cigarette smoke, medicines and colouring compounds, auxiliary materials can act as substrate and inducer or repressor as well. It causes drug side effects/nonwanted effects, the usual dose can become toxic.
Mechanism of enzyme induction, regulation of gene expression

- Receptors of lipophylic hormones, medicines, foreign compounds (xenobiotics) are nuclear transcriptional factors (proteins) that are bound to promoter or enhancer sequence of DNA and increase the transcription of mRNA, therefore more protein is translated from the many mRNA molecules, this is the enzyme induction.
- The opposite process is the repression, when mRNA transcription is prevented.
- Other mechanism: hydrophilic second messengers e.g. cAMP, cGMP are ligands of PKA and PKG kinases that phosphorylate and activate transcription factors to translocate and bind to DNA etc.
Cytochrome P450 enzyme system is a monooxygenase: 1 atom of oxygen is built into the molecule or called mixed function oxygenase, because the other atom of oxygen forms water.

Substrate-\(H + O_2 + NADPH + H^+ \rightarrow \text{Substrate-OH} + H_2O + NADP\)
Cytochrome P450 enzyme system is a monooxygenase:

$$S-H + O_2 + NADPH + H^+ \rightarrow S-OH + H_2O + NADP$$

or often called hydroxylase: this is the most frequent reaction type that can be followed by:

dealkylation,
desulfuration,
H$_2$O elimination
(other kind of reactions: epoxidation,
dehydrogenation,
dehalogenation,
oxidation to keto
group, aromatization)
Components of ER electron transport chain:
NADPH → cytochrome P450 reductase FAD, FMN → cyt. P450 isoenzyme

NADH → cytochrome b5 reductase FAD → cytochrome b5

cytochrome P450 reductase

Components in mitochondria:
NADPH → ferredoxin reductase FAD → ferredoxin FeS → CYP isoenzyme
= adrenodoxin reductase

Composition of cytochrome P450 enzyme system in ER and mt.

ADX: Adrenodoxin
ADR: NADPH-Adrenodoxin Reductase
FAD and FMN prosthetic groups can add electrons in a stepwise manner in cytochrome P450 reductase enzyme. Electrons come from NADPH.
Humans have 18 families of cytochrome P450 genes and 43 subfamilies

**CYP1 drug metabolism** (3 subfamilies, 3 genes, 1 pseudogene)
**CYP2 drug and steroid metabolism** (13 subfamilies, 16 genes, 16 pseudogenes)
**CYP3 drug metabolism** (1 subfamily, 4 genes, 2 pseudogenes)
**CYP4 arachidonic acid or fatty acid metabolism** (5 subfamilies, 11 genes, 10 pseudogenes)
**CYP5 Thromboxane A2 synthase** (1 subfamily, 1 gene)
**CYP7A bile acid biosynthesis 7-alpha hydroxylase** of steroid nucleus (1 subfamily member)
**CYP7B brain specific form of 7-alpha hydroxylase** (1 subfamily member)
**CYP8A prostacyclin synthase** (1 subfamily member)
**CYP8B bile acid biosynthesis** (1 subfamily member)
**CYP11 steroid biosynthesis** (2 subfamilies, 3 genes)
**CYP17 steroid biosynthesis** (1 subfamily, 1 gene) 17-alpha hydroxylase
**CYP19 steroid biosynthesis** (1 subfamily, 1 gene) aromatase forms estrogen
**CYP20 Unknown function** (1 subfamily, 1 gene)
**CYP21 steroid biosynthesis** (1 subfamily, 1 gene, 1 pseudogene)
**CYP24 vitamin D degradation** (1 subfamily, 1 gene)
CYP26A retinoic acid hydroxylase important in development (1 subfamily member)
CYP26B probable retinoic acid hydroxylase (1 subfamily member)
CYP26C probable retinoic acid hydroxylase (1 subfamily member)
CYP27A bile acid biosynthesis (1 subfamily member)
CYP27B Vitamin D3 1-alpha hydroxylase activates vitamin D3 (1 subfamily member)
CYP27C Unknown function (1 subfamily member)
CYP39 7 alpha hydroxylation of 24 hydroxy cholesterol (1 subfamily member)
CYP46 cholesterol 24-hydroxylase (1 subfamily member)
CYP51 cholesterol biosynthesis (1 subfamily, 1 gene, 3 pseudogenes)
    lanosterol 14-alpha demethylase

Humans have 57 sequenced CYP genes and 58 pseudogenes.
only full length functional genes are named below
1A1, 1A2, 1B1, 2A6, 2A7, 2A13, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2F1, 2J2, 2R1, 2S1, 2U1, 2W1, 3A4, 3A5, 3A7, 3A43, 4A11, 4A22, 4B1, 4F2, 4F3, 4F8, 4F11, 4F12, 4F22, 4V2, 4X1, 4Z1 5A1, 7A1, 7B1, 8A1, 8B1, 11A1, 11B1, 11B2, 17, 19, 20, 21A2, 24, 26A1, 26B1, 26C1, 27A1, 27B1, 27C1, 39, 46, 51
Reactions of endogenous CYP substrates: cholesterol and bile acids’ synthesis

CYP51 = lanosterol demethylase (ER)

squalene $\rightarrow$ squalene-epoxide $\rightarrow$ lanosterol $\rightarrow$ cholesterol

7α-hydroxylase =

Classic pathway of bile acid synthesis

Alternative pathway of bile acid synthesis

Cholic acid

Chenodeoxycholic acid
Synthesis of steroid hormones

**Major Pathways in Steroid Biosynthesis**

- **Cholesterol**
  - Pregnenolone (CYP17)
  - Progesterone (CYP21A2)
  - Deoxy-corticosterone (CYP11B1)
  - Corticosterone (CYP11B1)
  - Cortisol (CYP19)
  - Aldosterone (CYP11B2)

**Common name** | **Current name**
--- | ---
Side-chain cleavage enzyme; desmolase | CYP11A1
3 β-hydroxysteroid dehydrogenase | 3 beta-HSD
17 α-hydroxylase/17,20 lyase | CYP17
21-hydroxylase | CYP21A2
11 β-hydroxylase | CYP11B1
Aldosterone synthase | CYP11B2
Aromatase | CYP19

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Study these structural formulas.
CYP27B1
cholecalciferol = vitamin D3 $\rightarrow$ 25-OH-cholecalciferol $\rightarrow$ 1,25-dihydroxicholecalciferol =
  liver kidney, bone, placenta calcitriol (hormon)

CYP4=desaturases
linoleic ac. $\rightarrow$ arachidonic acid $\rightarrow$ prostaglandin H2 $\rightarrow$ prostacyclin
$\downarrow$CYP5A1= thromboxane synthase
thromboxane

CYP8A1= prostacyclin synthase

Prostacyclin and
Thromboxane synthesis

Prostacyclin
synthase

COX-2 (EC)
COX-1 (platelets)

PGG$_2$

PGH$_2$

Prostacyclin
synthase

Thromboxane
synthase

Thromboxane A$_2$
(TXA$_2$)

Cardiovascular homeostasis:
Balance between prostanoid products

Arachidonic Acid

$\text{C}_2\text{H}_4\text{H}_2$
$\text{CH} = \text{C}$
$\text{H}$
$\text{H}$
$\text{O}_2$
$2\text{H}^+$

O$_2$
$2e^-$

2 Fe(II)
$2e^-$
desaturase

2 Fe(III)

2 cyt b$_5$
Fe(III)

2 cyt b$_5$
Fe(II)
cytochrome b$_5$

FADH$_2$
$2e^-$
cytochrome b$_5$

FAD
$2e^-$

NAD$^+$
$2e^-$

NADH

Prostacyclin (PGI$_2$)
2nd phase: Conjugation reactions

1.) glucuronidation by UDP-glucuronyl transferase

\[
\text{UDP-glucuronidate} + \text{drug} = \text{drug-glucuronidate} + \text{UDP}
\]

UGT1 are formed by alternative splicing – bilirubin, amines, phenols are substrates
UGT2 are formed by different genes – steroids, bile acids, opioids are substrates

It is the most frequent conjugation reaction type. Enzymes are in ER and cytoplasm of liver, skin, breast, prostate, adipose tissue…

![UDP-Glucuronate](image1)

![UDP-Glucuronide](image2)
Deficiency

bilirubin heme degradation not enough induced

product in newborn + glucuronyl transferase in liver

bilirubin-diglucuronide is not produced in liver, it is not secreted to bile,
accumulated free bilirubin in skin, mucous membranes, sclera, it is jaundice = icterus

Free bilirubin = lipophylic,
it binds to albumin in blood,
high amount is toxic.
Bilirubin-monoglucuronide and bilirubin-diglucuronide are water-soluble,
secreted to bile,
gut bacteria convert them further.
2.) Sulfatation by sulfotransferase

PAPS + drug = drug-sulfate + PAP

alcohols, phenols, arylamines are exogenous substrates, steroids, heteropolysaccharides, glycolipids, glycoproteins, thyroid hormones are endogenous substrates, the hormones are inactivated in cytoplasm and Golgi apparatus
Conjugation sometimes causes activation:

adrenal cortex-derived androgen:
\[
\text{dihydroepiandrosteron = DHEA}
\]

hydroxysteroid sulfotransferase in steroid target cell

Dehydroepiandrosteron sulfate active metabolite

Other clinical aspects

17-alfa-etiilestradiol anticontraceptive + rifampicin antituberkulotic HSST induktor

sulfonated and noneffective estrogen, pregnancy is possible
3-4.) glutathion-conjugation by glutathione S-transferase
+ acetylation with acetyl-CoA by acetyltransferase

$$GSH + \text{drug} = \text{drug-S-glutathione} \rightarrow \text{Gly} + \text{Glu} + \text{drug-S-Cys} \rightarrow \text{acetyl-cysteinyldrug}$$

slow and fast acetylators according to enzyme polymorphism
isoniazid, an antituberculotic agent can be toxic in slow acetylators

electrophylic SH-group

GSH = glutathione = γ-glutamyl-cysteinyl-glycine tripeptide

Leukotrienes are formed by leukocytes, take part in inflammation. Exceptionally the glutathione conjugation leads to activation.
5.) amino acid conjugation by: glycine, taurine

Benzoyl-CoA + Gly = hippurate (way of elimination of N) + CoA
Phenylacetyl-CoA + Gln = phenylacetylglutamine (way of elimination of N) + CoA
chenodeoxycholate + taurine = taurochenodeoxycholate primary bile acid
cholate + Gly = glycocholate primary bile acid
6.) methylation by methyltransferase

dopamine + SAM = methyl-dopamine (inactive) + SAH  
by catechol-oximethyltransferase = COMT in catecholamine degradation

noradrenalin + SAM = adrenalin + SAH

This is the only one conjugation reaction when the product is slightly more lipophytic than the substrate, but remains water-soluble enough to become excreted.
3rd phase: excretion of lipohilic and conjugated compounds

MDR(1-P) = multidrug resistance gene product and MRP (1-7) = multidrug resistance proteins are members of ABC (ATP-binding cassette) transporters: when ATP is bound to their nucleotide binding domain the transporter opens and molecules are pumped out.

5A: MDR1-P-glycoprotein (substrates are recognized in, or near to the membrane lipid phase).
Abbreviations: hD, hydrophilic drugs; PL, phospholipid

5B: MRP1
Both hydrophobic drugs and anionic conjugates, such as glutathione conjugates, are transported. The transport of some hydrophobic drugs may be coupled to reduced glutathione (GSH) as GS-X molecules.
Metabolism of vitamin D

1,25(OH)₂D is ligand of **VDR (vitamin D receptor)** transcription factor, it causes induction of many proteins.
Metabolism of β-carotene and vitamin A

Trans-retinoic acid is the ligand of RAR and cis-retinoic acid is the ligand of RXR, these transcription factors control many-many processes.
A. Steroid hormone receptors (AR, ER, GR, MR) androgen receptor estrogen rec. glucocorticoid rec. mineralocorticoid rec.

B. Heterodimeric nuclear receptors (LXR, FXR, PPAR, RAR, PXR, VDR)
Liver X receptor (lipid synthesis)
Farnesoid X receptor (bile acid synthesis)
Peroxisome proliferation activating receptor

NR = nuclear receptors

NR = nuclear receptor = transcription factor protein that binds ligand
Transformation of medicines and xenobiotics

Drug metabolizing CYP enzymes

50 % - 3A4
20 % - 2D6
15 % - 2C9, 2C19
15 % - 1A2, 2A6, 2B6 …

Regulation of enzyme synthesis is done by induction:
inducer: drug, chemical, pollutant, contaminant, plant compound
    inducer binds to any of the following transcriptional factors: CAR, PXR, VDR
that forms a heterodimer with another transcriptional factor: RXR
    own ligand binds to RXR: retinic acid
more mRNA is transcribed,
more CYP isoenzyme is translated,
bigger amount of enzymes catalyze the reactions with bigger velocity,
medicines are converted, degraded faster.
In mammals several transcription factors regulate the expression of the same gene.

- **PXR** = pregnane X receptor (inducers: phenobarbital, androstanol)
- **CAR** = constitutive androstane receptor
- **VDR** = vitamin D receptor (inducer: vit. D)
- **HNF** = hepatic nuclear factor

In the DNA, the **xenobiotic responsive enhancer module** is located between **HNF** and **CYP3A4**. This module consists of direct and everted repeats, which are essential for the transcription of the gene.

**PXR** and **CAR** can form complexes with **RXR**, which are involved in the induction of genes involved in drug metabolism. Additional factors such as **VDR** can also bind to **RXR**.

**Drug A** acts as an inducer, stimulating the transcription of genes like **CYP3A4**.

**Examples** of drugs that can activate this pathway include:
- Ethinylestradiol
- Efavirenz
- Warfarin
- Tamoxifen
- Doxorubicin

**Drug B** is a substrate, and the **HO** enzyme converts it into a product.

**DNA chain**:
- **HNF**
- **DR3**
- **ER6**

The **proximal promoter** is located downstream of this module.
Drug interactions; metabolism of medicines, food components and pollutants by the same enzyme system

Clinical aspects
**Substrates:** these are degraded and compete for the enzyme

- Amitriptyline* (Elavil)
- Benzodiazepines
  - Alprazolam (Xanax)
  - Triazolam (Halcion)
  - Midazolam (Versed)
- Calcium blockers
- Carbamazepine (Tegretol)
- Cisapride (Propulsid)
- Dexamethasone (Decadron)
- Erythromycin
- Ethinyl estradiol (Estraderm, Estrace)
- Glyburide (Glynase, Micronase)
- Imipramine* (Tofranil)
- Ketoconazole (Nizoral)
- Lovastatin (Mevacor)
- Nefazodone (Serzone)
- Terfenadine (Seldane)
- Astemizole (Hismanal)
- Verapamil (Calan, Isoptin)
- Sertraline (Zoloft)
- Testosterone
- Theophylline*
- Venlafaxine (Effexor)
- Protease inhibitors
  - Ritonavir (Norvir)
  - Saquinavir (Invirase)
  - Indinavir (Crixivan)
  - Nelfinavir (Viracept)

**Inhibitors**

- Antidepressants
  - Nefazodone > fluvoxamine (Luvox) > fluoxetine
    (Prozac) > sertraline
  - Paroxetine (Paxil)
  - Venlafaxine
- Azole antifungals
  - Ketoconazole (Nizoral) > itraconazole (Sporanox)
  - > fluconazole (Diflucan)
- Cimetidine (Tagamet)
- Clarithromycin (Biaxin)
- Diltiazem
- Erythromycin
- Protease inhibitors

**Inducers**

- Carbamazepine
- Dexamethasone
- Phenobarbital
- Phenytoin (Dilantin)
- Rifampin (Rifadin, Rimactane)

Inhibitors cause slower degradation of drug substrates, medicine concentration remains high, can be toxic.

Inducer drugs cause faster metabolism of substrate medicines, so medicines will not be effective enough, they do not reach the therapeutic concentration.

**Localization of CYP3A4:**

- liver, GI: from esophagus till colon, resp. tract: nose and lung, kidney tubules, skin, blood cells, ovary, testis Leydig-cells, adrenal gland zona glomerulosa, parathyroid gland, adenohypophysis

Medicines are not required to study in Biochemistry from the figure.
Km = 0.2 - 2 mM

ROS = reactive oxygen species = \( \text{O}_2^-, \text{OH}^- \)

ROS = reactive oxygen species = \( \text{O}_2^-, \text{OH}^- \)

fatty acid oxidation ↓

gluconeogenesis ↓→ blood sugar level ↓

triglyceride synthesis ↑→ fatty liver

fekhérjeadduktumok immunválaszt okoznak

liver, stomach

Km = 8 - 10 mM

fatty acid oxidation ↓

gluconeogenesis ↓→ blood sugar level ↓

triglyceride synthesis ↑→ fatty liver

NADPH + H^+ + O_2 → NADP^+ + 2H_2O

CYP2E1

H - C - C - OH

H - C - C - H - O

ETHANOL

ACETALDEHYDE

NAD^+ → NADH + H^+

ADH

H_2O_2

H_2O

CATALASE

ALDH

ACETIC ACID

Mitochondria
Alcohol oxidation by CYP2E1 in endoplasmatic reticulum

Only this one can be induced among the ethanol degrading enzymes, in alcoholists its amount is significantly increased.

The ethanol is not only a substrate, but the inducer of the enzyme, too. It accelerates its own metabolism.
Metabolism of acetaminophen = paracetamol by CYP2E1

According to the statistics in USA, alone acetaminophen is responsible for the 1/3 of acute liver failure cases (50% in adults and 10% in children) among all the possible causes: toxins, virus, other organ failure, mushroom, alcohol, drug - and causes kidney failure too.
ROS = reactive oxygen species (OH·, O₂−, H₂O₂)
- are produced by CYP isoenzymes in ER,
- by mitochondrial electron transport chain,
- in peroxisome during FA oxidation and
- by xanthine oxidase,
- by NADPH oxidase in cytoplasm,
- spontaneously by metal ions.

We have antioxidant, protective enzymes:
- superoxide dismutase, (SOD)
- catalase,
- glutathione peroxidase (GPX)
- thioredoxin (TRR)
- peroxiredoxin

And by antioxidant compounds:
- ascorbate = vitamin C
- glutathione = GSH,
- vitamin E = α-tocoferol
- urate

Inflammation
Ischemia/Reperfusion
Diabetes
Angiotensin II
Obesity

\[ \text{HOCI} \rightarrow \text{OCl}^- \]

\[ \text{Catalase} \]

\[ \text{MPO} \]

\[ \text{NAD(P)H oxidase, XO, COX, NOS} \]

\[ \text{O}_2^- \]

\[ \text{SOD} \]

\[ \text{L-Arg} \]

\[ \text{NOS} \]

\[ \text{ONOO}^- \]
DDT = dichlordiphenyl-trichloretan is an insecticide. Insect-killing effect was discovered in 1934. In world war II the DDT was used against louse, flea and in tropic countries against malaria and yellow fever spreading mosquitoes, against typhus, plague = pestilence, colorado-beetle.

Rate of degradation of DDT in soil, water, plant, animal is 0-5% / year. It is accumulated in fat and milk. Most, but not all countries have withdrawn it from the market, now Mexico, China, India etc. produce it.

Europe and North America gets DDT back with Brasil crude coffee bean, African cocoa seeds and chocolate, Chinese peanut, Spanish and Greek etc. orange peel. Most polluted countries: Costa Rica, Zaire, India, Mexico, Pakistan, China.
The effect of DDT in animals and human:

a) induces aromatase → testosterone is converted to estrogen in males (and females)

b) CYP2B and CYP3A enzymes are induced → testosterone hydroxylation and inactivation is accelerated, degradation of 70% of medicines is increased, drugs have no effect

c) sulfotransferase enzyme is induced → testosterone and other steroid hormone sulfatation and inactivation is faster

d) it has a direct androgen receptor antagonist effect

Because of above mentioned effects in embryo, the inner gonad formation is disturbed, in adult males the androgen is inactivated, the male is femininized, becomes impotent.

The similar dicofol, endosulfan and methoxychlor is used in USA, too.
CYP1A2 SUBSTRATES, INHIBITORS AND INDUCERS

Substrates
Amitriptyline* (Elavil)
Clomipramine (Anafranil)*
Clozapine (Clozaril)*
Imipramine (Tofranil)*
Propranolol (Inderal)*
R-warfarin*
Theophylline*
Tacrine (Cognex)

Inhibitors
Fluvoxamine (Luvox)
Grapefruit juice
Quinolones
  Ciprofloxacin (Cipro)
  Enoxacin (Penetrex) > norfloxacin (Noroxin) > ofloxacin (Floxin) > lomefloxacin (Maxaquin)

Inducers
Omeprazole (Prilosec)
Phenobarbital
Phenytoin (Dilantin)
Rifampin (Rifadin, Rimactane)
Smoking
Charcoal-broiled meat*
TCCD

Smokers require higher dose of theophylline and other drug

in war in VIETNAM 1962-1971 the herbicide agent orange = phenoxy-acetate + TCCD as contaminant was used

TCCD is strong CYP1A inducer, the strongest carcinogen

R-Warfarin is an antithrombotic drug, a vitamin K antagonist, that prevents formation of prothrombin in liver. If a CYP1A2 inducer drug is added together with Warfarin, bigger amount of enzyme will fast degrade Warfarin, so the ineffective dose can not prevent new thrombus formation.
If CYP2A2 inhibitor = repressor drug is added together with Warfarin, it is not degraded, its concentration is toxically high, and in case of hurt of the patient, the bleeding will not stop.
There are reported to be over 4000 toxic chemicals contained in cigarettes, many of which are exhaled in smoke causing harm to others as well as the smoker.

PAH = polyaromatic hydrocarbon

Nicotine: induces CYP2E1 and inhibits CYP2A6

Acetone, pyridine, heavy metals, benzene, carbon monoxide: minor interactions with hepatic enzymes

PAH: potently induce CYP1A1, CYP1A2 (and possibly CYP2E1), induce drug glucuronidation

Hundreds of other components: metabolic effects largely unknown

DANGER POISON!

Acetone (solvent)

* Naphtylamine

Methanol (used as rocket fuel)

* Pyrene

Naphtalène (moth-repellent)

* Urethane

Toluene (industrial solvent)

Arsenic (lethal poison)

* Dibenzacridine

* Polonium 210 (a radioactive element)

Carbon monoxide (found in exhaust fumes)

DDT (insecticide)

Viny chloroide (used in plastic materials)

* Known carcinogenic substances

STOP SMOKING!