FONTI DI INFORMAZIONE

http://rushim.ru/books/spravochniki/mackay1.pdf

1 2 3 4

http://echa.europa.eu/documents/10162/8059e342-1092-410f-bd85-80118a5526f5

http://enveurope.springeropen.com/articles/10.1186/2190-4715-24-16

Valutazione del rischio chimico

CdL Magistrale Interateneo in
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Università di Udine e Università di Trieste

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Valutazione della tossicità per la valutazione del rischio per la salute umana (*RAoC cap.6*)

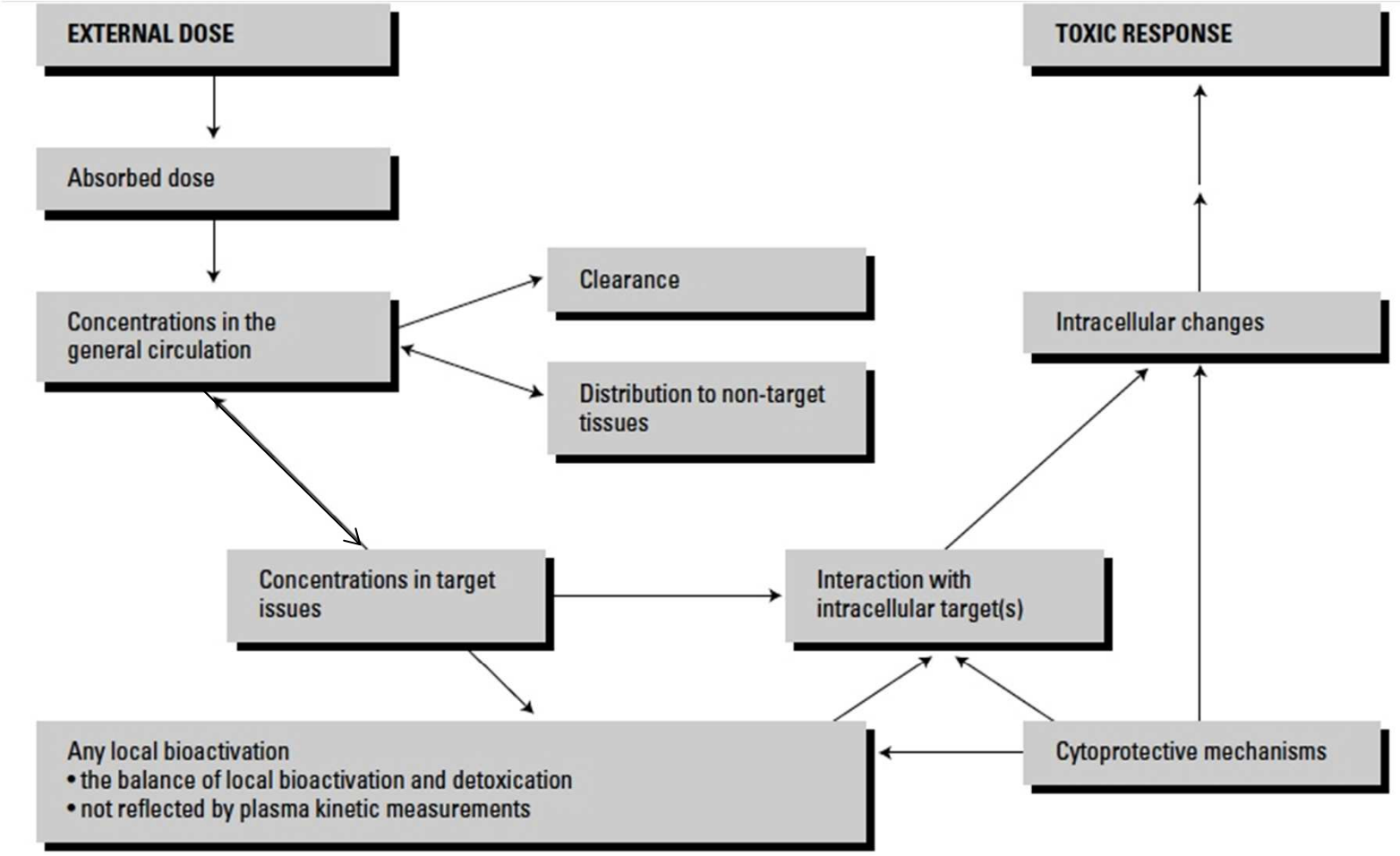
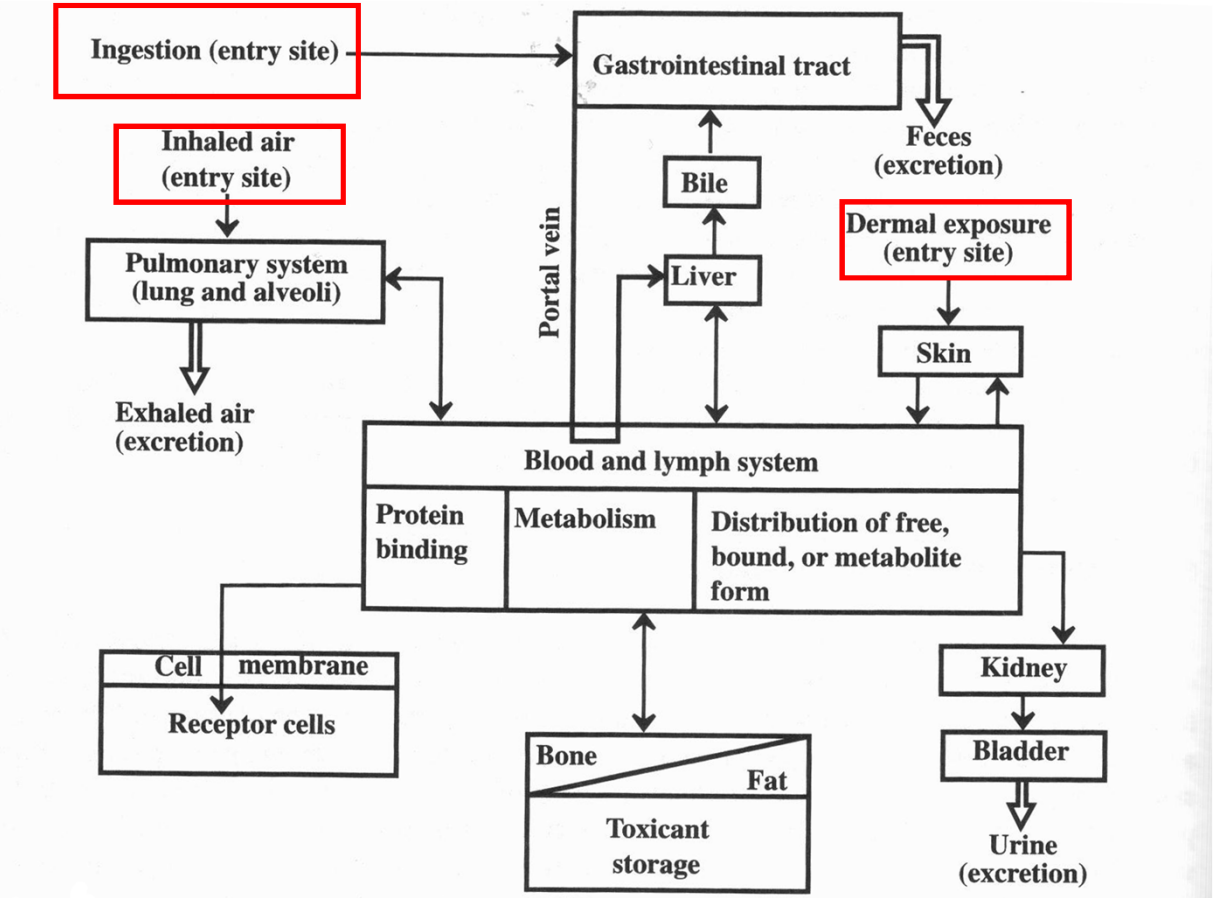
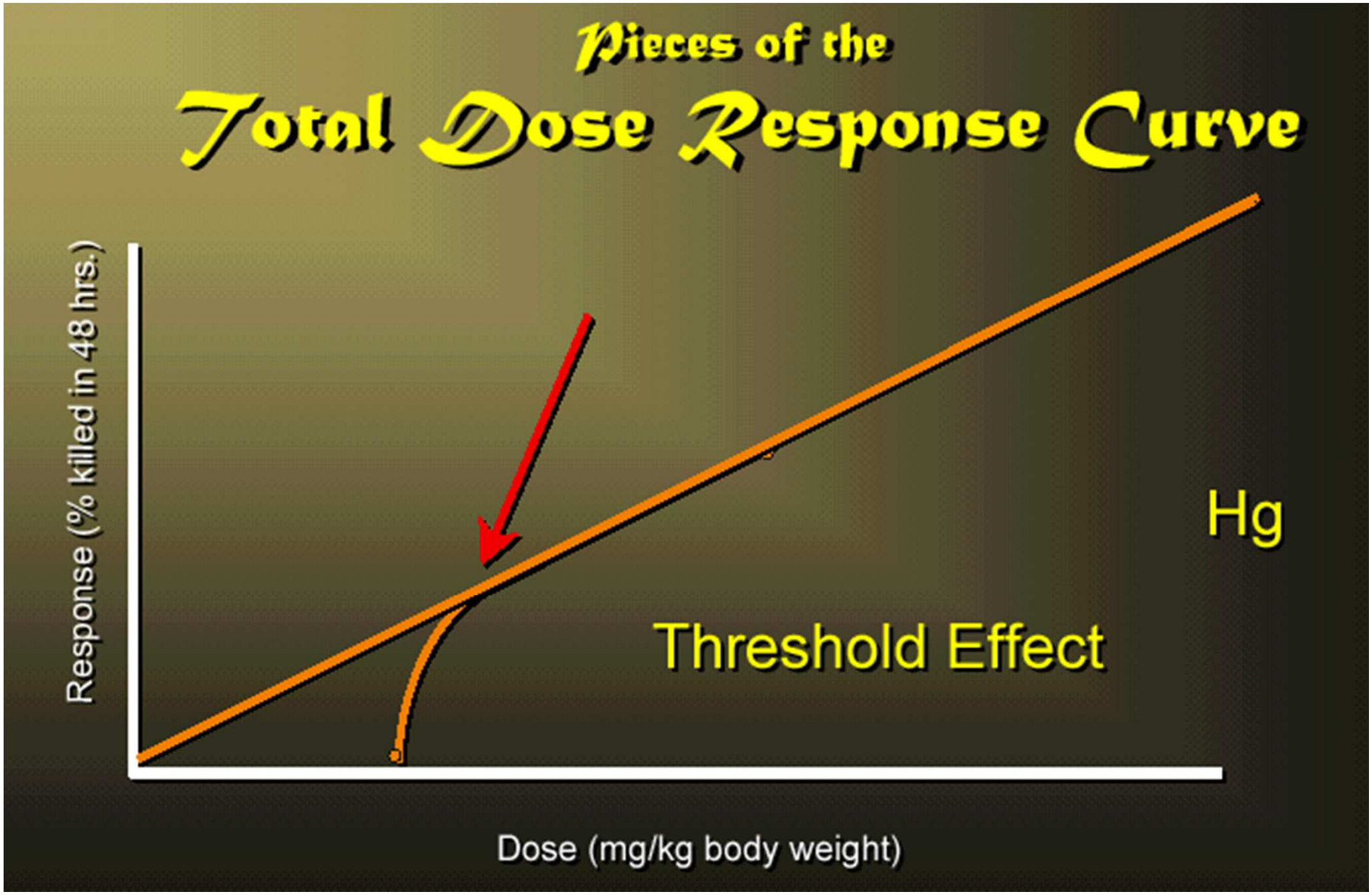


Figure 6.1. Processes leading to the generation of a toxic response [2].
Note:"Concentrations" refers to the relevant active form delivered by the general circulation and may be the parent compound or an active metabolite produced in another tissue and delivered to the target tissue or organ

Tossicologia – esposizione alle sostanze tossiche



Major sites of exposure, metabolism, and storage, and routes of distribution and elimination of toxic substances in the body.


Pieces of the
Total Dose Response Curve
Response (% killed in 48 hrs.)
Hg
Threshold Effect
Dose (mg/kg body weight)

Tossicologia – relazioni dose risposta

Relazioni dose-risposta

Risposta fisiologica rilevata

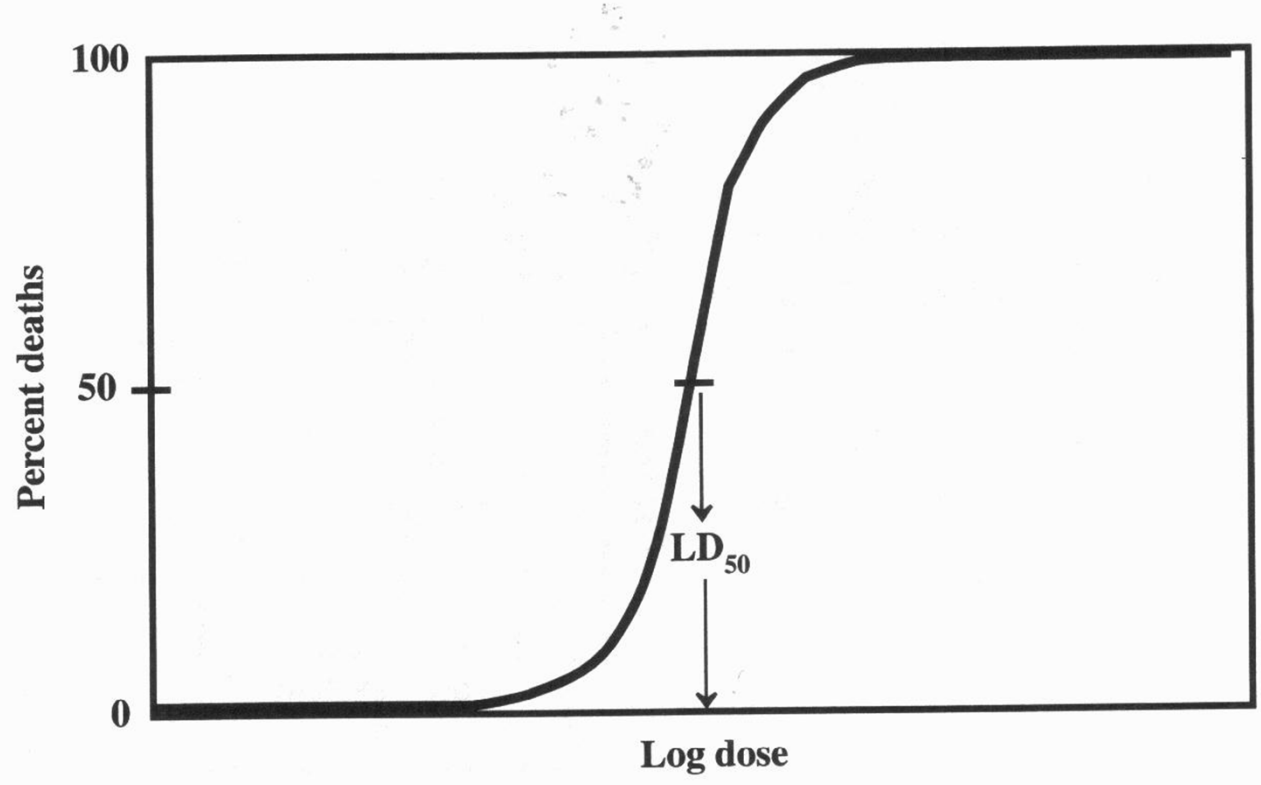


Illustration of a dose–response curve in which the response is the death of the organism. The cumulative percentage of deaths of organisms is plotted on the y axis. Although plotting log dose usually gives a better curve, with some toxic substances it is better to plot dose.

Tossicologia – tossicità relative

Tossicità acuta

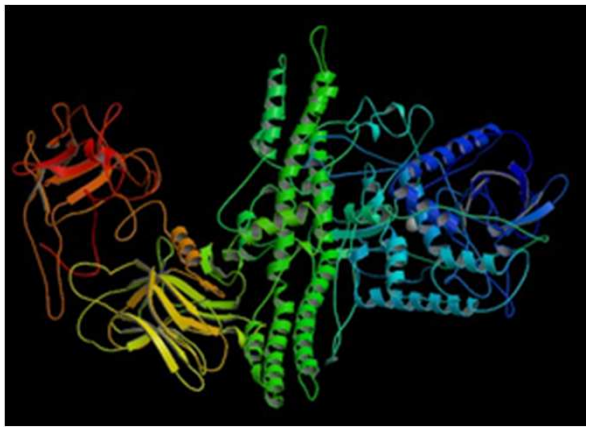


Table 6.1 Toxicity Scale with Example Substances[a]

Toxic Substance	Approximate LD_{50}	Toxicity Rating
	10^5	1. Practically nontoxic, $> 1.5 \times 10^4$ mg/kg
DEHP[b]		
Ethanol	10^4	2. Slightly toxic 5×10^3–1.5×10^4 mg/kg
Sodium chloride		
Malathion	10^3	3. Moderately toxic 500–5000 mg/kg
Chlorane		
Heptachlor	10^2	4. Very toxic 50–500 mg/kg
Parathion	10	5. Extremely toxic 5–50 mg/kg
TEPP[c] / Nicotine	1	
Tetrodotoxin[d]	10^{-1}	
	10^{-2}	6. Supertoxic <5 mg/kg
TCDD[e]	10^{-3}	
	10^{-4}	
Botulinus toxin	10^{-5}	

[a] Doses are in units of mg of toxicant per kg of body mass. Toxicity ratings on the right are given as numbers ranging from 1 (practically nontoxic) to 6 (supertoxic), along with estimated lethal oral doses for humans in mg/kg. Estimated LD_{50} values for substances on the left have been measured in test animals, usually rats, and apply to oral doses.

[b] Bis(2-ethylhexyl)phthalate.

[c] Tetraethylpyrophosphate.

[d] Toxin from pufferfish.

[e] TCDD represents 2,3,7,8-tetrachlorodibenzodioxin, commonly called "dioxin."

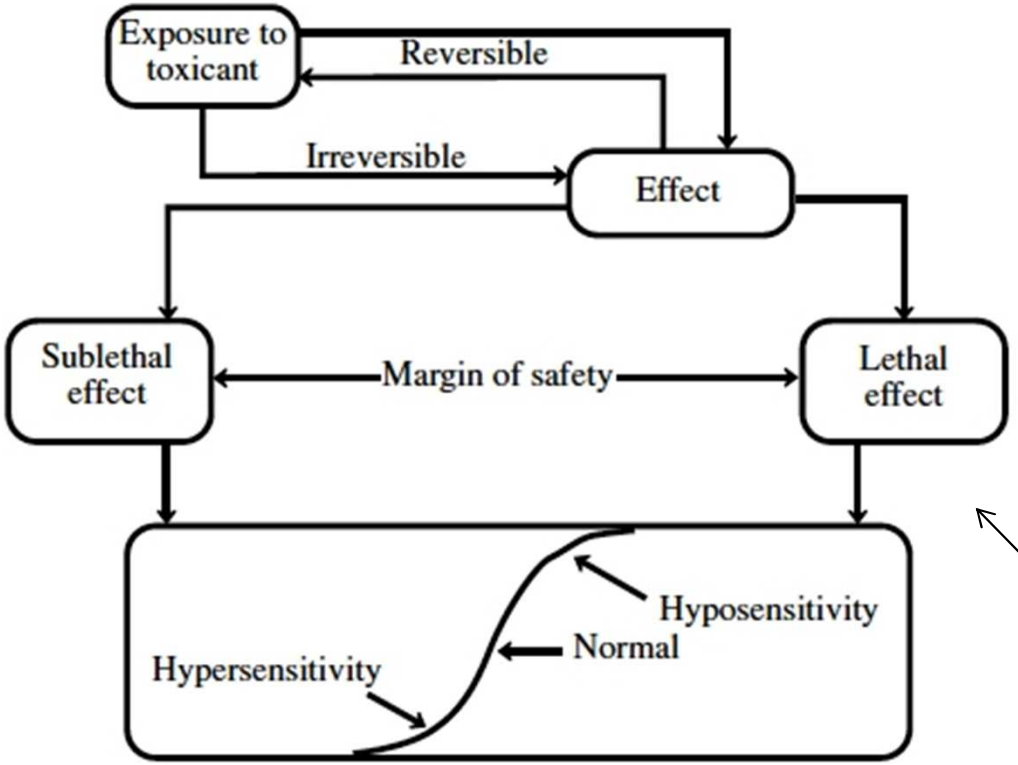
Le DL_{50} hanno un valore limitato nell'esprimere i pericoli per l'uomo.

Questo è perché la morte a seguito dell'esposizione (ambientale) ad una sostanza tossica è un effetto irreversibile relativamente raro.

Maggiormente preoccupanti sono gli effetti subletali che sono spesso reversibili, come le allergie e difetti congeniti, o effetti che possono essere letali ma che non sono acuti come la cancerogenesi.

Tossicologia –Reversibilità e sensibilità

Iper e iposensibilità, risposte “normali”



Effects of and responses to toxic substances.

Effetti irreversibili, permangono dopo l’eliminazione del tossico dall’organismo

MoS è la differenza tra concentrazione di esposizione e conc. letale

Reazioni allergiche indotte - penicilina
Tolleranza - es Cd^{2+} metallotioneine

//

Tossicologia non cinetica: effetti dannosi di una specie chimica che si verificano nel sito di esposizione (HNO_3 sulla pelle)

Specie non metabolizzate / trasportate / eliminate dal corpo

Caratteristiche della specie

Sito (area e durata) di esposizione

(Anche nota come

t. non metabolica o t. non farmacologica)

//

Tossicologia cinetica: Specie trasportate / metabolizzate

Veleni sistemici, possono attraversar membrane e agire su **recettori**

Quando consideriamo la pericolosità di una ***sostanza*** assumiamo che gli effetti avvengano per ***interazione tra essa ed un sito recettore***. Si ha una *risposta solo se un quantitativo sufficiente della specie o di un suo metabolita attivo raggiunge il recettore*. Ciò evidenzia la rilevanza dell'informazione sui processi di **assorbimento, distribuzione, metabolismo ed escrezione** (ADME), molto studiati in farmacologia, che determinano il destino all'interno del corpo e le dosi interne al sito bersaglio.

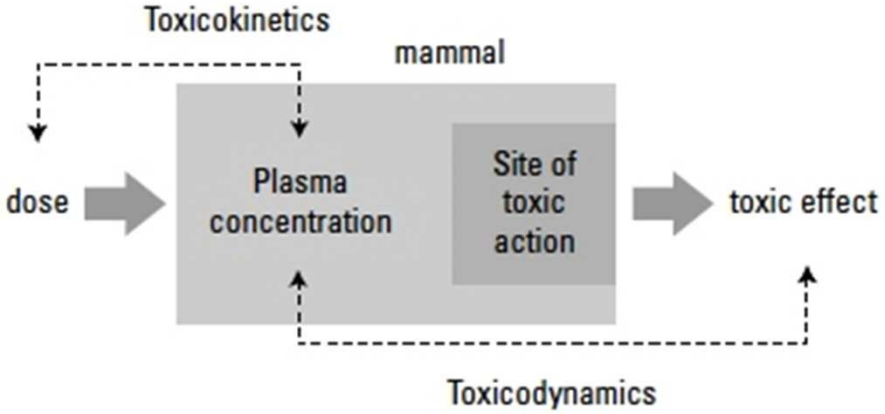
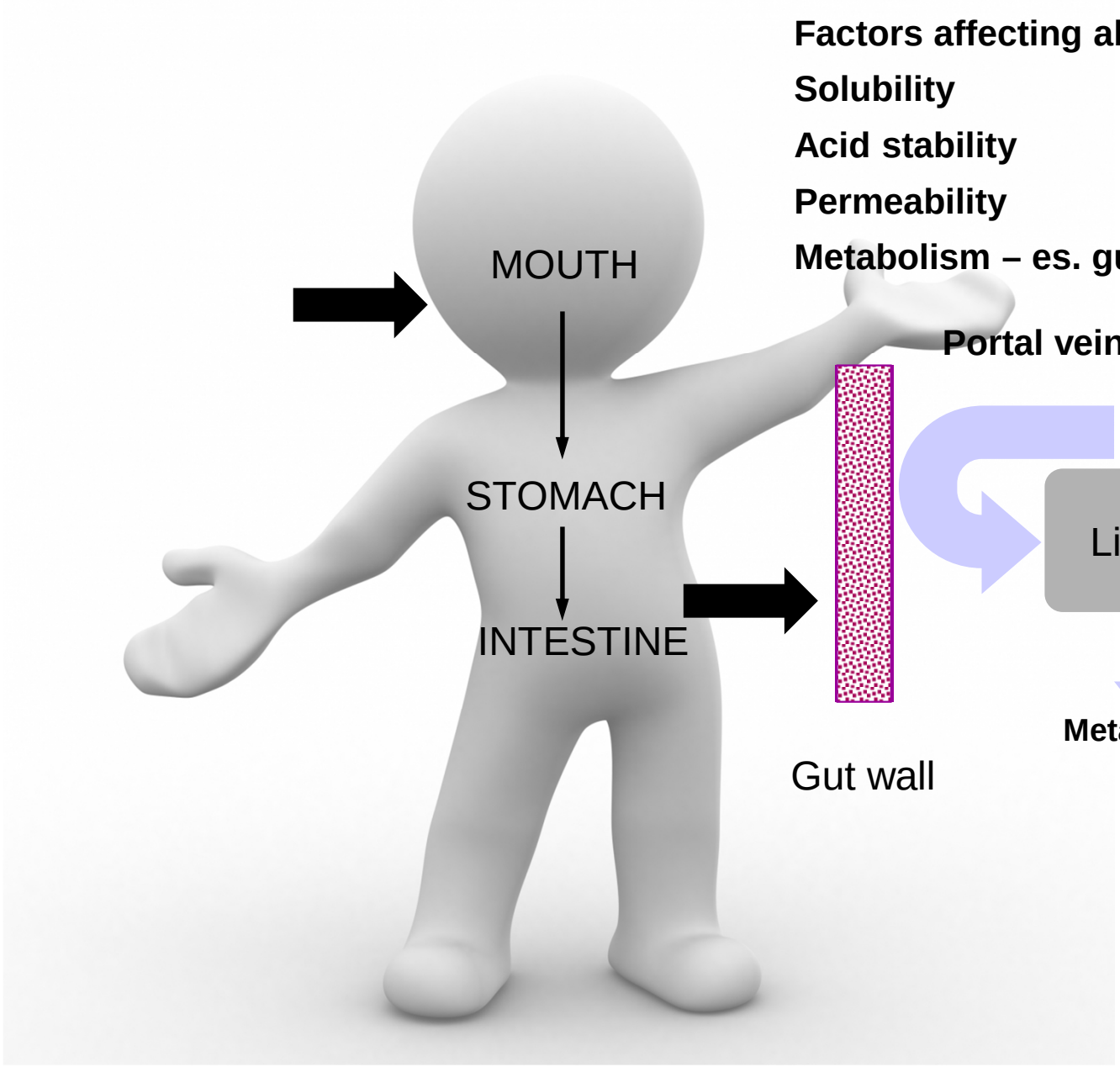


Figure 6.2. Toxicokinetics

Absorption



Factors affecting absorption:

Solubility

Acid stability

Permeability

Metabolism – es. gut wall

Portal vein

Liver

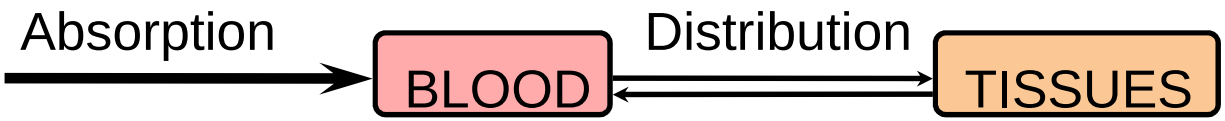
BLOOD

Metabolism

Gut wall

Distribution

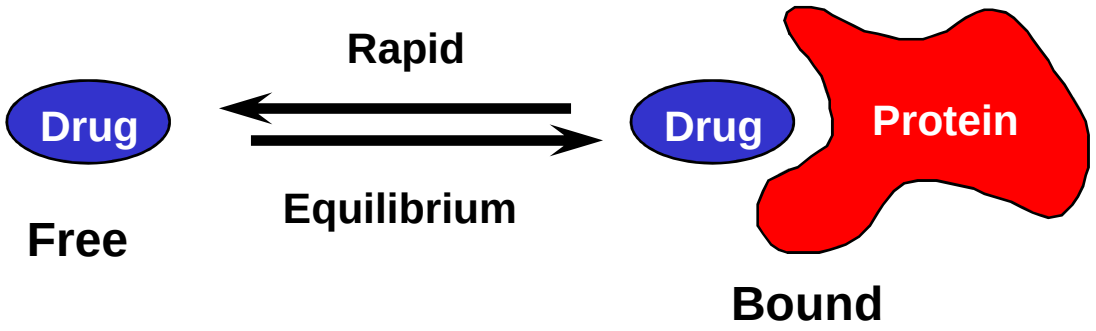
Distribution: the *reversible* transfer of a chemical to and from the systemic circulation



Compounds can distribute out of plasma into tissues:

Main factors influencing distribution are pKa, lipophilicity, plasma protein binding (only unbound chemical is free to distribute in tissues).

Plasma Protein Binding (PPB)



Drugs/chemicals can bind to macromolecules in the blood – known as plasma protein binding (PPB)

Only unbound compound is available for distribution into tissues

Acids bind to basic binding sites on *albumin*, bases bind to *alpha-1 acid glycoprotein*

0-50% bound	**= negligible**
50-90%	**= moderate**
90-99%	**= high**
>99%	**= very high**

For bases and neutrals, PPB is proportional to logD.

Acidic drugs tend to have higher PPB than neutral/basic drugs.

Metabolism

Definition: Any chemical alteration of a drug/chemical by the living system

Purpose: To enhance water solubility and hence excretability

Types of metabolism

- Phase I: production of a new chemical group on the molecule
- Phase II: addition of an endogenous ligand to the molecule

Sites of metabolism

- Main site of metabolism is the liver.
- Other sites include the gastrointestinal wall (CYP-450), kidneys, blood etc.

Factors affecting metabolism

- The structure of a drug influences its physicochemical properties. (blocking/altering sites of metabolism can improve DMPK properties)
- MW, LogP/LogD, pKa
- The more complex the structure, the more the potential sites for metabolism.

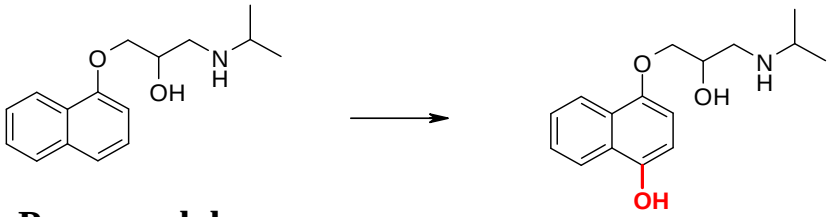
Phase I Metabolism

(i) Oxidation

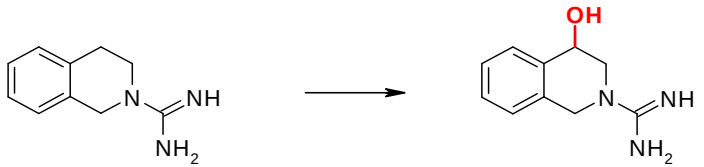
Aliphatic or aromatic hydroxylation

N-, or S-oxidation

N-, O-, S-dealkylation



Propranolol
(β-blocker)

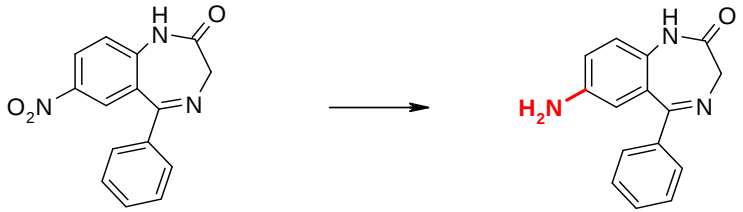


Debrisoquine
(anti-hypertensive)

(ii) Reduction

Nitro reduction to hydroxylamine/ amine

Carbonyl reduction to alcohol

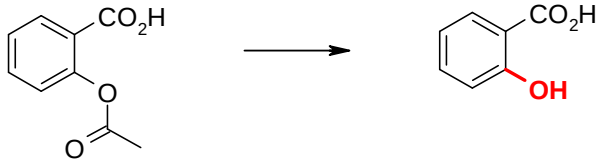


Nitrazepam
(hypnotic)

(iii) Hydrolysis

Ester or amide to acid and alcohol or amine

Hydrazides to acid and substituted hydrazine

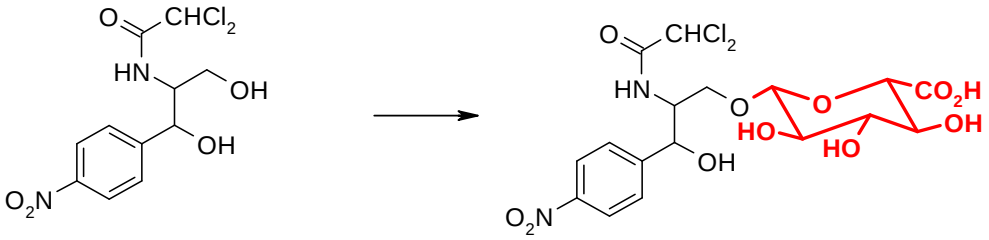


Aspirin
(Analgesic)

Phase II Metabolism

(i) Glucuronidation

Carboxylic acid, alcohol, phenol, amine



Chloramphenicol (antibiotic)

(ii) Amino acids

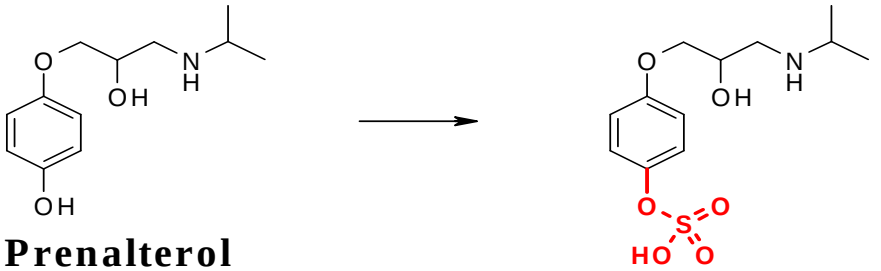
Carboxylic acids

(iii) Acetylation

Amines

(iv) Sulfation

Alcohol, phenol, amine



Prenalterol (β-blocker)

(v) Glutathione conjugation (gly-cys-glu)

Halo-cpds, epoxides, arene oxides, quinone-imine

Cytochrome P450 Enzymes (CYP-450)

$$RH + O_2 \xrightarrow[\text{CYP-450}]{2e^-,\ 2H^+} ROH + H_2O$$

Many Phase I oxidations are mediated by cytochrome P450 enzymes.

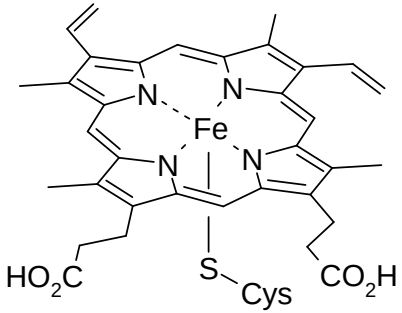
Membrane bound proteins - found on the endoplasmic reticulum.

Heme-containing proteins – porphyrin ring co-ordinating iron at the active site.

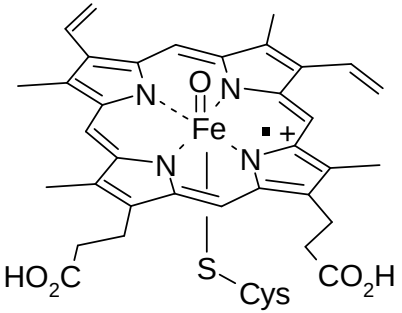
Many iso-forms with different substrate specificities:

Major human CYP's: 1A2, 2C9, 2C19, 2D6, 3A4

CYP inhibition/induction:

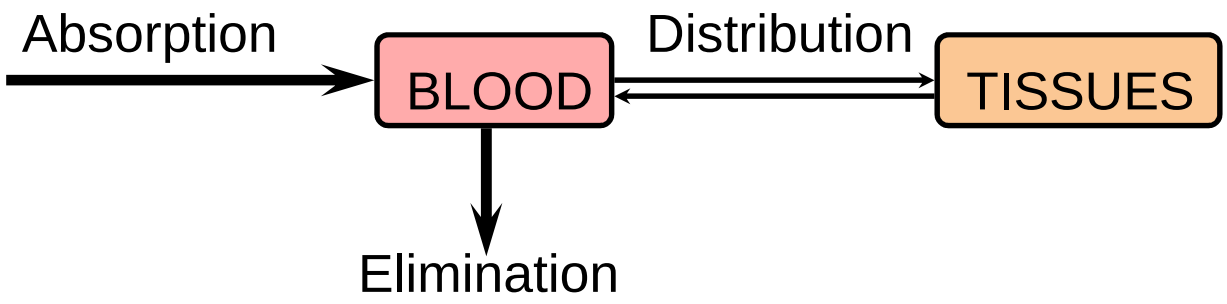


Iron(III) porphyrin



Active oxygen Fe (IV) species

Excretion (Elimination)



Elimination: the *irreversible* transfer of a drug from the systemic circulation

Major routes of elimination:

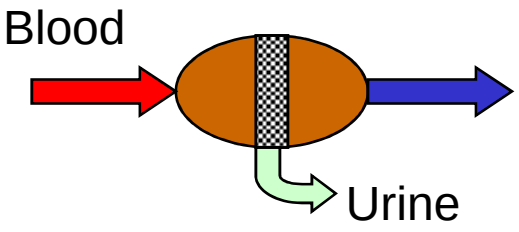
Metabolism

Renal excretion (for free drug, ie low logD)

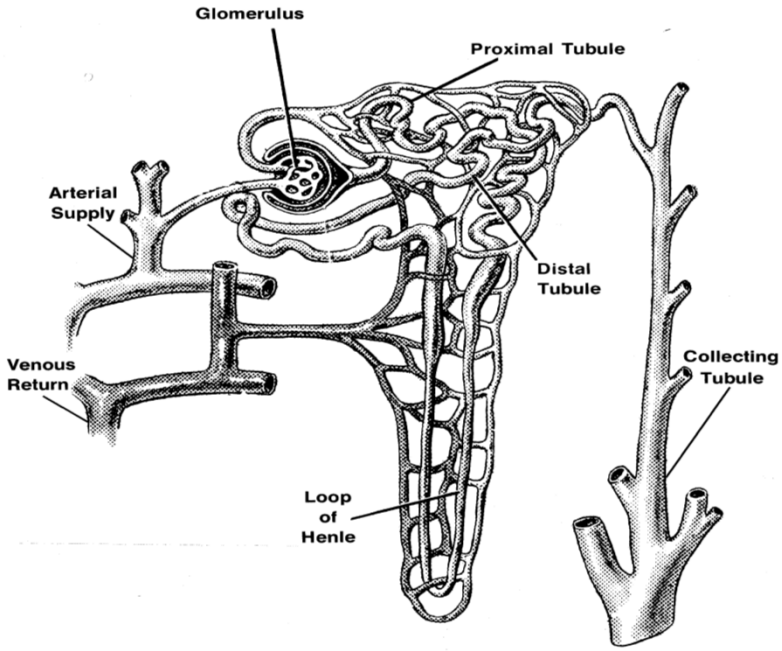
Biliary excretion

Also lungs, sweat etc.

Renal Excretion



Nephron



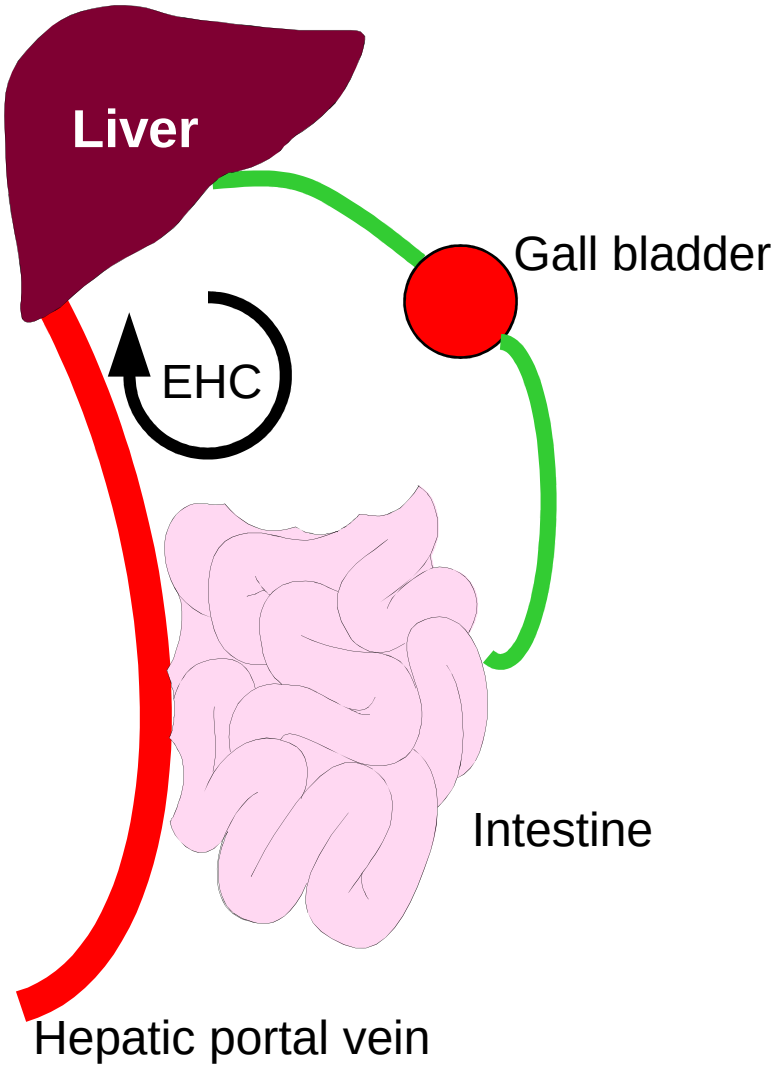
1. *All* **unbound** drug/chemical in plasma is filtered in the glomerulus. Only significant for very polar compounds, log D < 0.

2. Some compounds are actively secreted into urine along the proximal tubule.

3. Unionised drug can undergo passive reabsorption from urine into blood along the length of the nephron (net excretion may be zero).

4. Drug that is bound to plasma proteins is not filtered.

Biliary Excretion

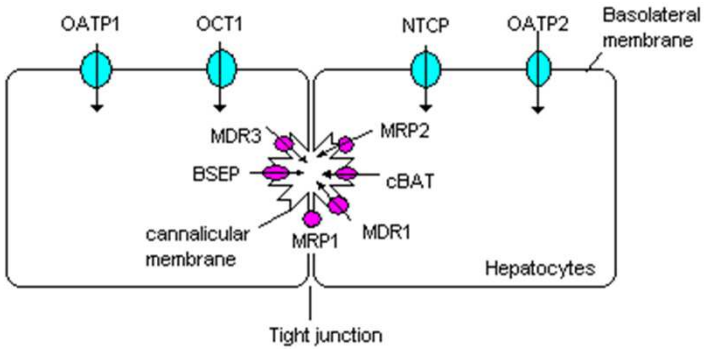


In the liver drugs/chemicals can be secreted into the bile

Transporters in the basolateral and canalicular membranes of hepatocytes mediate uptake into the hepatocyte and efflux into bile

Biliary clearance is commonly higher in Rats/Mice than in Dog/Man

Bile collects in gall bladder, then released into intestine upon food intake. Drug/chemical may then be reabsorbed - known as enterohepatic recirculation (EHC).



Biocinetica - decorso temporale di una sostanza chimica in un organismo vivente, vale a dire, aumento o la diminuzione di sostanza presso il sito di misura dovuti al trasporto o per la formazione o la rottura. Il termine "tossicocinetica" è spesso usato come sinonimo

Deve rispondere a domande in termini di
Cosa e quanto?
Dove?
Quando (velocità/tasso)?

Es un composto ha un'emivita di 6h nel plasma (dove?)

Toxicokinetic Modeling of Persistent Organic Pollutant Levels in Blood from Birth to 45 Months of Age in Longitudinal Birth Cohort Studies
http://ehp.niehs.nih.gov/wp-content/uploads/121/1/ehp.1205552.pdf

Le curve della concentrazione contro il tempo di una sostanza nel plasma o nel sangue sono risultati importanti per gli studi cinetici: sono surrogati per descrivere le concentrazioni al tessuto bersaglio. Si calcola la dose interna/ ***esposizione interna*** *come* ***AUC - area sotto la curva*** *(concentrazione nel plasma vs tempo). Le AUC sono usate per varie estrapolazioni (es interspecie)*

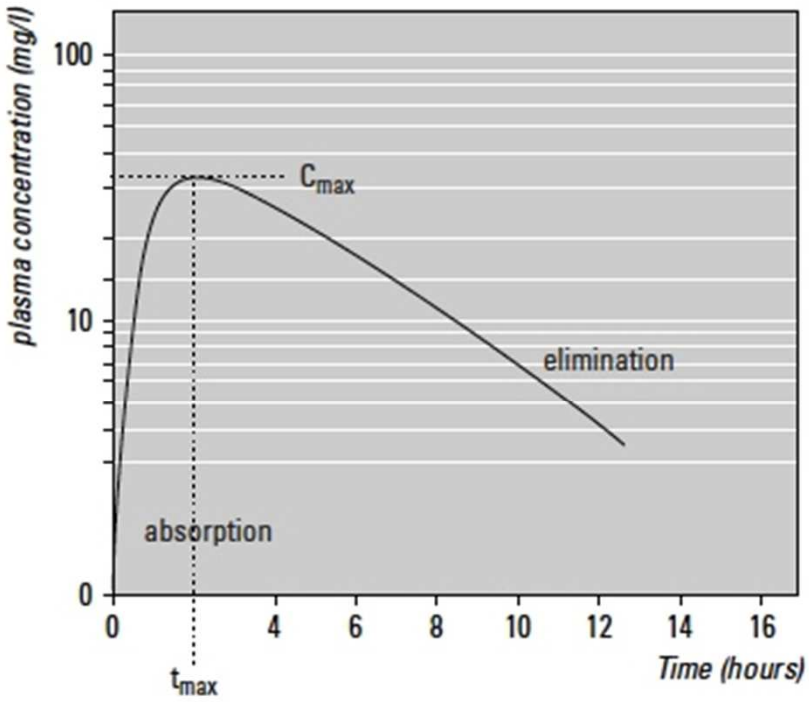


Figure 6.3. Absorption and elimination (http://coo.lumc.nl/TRC/).

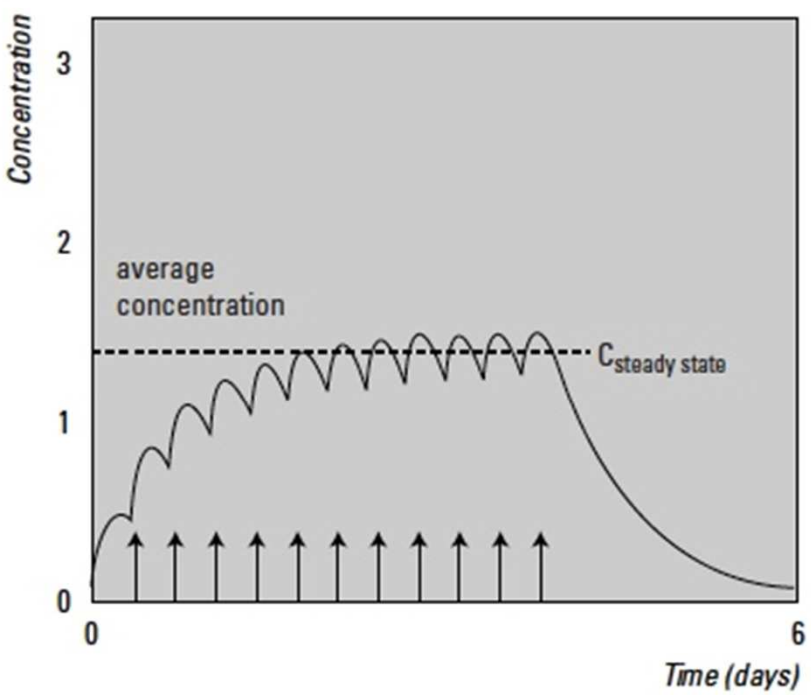


Figure 6.4. Steady-state (http://coo.lumc.nl/TRC/).

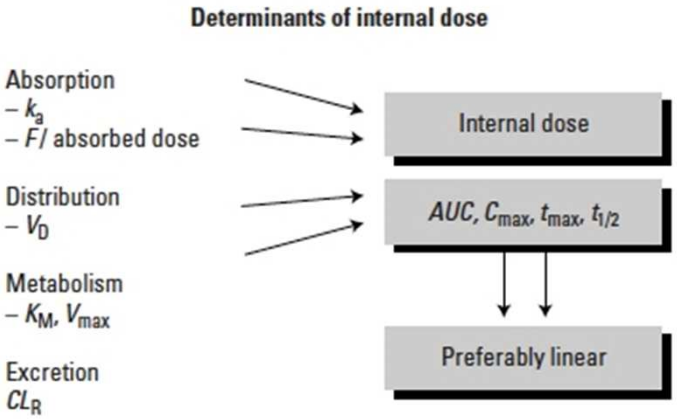


Figure 6.5. Determinants of internal dose (for symbols see Table 6.2).

Table 6.2. Primary parameters of ADM...

Process	Primary parameter
Absorption	absorption rate constant (k_a) and bioavailability (F)[1]
Distribution	apparent volume of distribution ($V_D = A / C$)[2] as an indicator of the tissues involved
Metabolism	intrinsic clearance, described by V_{max} and K_M
Excretion	sum of biliary excretory and renal clearance (CL), irreversible loss of compound from the body

[1] F = Fraction of dose reaching the systemic circulation. It should be noted that bioavailability has a different meaning in environmental toxicity issues, where the bioavailable fraction is the fraction of the total amount of a chemical present in a specific environmental compartment that, within a given time span, is either available or can be made available for uptake by organisms, micro-organisms or plants. Substances that are irreversibly bound to, e.g. soil or sediment, are not bioavailable.

[2] A = amount in body at equilibrium, C = concentration in blood.

Intrinsic Clearance (CLint),
Maximum Velocity of the Metabolic Reaction (Vmax),
Michaelis Constant (Km)

Approfondimenti
Clinical Pharmacokinetics Concepts and Applications by M. Rowland , T. Tozer

Biodisponibilità F: paragone tra AUC per la via di esposizione d'interesse e per la somministrazione intravenosa

$F = D_{i.v.} / D_x * AUC_x / AUC_{i.v.}$

X è la via di esposizione considerata

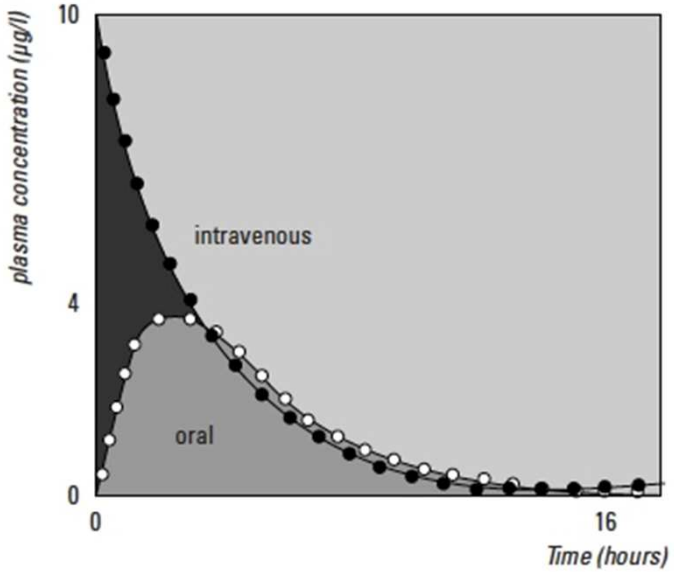


Figure 6.7. AUC oral (○○○) versus AUC intravenous (●●●).
Source: http://coo.lumc.nl/TRC/.

Assorbimento = passaggio di membrana (epitelio polmonare, epidermide, tratto gastrointestinale), **che può essere seguito da biotrasformazione** (può diminuire la biodisponibilità!!!)

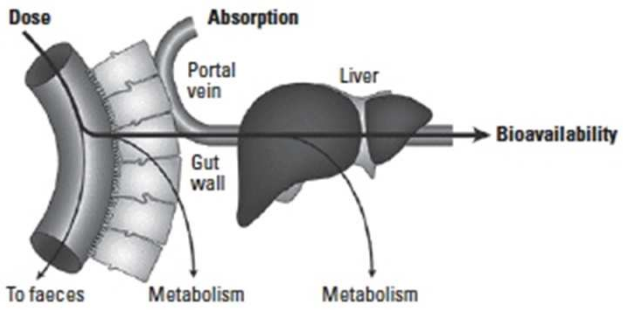


Figure 6.6. Bioavailability [22]. With permission.

Bioavailability