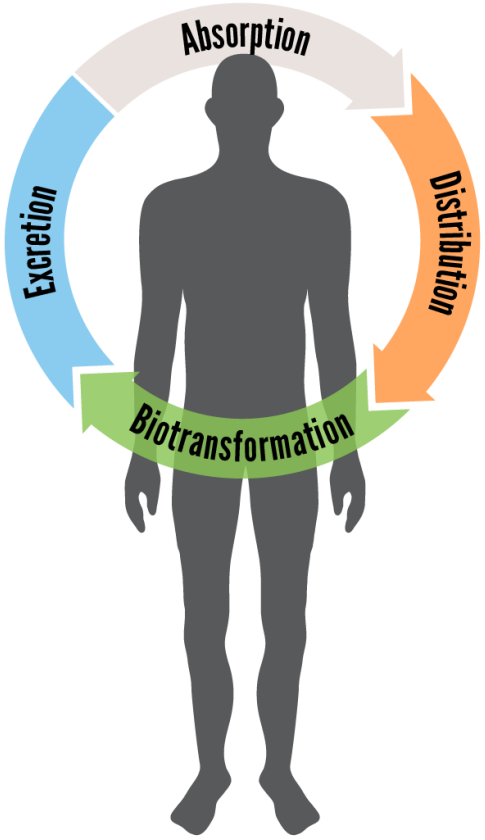


Toxicokinetics

Refer lecturer for course updated notes.

Students are oblidged to follow the courses for evaluation process and presented notes are preliminary drafts for the whole evaluation process.

Introduction

- "how a substance gets into the organism and what happens to it in the body.«
- «what body does to the drug»
- «description of both what rate a chemical will enter the body and what occurs to excrete and metabolize the compound once it is in the body»
- «absorption, distribution, biotransformation (biotransformation) and excretion of chemicals.»
- «Toxicokinetics is the mathematical description of the uptake and disposition of a chemical in the body»
- To define its toxic effects

Definition 1

- Toxicokinetics refers to the study of absorption, distribution, metabolism/biotransformation, and excretion (ADME) of toxicants/xenobiotics in relation to time
- extension of pharmacokinetic principles to define adverse drug effects
- disposition kinetics-xenobiotics - either natural or environmental sources -deleterious effects on organisms

Data relates the exposure achieved in toxicity studies

- Contribute to the assessment of the relevance of these findings to human safety.
- Provides information on linear/non-linear pharmacokinetics, accumulation,
- The effects are related to Cmax (peak concentration) or total exposure (AUC).
- Determine the appropriate species, study design, and treatment regimen in subsequent non-clinical toxicity studies. T
- Helps in evaluating the impact of a proposed change in the clinical route of administration

Factors Determining the Severity of Toxicity

The disposition of a toxicant and its biological reactivity are the factors that determine the severity of toxicity that results when a xenobiotic enters the body. The most important aspects of disposition include:

- **Duration and concentration** of a substance at the portal of entry.
- **Rate and amount** of the substance that can be absorbed.
- **Distribution** in the body and **concentration** of the substance at specific body sites.
- **Efficiency** of biotransformation and nature of the metabolites.
- **Ability** of the substance or its metabolites **to pass through cell membranes** and come into contact with specific cell components (for example, DNA).
- **Amount and duration of storage** of the substance (or its metabolites) in body tissues.
- **Rate and sites of excretion** of the substance.
- **Age and health status** of the person exposed.

Here are some examples of how toxicokinetics of a substance can influence its toxicity:

- **Absorption** — A highly toxic substance that is poorly absorbed may be no more hazardous than a substance of low toxicity that is highly absorbed.
- **Biotransformation** — Two substances with equal toxicity and absorption may differ in how hazardous they are depending on the nature of their biotransformation. A substance that is biotransformed into a more toxic metabolite (bioactivated) is a greater hazard than a substance that is biotransformed into a less toxic metabolite (detoxified).

Defining Factors Alter Response to Toxicants

1. Changes in chemical composition

- Valence state- Trivalent arsenicals are of inorganic agents much more toxic than pentavalent arsenic.
- Salts - barium carbonate is cardiotoxic, whereas barium sulfate is insoluble and nearly nontoxic).

Defining Factors Alter Response to Toxicants

2. Instability-Decomposition

- Adverse storage conditions can decompose to form more toxic degrade products- OPs

3. Impurities or contaminants

- Manufacturing byproducts (phenoxy herbicides- dioxin)

4. Ionization

- Compounds that are highly ionized are poorly absorbed and thus less toxic

Defining Factors Alter Response to Toxicants

5. Vehicle

- Nonpolar and lipid-soluble vehicles-increased toxicity by promoting absorption and membrane penetration

6. Protein binding

- Limitation of the bioavailability of the agent-reduced toxicity

7. Chemical-Drug Interaction

- Chemicals bind-inactivate-potentiate one another
- Microsomal enzyme alteration

Defining Factors Alter Response to Toxicants

8. Biotransformation

- Increased metabolic activity of microsomal mixed function oxidases (MFOs)- Phase I and phase II metabolism- bioactivated compounds (more toxic), biodegraded compounds (less toxic)

9. Liver disease

- Reduced synthesis of glutathione, metallothioneine, and coagulation factors may alter response to acetaminophen, cadmium, and anticoagulant rodenticides,respectively.

Defining Factors Alter Response to Toxicants

10. Nutrition-Diet

- calcium and zinc, may affect absorption and response to lead.
- Vitamin C and vitamin E can aid in scavenging of free radicals and repair of cellular protective mechanisms

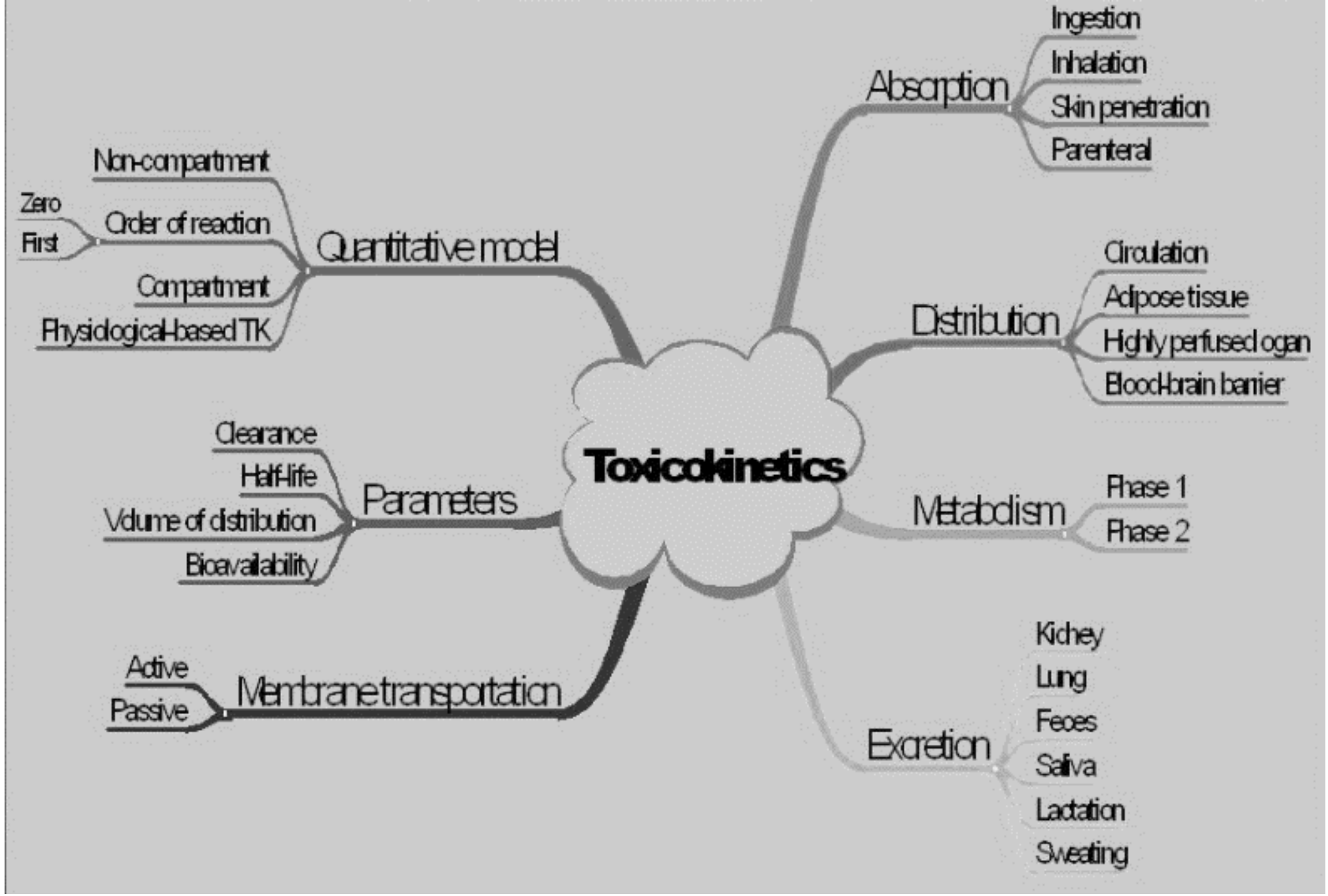
Processes

- 1. Absorption — the substance enters the body.
- 2. Distribution — the substance moves from the site of entry to other areas of the body.
- 3. Biotransformation — the body changes (transforms) the substance into new chemicals (metabolites).
- 4. Excretion — the substance or its metabolites leave the body.

1 ppm	1 mg/kg or 1 mg/L
1 ppm	1 μg/g or 1 μg/mL
1 ppm	0.0001%
1 ppm	1000 ppb
1 ppm	1,000,000 ppt
1 ppb	0.000001%
1 ppb	1 ng/g
1 ppb	1 μg/kg
1%	10,000 ppm
(Convert % to ppm by moving decimal point 4 places to the right)	
1 mg/dL	10 ppm or 10 mg/L
1 ounce	28.35 g
1 pound	453.6 g
1 kg	2.205 lbs
1 liter	0.908 quarts
1 gallon	3.785 liters
1 teaspoon	5 milliliters
1 tablespoon	15 milliliters
1 cup	8 ounces or 227 milliliters
1 quart	32 ounces or 946 milliliters

Comparison of Body Weight to Surface Area for Animals of Representative Sizes

Body Weight (kg)	Body Surface (m^2)
0.5	0.06
1.0	0.10
5.0	0.29
10.0	0.46
20.0	0.74
40.0	1.17


Toxicokinetics
Absorption
Ingestion
Inhalation
Skin penetration
Parenteral
Distribution
Circulation
Adipose tissue
Highly perfused organ
Blood-brain barrier
Metabolism
Phase 1
Phase 2
Excretion
Kidney
Lung
Feces
Saliva
Lactation
Sweating
Quantitative model
Non-compartment
Order of reaction
Zero
First
Compartment
Physiological-based TK
Parameters
Clearance
Half-life
Volume of distribution
Bioavailability
Membrane transportation
Active
Passive

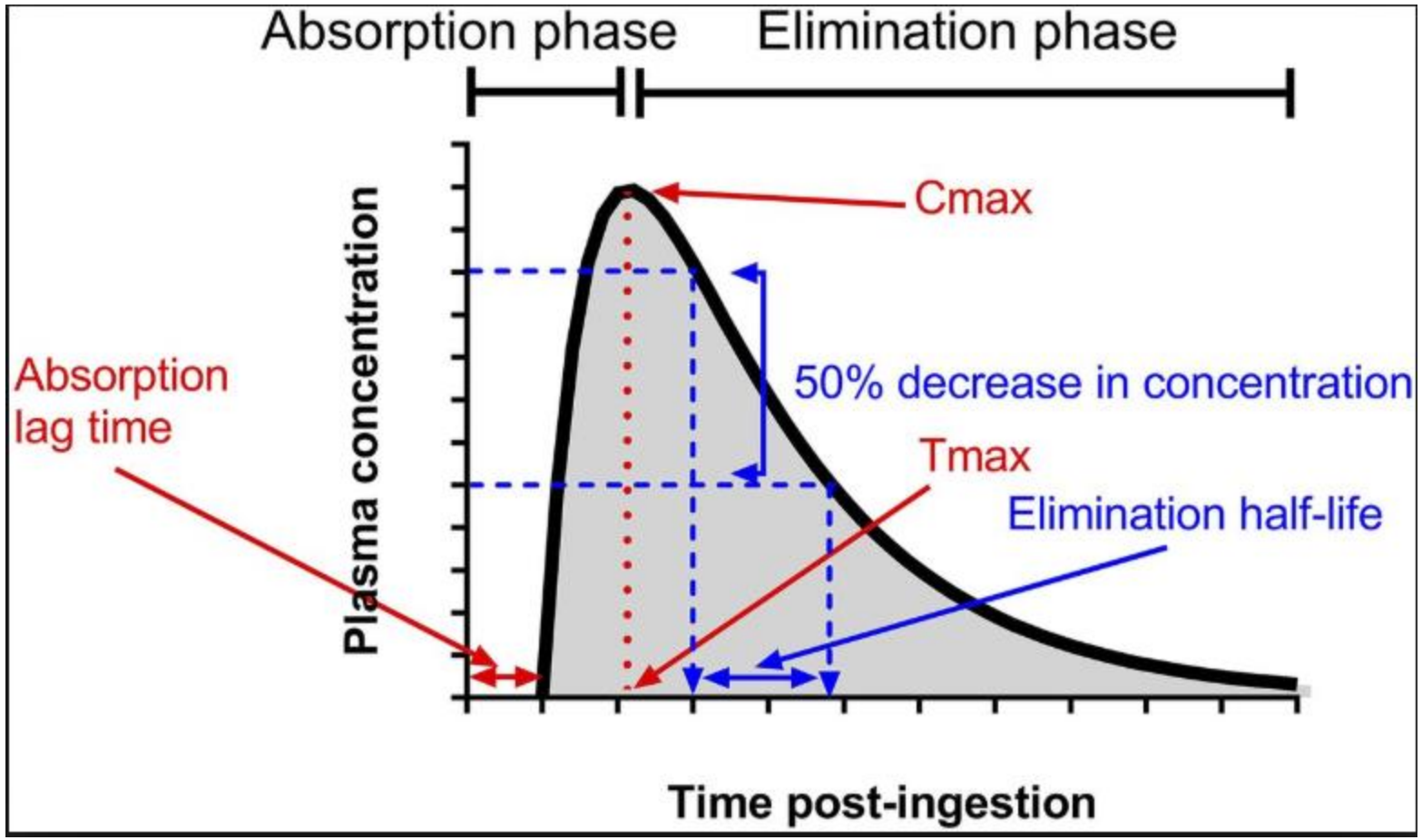

Absorption phase
Elimination phase
Cmax
Absorption
lag time
50% decrease in concentration
Tmax
Elimination half-life
Plasma concentration
Time post-ingestion

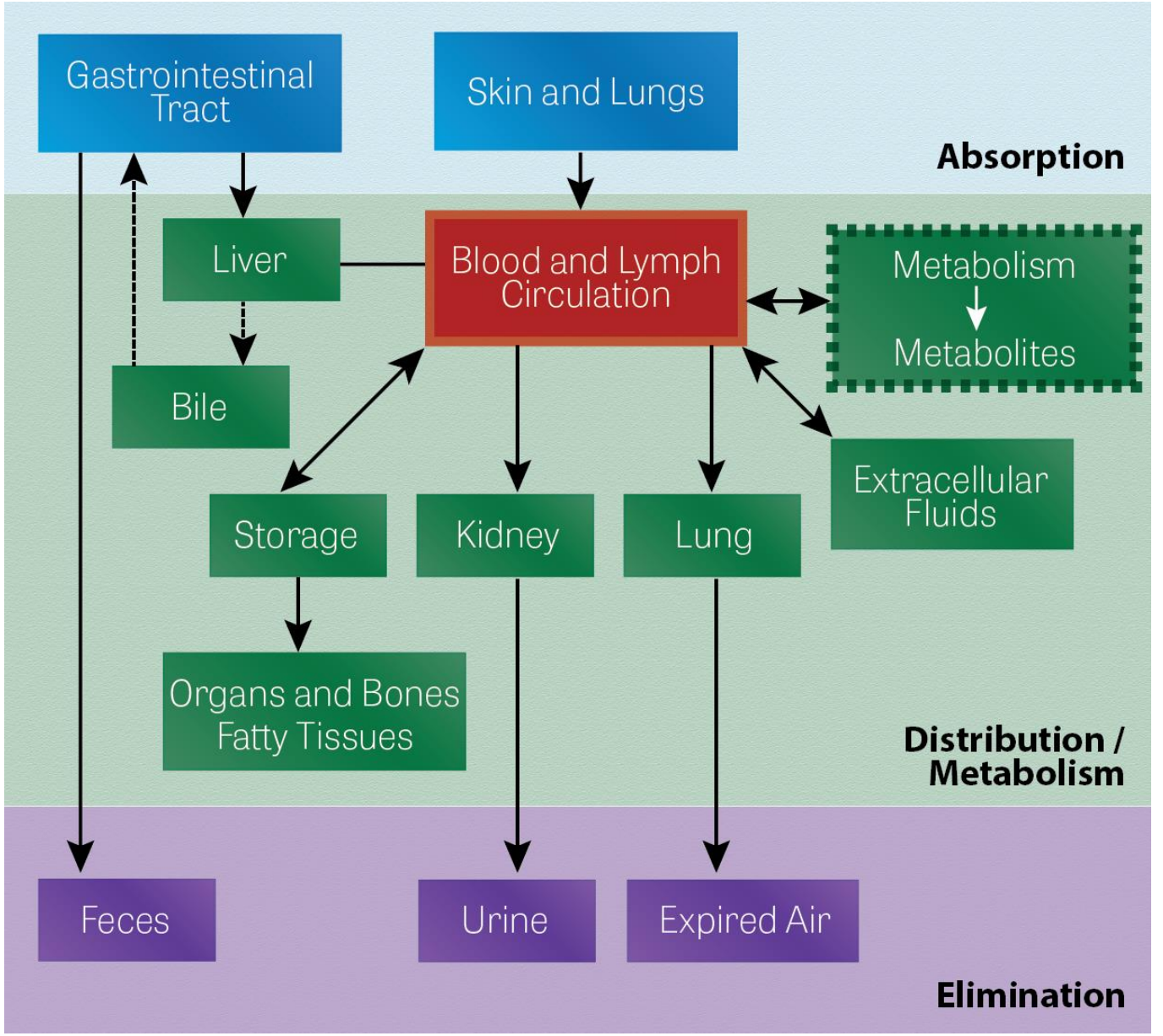
TABLE 1.2 Common Terms Used to Describe the ADME Characteristics of Chemicals

Term	Abbreviation	Definition
Concentration	C_p	Concentration of a chemical in plasma (p) at a specific time (t)
Time	t	Chronological measurement of a biological function
Half-life	$t_{1/2}$	Time required for exactly 50% of a drug to undergo some defined function (i.e., absorbed, distributed, metabolized, or excreted)
Volume of distribution	V_d	Unitless proportionality constant that relates plasma concentration of a chemical to the total amount of that chemical in the body at any time after some pseudo equilibrium has been attained
Volume of distribution (steady state)	$V_{d(ss)}$	Same as V, except measured when the chemical has reached a steady state in the body
Area under the curve	AUC	Total area under the plasma chemical concentration curve from $t = 0$ to $t = \infty$ after the animal receives one dose of the chemical
Body clearance of a chemical	Cl_B	The sum of all types of clearance from the body
Renal clearance of a chemical	Cl_R	Volume of chemical that is completely cleared by the kidneys per unit of time (ml/min/kg)
Nonrenal clearance of a chemical	Cl_{NR}	Volume of chemical that is completely cleared by organs other than the kidneys per unit of time (ml/min/kg)
Dose	D	The amount of chemical that is administered to an animal; can be further defined as the total dose, that total dose the animal was exposed to, or the absorbed (effective) dose, that being the fraction of the total dose that was actually absorbed by the animal
Bioavailability	F	Also known as systemic availability of a chemical. The quantity of percentage portion of the total chemical that was absorbed and available to be processed (CME) by the animal, in the case of intravenous administration, $F = 100\%$

ADME: absorption, distribution, metabolism and excretion; CME: chemical metabolism and excretion.
Adapted from Spoo, W. (2004). Toxicokinetics. In: Plumlee, K.H. (Ed.), Clinical Veterinary Toxicology. Elsevier, pp. 8–12 (Spoo, 2004).

ADME

- Substance- Absorbed- Distributed through the blood, lymph circulation, and extracellular fluids into organs or other storage sites-Metabolized- substance or its metabolites are eliminated through the body's waste products.



Absorption

- Route of exposure
- Physicochemical properties
  - Molecular size
  - Relative lipid/water solubility
  - Magnitude of molecule’s association constant
  - Weak acid-base

Absorption

Routes of exposure

- For toxiocology, common routes: oral (GI), dermal (percutaneous), inhalation (pulmonary)
- Also iatrogenic- subcutaneously, intramuscularly, intraperitoneally, or even intravenously

Absorption
Bioavailability (F)

- Fraction of the total dose of a toxicant absorbed by an animal.
- Intravenous exposures, F= 100% since the entire dose of the toxicant reaches the peripheral circulation.
- Inhatalation exposure, Equilibrium concentrations of the toxicant dissolved in the blood and the gaseous phase of the toxicant in the alveolar (blood-to-gas partition coefficient) in respiratory tract
  - size of aerosolized particles - nasopharyngeal region (particles >5 µm) or within the alveoli of the lungs (<1 µm).

Absorption

Percutaneous absorption

- The stratum corneum & associated keratinized structures
- Skin in different anatomical locations.
- Dependent on the vehicle in which a toxicant is dissolved
- >>> greater for lipid soluble compounds as compared with chemicals that are highly soluble in water

Absorption

Gastrointestinal

- Acidic degradation in the stomach
- Enzymatic breakdown in the small intestine.
- Decreased GI transit time
- Resemblance essential minerals such as calcium and zinc for lead&cadmium tox- regulate GI uptake

Absorption

Hepatic biotransformation

- Influence- bioavailability

- First pass effect/Presystemic elimination: Oral exposure- absorption- GI tract-hepatic portal circulation-liver- hepatic degradation- prevents access of the compound to the systemic circulation - decreased bioavailability

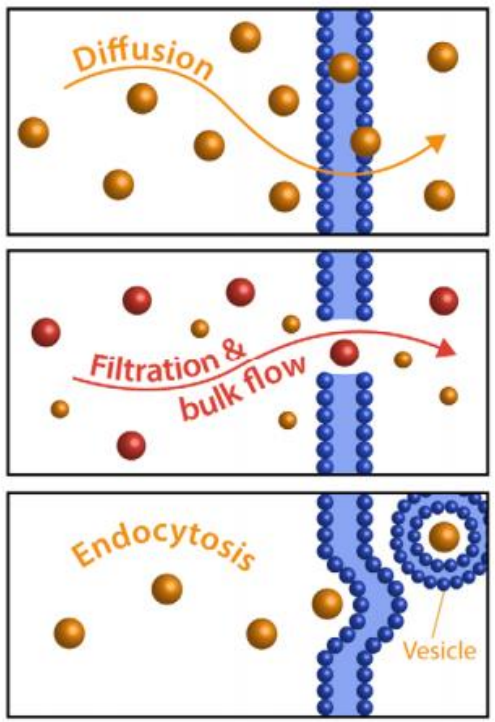
- Enterohepatic recirculation: Bioavailability enhanced - biliary excretion- subsequent reuptake from the intestines referred to as “.

Mechanisms of absorption

- energy-independent (“passive” transport) – Simple diffusion or filtration
- require the expenditure of energy through “specialized” or “active” transport systems.

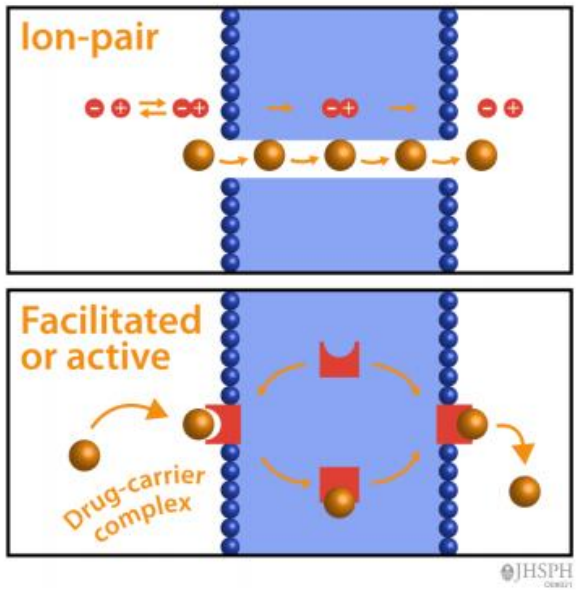
Factors affecting membrane transport of chemicals:

- Molecular weight/shape
- Charge
- Lipid solubility
- Membrane composition
- Membrane thickness



Non-electrolytes and un-ionized form of weak acids and weak bases

Molecules of varying sizes



- Simple diffusion
- Facilitated diffusion
- Active transport
- Pinocytosis/receptor-mediated uptake
- Filtration

ocw.jhsph.edu/courses/publichealthtoxicology/PDFs/Lecture1_Trush.pdf

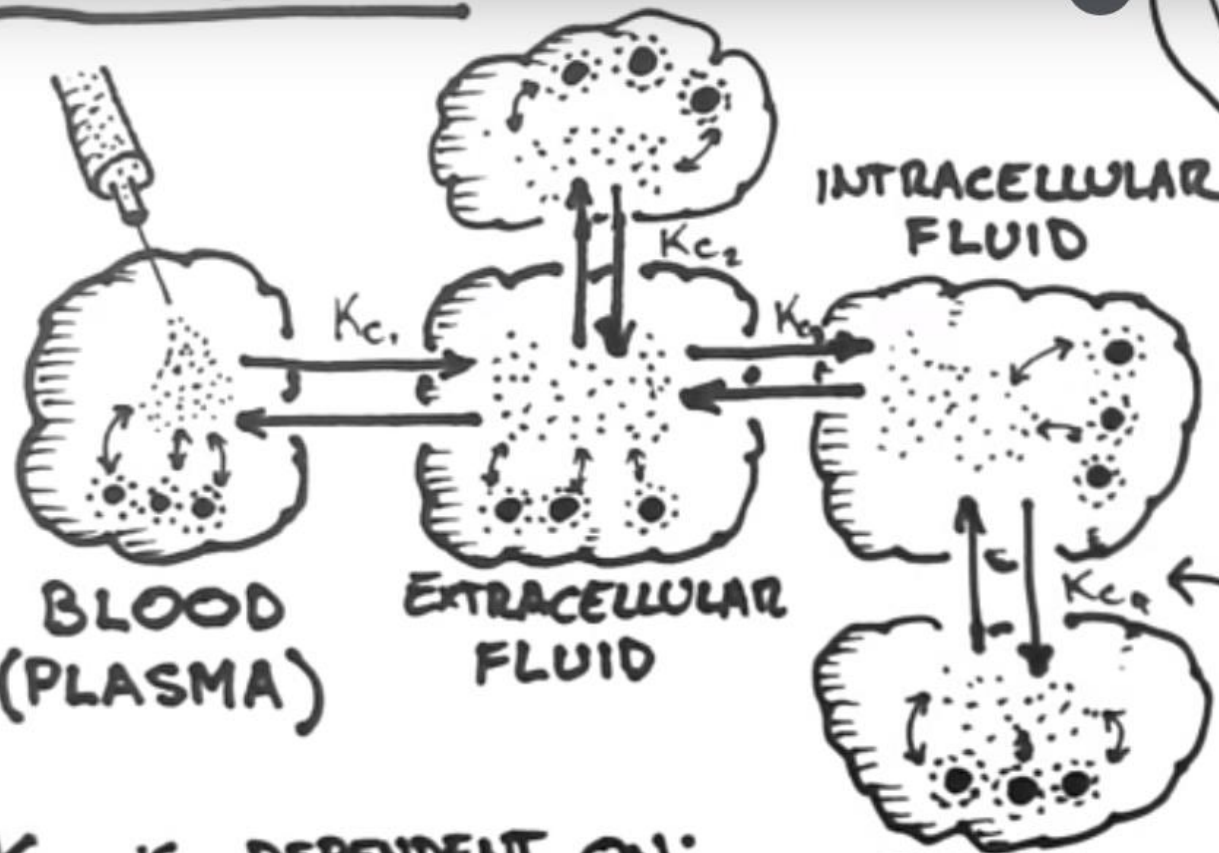
Distribution

- translocation of a xenobiotic from the site of absorption to various body organs and tissues
  - involves both transport of the chemical within the circulation
  - cellular uptake of the xenobiotic

- The “volume of distribution” (V_d)= the quotient of the total amount of that chemical in the body divided by the concentration of the xenobiotic within the blood
  - describe the extent to which a xenobiotic is distributed within the body

DISTRIBUTION

FAT



EQUILIBRIUM CONSTANT

VOLUME OF DISTRIBUTION (V_D)

$$V_D = \frac{\text{TOTAL AMOUNT OF DRUG IN BODY}}{\text{CONC. OF DRUG IN PLASMA}}$$

E.G. V_D MORPHINE = 5 L/kg BW.

Plasma [ ] = $^3/_{70}$ mg / L

DOSE = V_D x Plasma [ ]

= 5 L/kg BW x $^3/_{70}$ mg / L

= $^{15}/_{70}$ mg / kg BW

∴ 70kg person

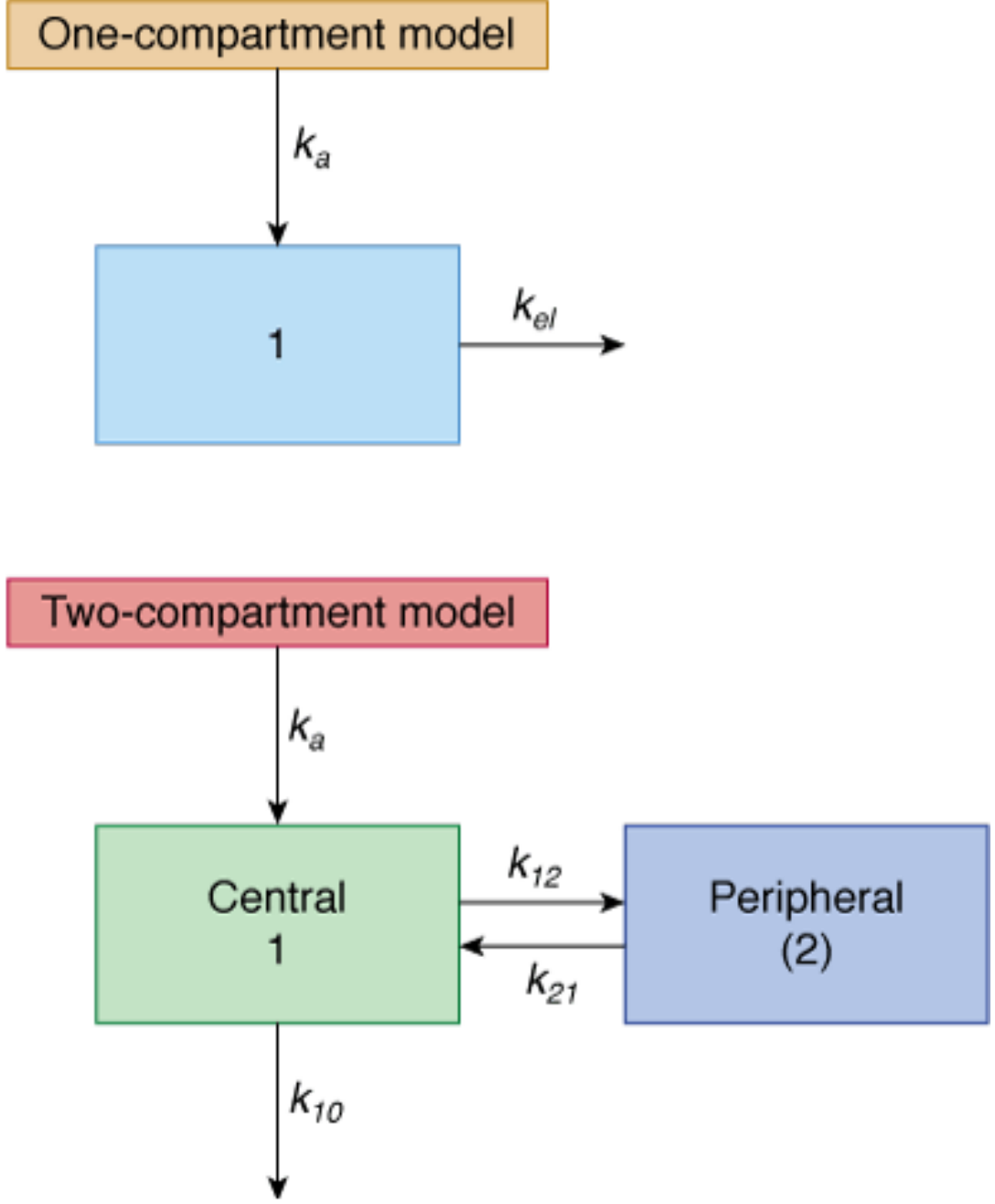
Need Dose = 15mg

K_C IS DEPENDENT ON:

- PERMIABILITY OF BARRIERS
- pH OF COMPARTMENTS
- BINDING CAPACITY

OTHER

- CSF
- PERITONEUM
- SYNOVIAL FLUID
- FETUS



Source: Klaassen CD, Watkins JB: *Casarett & Doull's Essentials of Toxicology, 2nd Edition:* http://www.accesspharmacy.com

Distribution

After entry into the body, the chemical will be distributed to different tissues and organs, depending on where it entered the body and on its chemical properties. For example, a substance entering through the skin, can be taken up by the lymphatic system and first reach lymph nodes before any other organs following the skin, while a substance entering through the lungs will directly come into the blood stream and reach the heart as the first organ following the lungs. Substances absorbed by the gut will directly reach the blood stream and pass the liver as the first organ following the gut. As another example, substances that are very hydrophobic will eventually accumulate in the body fat, in contrast to hydrophilic substances. Such substances, accumulated in fat tissues, can be released in relatively large amounts when the fat is digested, e.g. during a diet or during a breast-feeding period. Babies can then become exposed to lipophilic substances through their mothers' milk.

Distribution depends

- the binding of the substance to plasma proteins
- the partition between blood and specific tissues
- the permeability of the substance to cross specialized membranes, so-called barriers (e.g. blood–brain barrier/BBB, blood–placental barrier/BPB, blood–testis barrier/BTB)

Xenobiotic storage depots

- Plasma proteins- salicylates, barbiturates, cardiac glycosides, steroid hormones, vitamins, and various essential minerals
  - Dependent to bound-unbound ratio
- Liver and kidneys- cadmium
- Fat- Persistent organic pollutants
- Bone-Minerals

Tissue barriers

- Blood-brain barrier
- Blood-testes barrier
- Blood-placenta barrier

Metabolism/Biotransformation

- Metabolism-refer to the fate or disposition of a xenobiotic
- Biotransformation- general term referring to the metabolic conversion of both endogenous and xenobiotic chemicals into more water-soluble forms
- Several organs within the body have biotransformation capabilities, most xenobiotics are biotransformed in the liver
  - Xenobiotics are usually biotransformed in two phases (I and II), which involve enzymes having broad substrate specificity

Results of Biotransformation

- Biodegredation- Toxicant inactivation - inactive or less active (Propranolol,Pentobarbitone,Morphine, Chloramphenicol,Paracetamol,Ibuprofen, lignocaine
- Bioactivation-
  - Active toxicant to active metabolite- active metabolite Effect is due to parent drug and its active metabolite

Phenacetin	-	Paracetamol
Phenyl butazone	-	Oxyphenbutazone
Primidone	-	Phenobarbitone
Diazepam	-	Desmethyl diazepam
Digitoxin	-	Digoxin
Imipramine	-	Desipramine
Amitriptyline	-	Nortriptyline
Procainamide	-	N Acetyl procainamide
Codeine	-	Morphine
Spironolactone	-	Canrenone
Allopurinol	-	Alloxanthine
Cefotaxime	-	Des acetyl cefotaxime
Morphine	-	Morphine 6 glucuronide

- Bioactivation-cont’ed
  - Inactive drug (prodrug)-active drug

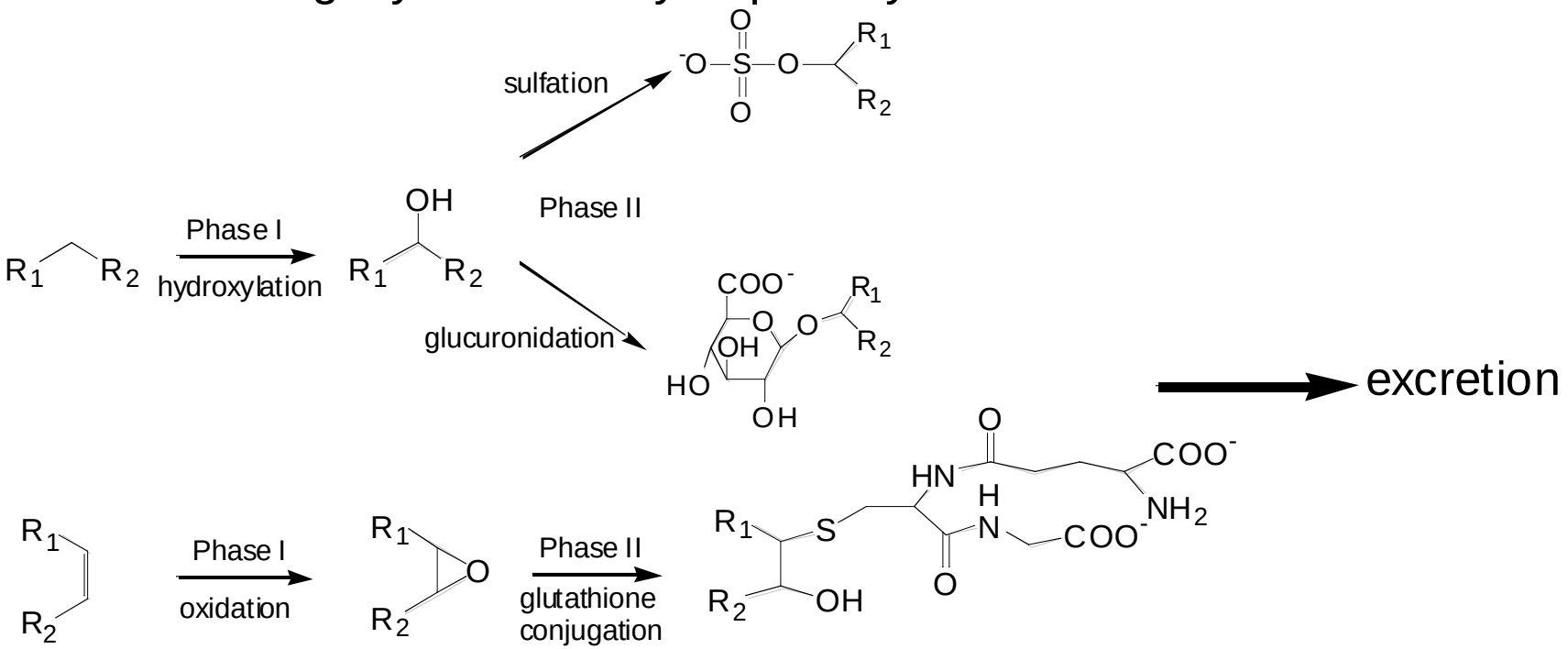
Levodopa	-	Dopamine
Enalapril	-	Enalaprilat
αMethyl dopa	-	αMethyl Norepinephrine
Dipivefrine	-	Epinephrine

Proguanil	-	Proguanil triazine
Prednisone	-	Prednisolone
Bacampicillin	-	Ampicillin
Sulfasalazine	-	5amino salicylic acid
Cyclophosphamide	-	Aldophosphamide
Mercaptopurine	-	Methyl Mercaptopurine
Prontosil	-	Sulfanilamide
Acyclovir	-	Acyclovir triphosphate

Phase I and Phase II Biotransformation

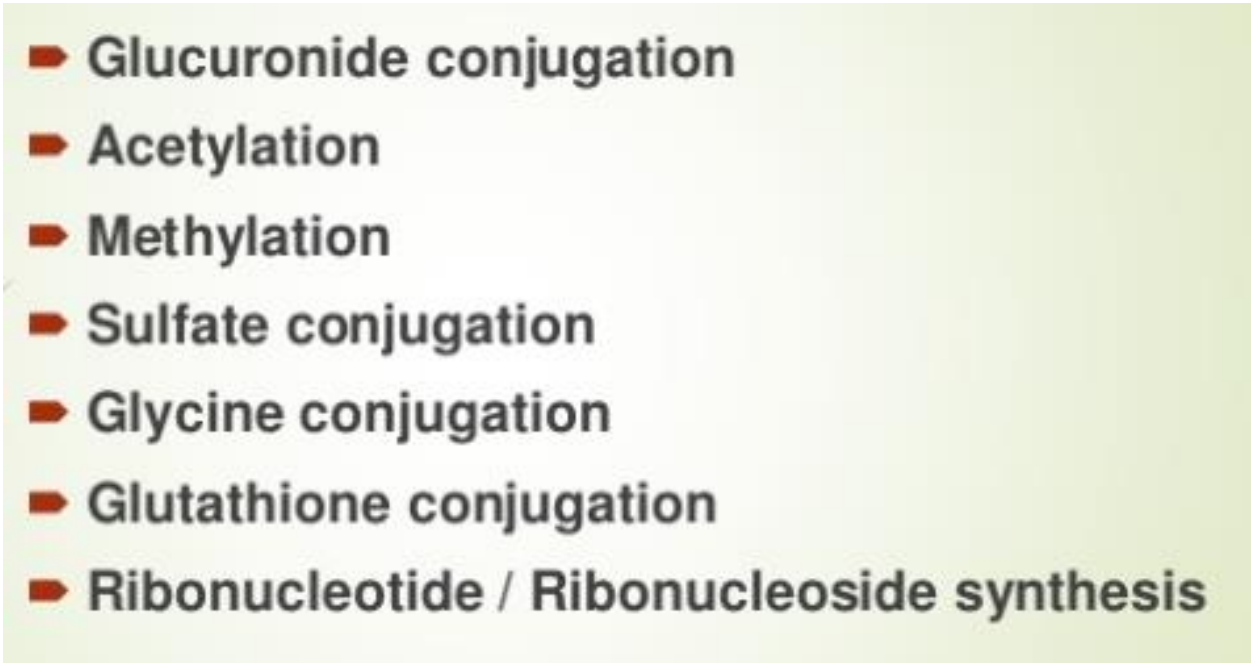
Reactions catalyzed by xenobiotic biotransforming enzymes are generally divided into two groups: Phase I and phase II.

1. Phase I reactions involve hydrolysis, reduction and oxidation, exposing or introducing a functional group (-OH, -NH_2, -SH or –COOH) to increase reactivity and slightly increase hydrophilicity.



- Oxidation
- Reduction
- Hydrolysis
- Cyclization
- Decyclization

- 2. Phase II reactions -increase hydrophilicity.



CYPs catalyze several types of oxidation reactions including:

Hydroxylation of an aliphatic or aromatic carbon

Epoxidation of a double bond

Heteroatom (S-, N-, and I-) oxygenation and *N*-hydroxylation

Oxidation/reduction

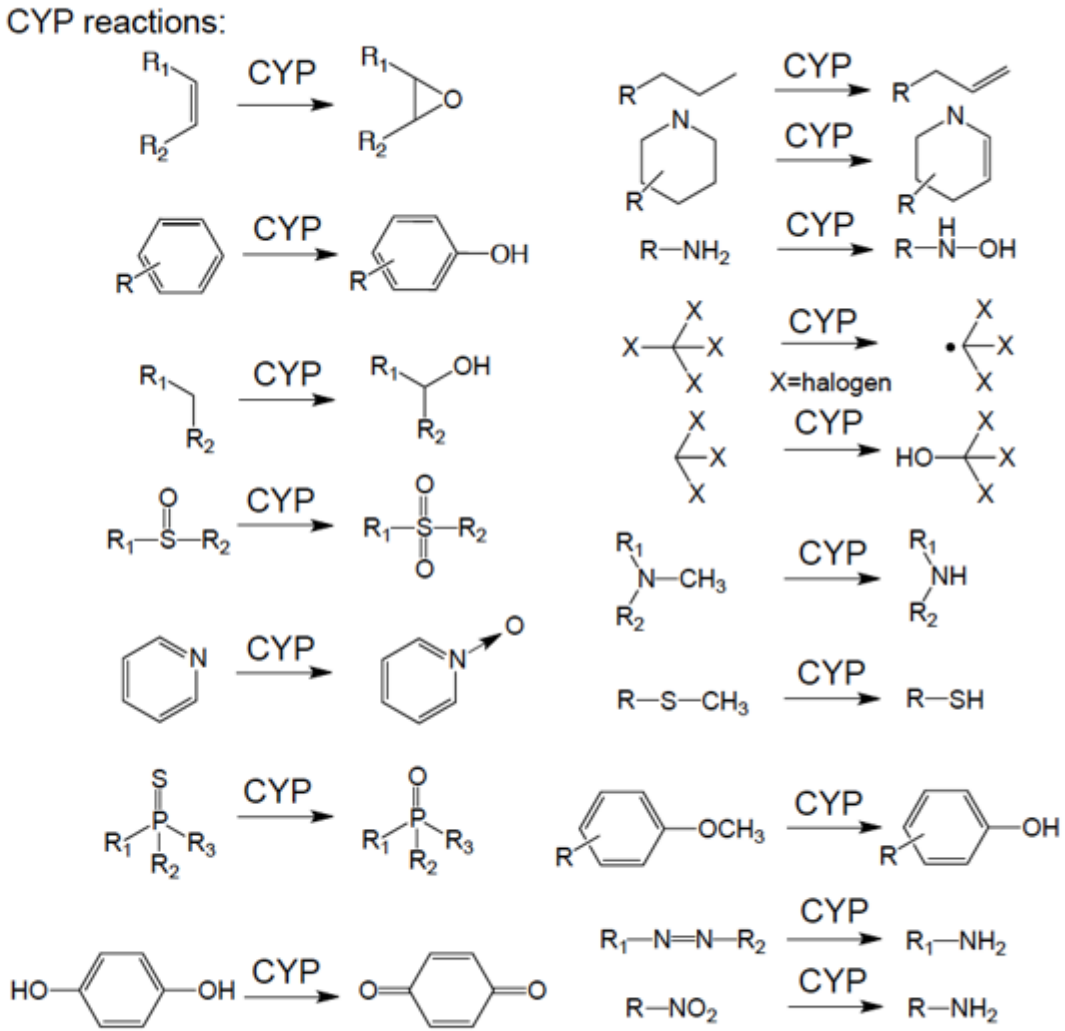
Reductive dehalogenation

Oxidative dehalogenation

Cleavage of esters

Dehydrogenation

dealkylation



Microsomal Enzyme Induction

- Drug-drug interaction
- Increased toxicity

CYP450

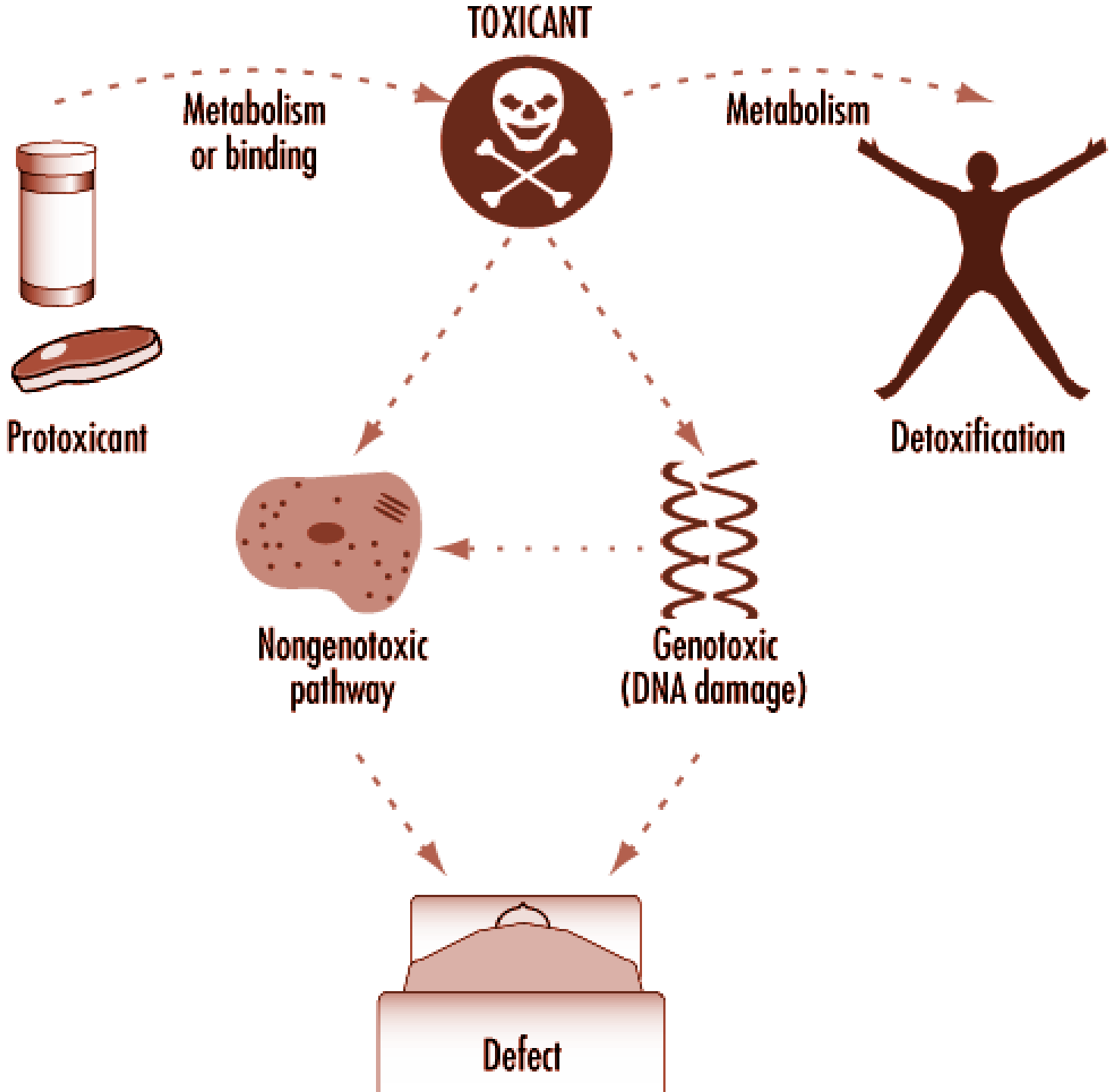
- CYP activation/inhibition routes for management of toxicoses
- Toxicogenetics
- CYPs in veterinary medicine

Toxicokinetic aspects of xenobiotic elimination

- Clearance
- Compartmental models (One-compartment/muticompartment)
- First order/zero orde rkinetics
- Half life

Excretion

- removal through the faeces (including bile), urine, breath, and to a lesser extent via sweat, hair nails, milk, placenta or eggs.
- The route and extent of excretion of a substance depends on its physical and chemical properties.
- Volatile compounds - quickly leave the body via exhalation.
- Hydrophilic substances - remain dissolved in the urine and hardly be reabsorbed in the kidney tubules.
- Larger (typically >350 Da in rats and > 450-500 Da in humans, substances are mainly excreted via the bile into the intestines and are subsequently excreted via faeces or re-absorbed into the body (enterohepatic cycle)


TOXICANT
Metabolism or binding
Metabolism
Protoxicant
Detoxification
Nongenotoxic pathway
Genotoxic (DNA damage)
Defect