MUNI
PHARM

TOXICOKINETICS

Assoc. Prof. PharmDr. Peter Kollár, Ph.D.
Department of Pharmacology and Toxicology
Faculty of Pharmacy MU

Paracelsus (1493 – 1541)

– *„All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy.“*

There are not harmless substances, only a harmless ways of their using.

MUNI PHARM

Toxicokinetics

- Mathematical modeling of the temporal changes in concentration of xenobiotics that occurs during deposition, absorption, distribution, metabolism, and excretion

MUNI
PHARM

Toxicokinetics

- helps to predict the highest concentrations of xenobiotics, which may occur in organism

- helps to predict the time when the concentration of xenobiotics in the organism is close to Ø

MUNI
PHARM

Toxicokinetic methods

- 2 approaches:
  - *Compartment model*
    does not consider anatomy or physiology
  - *Use physiological based toxicokinetic modeling*
    considers physiology and rate limiting biotransformation pathways

MUNI
PHARM

Mathematical Modeling
Classical Method

- Plot concentration in blood or tissue with time

  - Rate of xenobiotic disappearance is *proportional* to the concentration of xenobiotic in blood or tissue

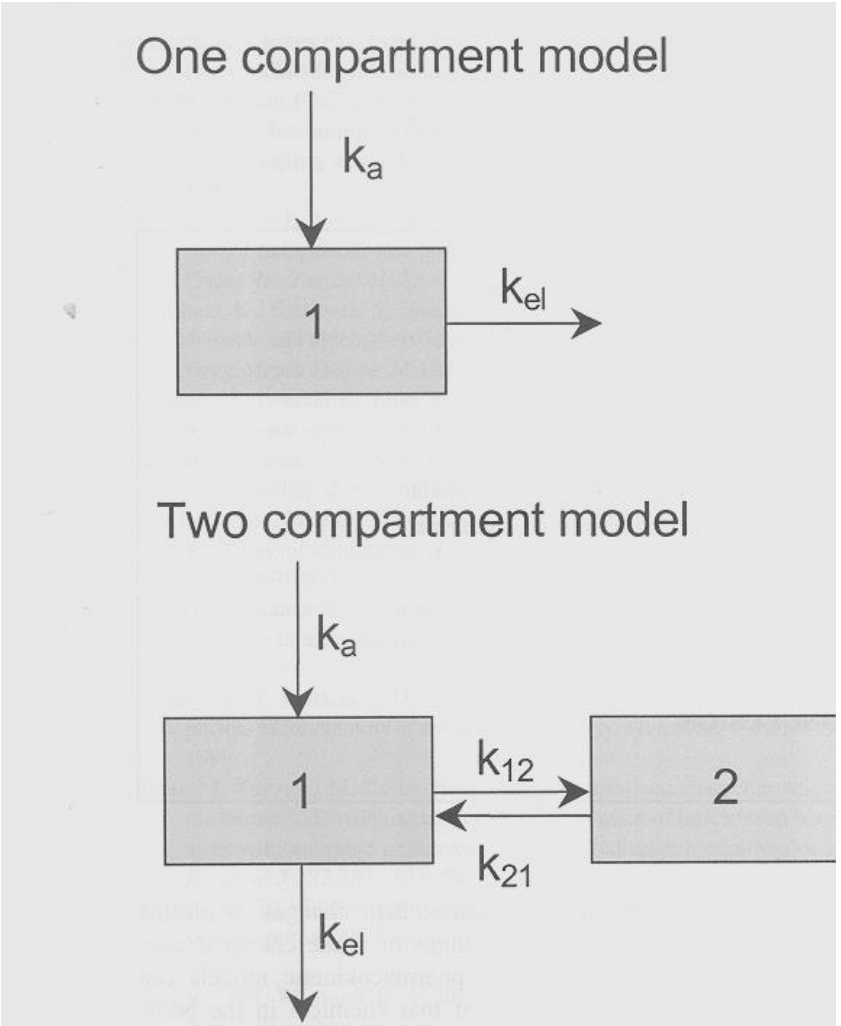
    1st order kinetics

  - Rate of xenobiotic disappearance is *independent* of the concentration of xenobiotic in blood or tissue

    Ø order kinetics

MUNI PHARM

1 and 2 compartment models



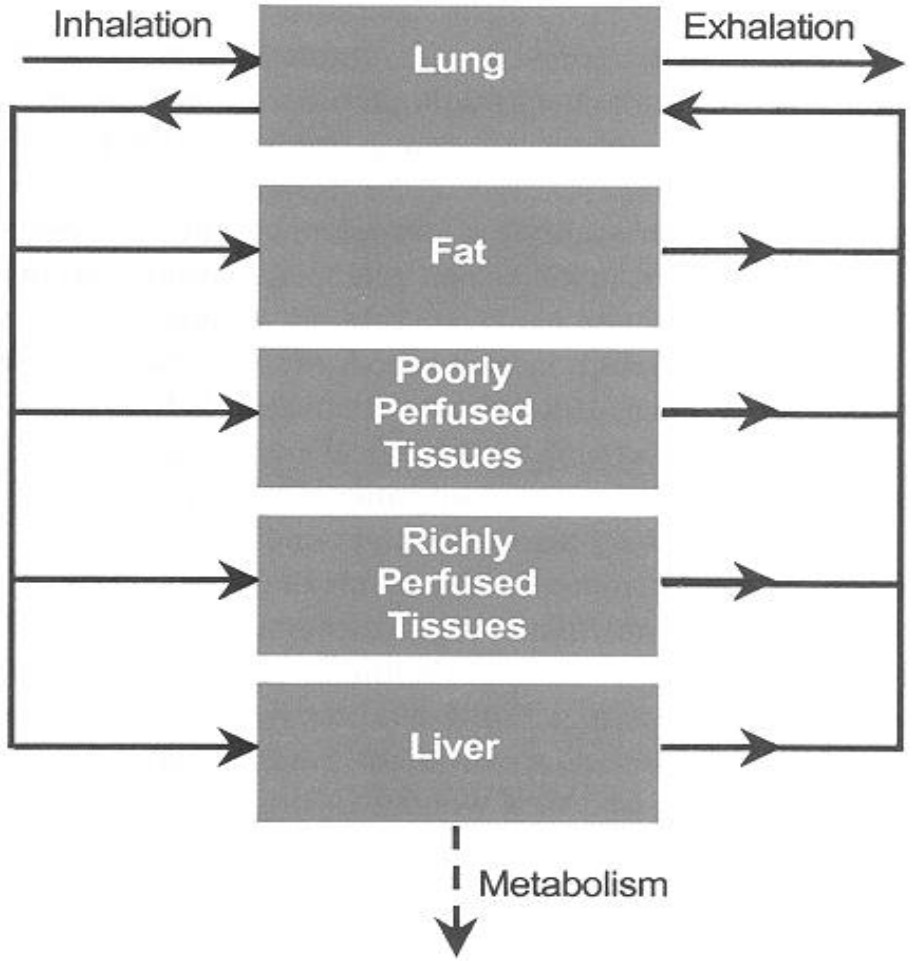
MUNI PHARM

Physiology-based toxicokinetics

- Rate constants for movement of xenobiotic(s) between the various compartments have been measured
- Model structure has been derived and tested

MUNI
PHARM

Example of physiology-based model for inhaled volatile substance



MUNI PHARM

Physiology-based toxicokinetics

- Use rate limiting elimination steps in the model

- Applications are species specific

MUNI
PHARM

Physiology influences toxicity

– eg.: cycasin – naturally occuring alkaloid (methylazoxymethanol glycoside)

Cycas revoluta

– Bacterial hydrolysis converts cycasin into the strong carcinogen (methylazoxymethanol)

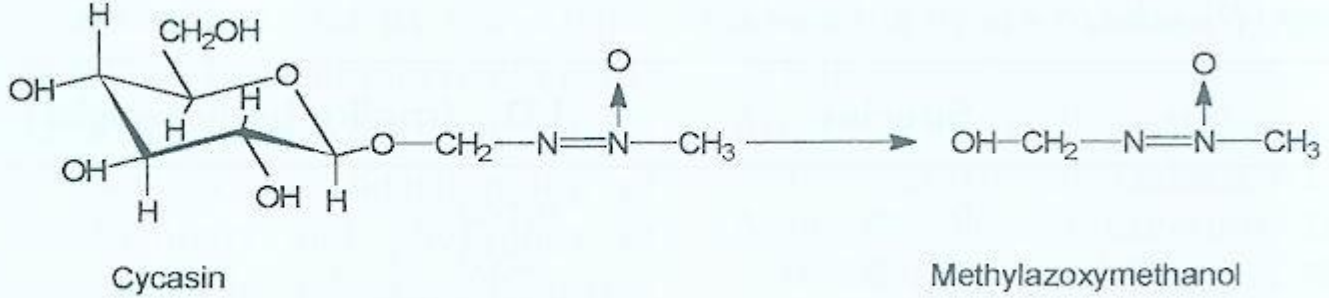


FIGURE 1.1 *Bacterial hydrolysis of cycasin.*

MUNI PHARM

1. Relationship between the substance, dose and toxic effect

- Absolute toxic value for substances does not exist, however, some compounds have much higher relative toxicity than others

MUNI PHARM

TABLE 1.1 *Acute LD_{50} values for a variety of chemical agents*

Agent	Species	LD_{50} (mg/kg body weight)
Ethanol	Mouse	10 000
Sodium chloride	Mouse	4000
Ferrous sulphate	Rat	1500
Morphine sulphate	Rat	900
Phenobarbital, sodium	Rat	150
DDT	Rat	100
Picrotoxin	Rat	5
Strychnine sulphate	Rat	2
Nicotine	Rat	1
d-Tubocurarine	Rat	0.5
Hemicholinium-3	Rat	0.2
Tetrodotoxin	Rat	0.1
Dioxin (TCDD)	Guinea-pig	0.001
Botulinum toxin	Rat	0.00001

Data from Loomis, T. A. (1974) *Essentials of Toxicology* (Philadelphia: Lea & Febiger).

MUNI PHARM

- Toxicity of substances is based on the dose-response relationship

- From the dose-response curve values could be derived:

  ED_{50}, TD_{50}, LD_{50}

  and

  therapeutic index (TI):

  $TI = TD_{50} / ED_{50}$

  or

  $TI = LD_{50} / ED_{50}$

MUNI PHARM

– The route of toxic substance entry into the body affects final toxicity

TABLE 2.1 *Effect of route of administration on the toxicity of various compounds*

	Pentobarbital[1]		Isoniazid[1]		Procaine[1]		DFP[2]	
Route of administration	**LD_{50} (mg/kg)**	**Ratio to i.v.**	**LD_{50} (mg/kg)**	**Ratio to i.v.**	**LD_{50} (mg/kg)**	**Ratio to i.v.**	**LD_{50} (mg/kg)**	**Ratio to i.v.**
Oral	280	3.5	142	0.9	500	11	4.0	11.7
Subcutaneous	130	1.6	160	1.0	800	18	1.0	2.9
Intramuscular	124	1.5	140	0.9	630	14	0.85	2.5
Intraperitoneal	130	1.6	132	0.9	230	5	1.0	2.9
Intravenous	80	1.0	153	1.0	45	1	0.34	1.0

[1]Mouse toxicity data.
[2]Rabbit toxicity data on di-isopropylfluorophosphate.
Data from Loomis, T. A. (1968) *Essentials of Toxicology* (Philadelphia: Lea & Febiger).

MUNI PHARM

- Toxic effect could be as follows:
  - Immediate or delayed
  - Direct or indirect
  - Local or systemic
  - Reversible or non-reversible

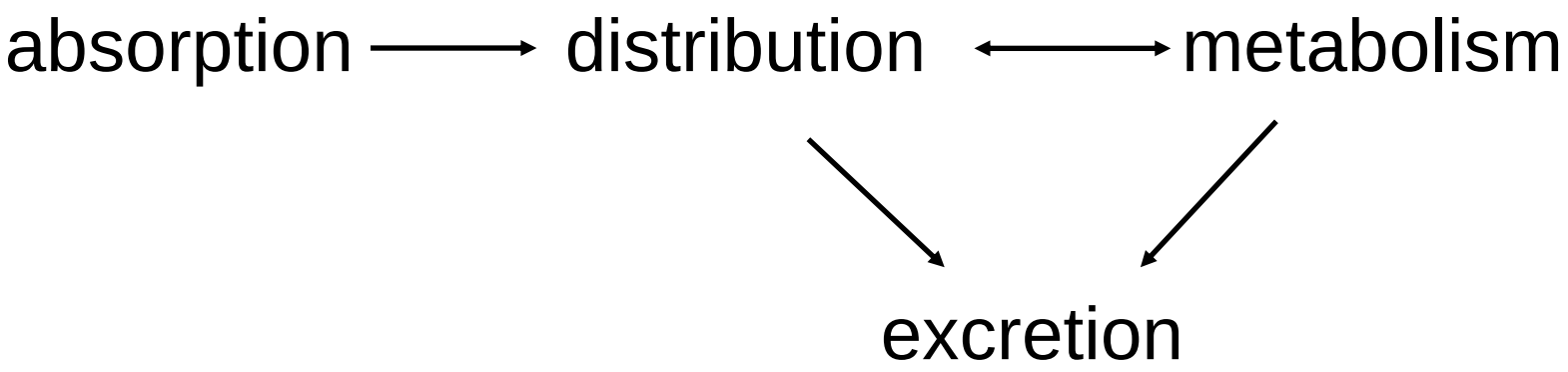
- Mixture of toxic compounds could lead to:
  - Toxic eff. equals the sum of individual components (addition)
  - Toxic effect higher than the sum (potentiation, synergy)
  - Different from the individual components of the mixture

- Repeated exposure to toxic substance can reduce the toxic effect (tolerance)

MUNI
PHARM

2. Factors influencing the toxic response

– appear on the level of:



MUNI
PHARM

Absorption

- is essential for the induction of systemic toxic effects of substances

- depends on:
  - phys.-chem. characteristics of compound (size, structure, solubility, polarity)
  - way of transport (diffusion, endocytosis, active / passive)
  - absorption site (skin, GIT, lungs)

MUNI
PHARM

Skin

- Large surface area
- Weak blood flow
- hardly permeable

MUNI
PHARM

TABLE 3.2 *Physicochemical properties of various pesticides and their oral absorption and skin penetration in mice*

Compound	Partition coefficient	Water solubility (ppm)	Penetration Half-life		% Penetrated	
			Skin	Oral	Skin	Oral
DDT	1775	0.001	105	62	34	55
Parathion	1738	24	66	33	32	57
Chlorpyrifos	1044	2	20	78	69	47
Permethrin	360	0.07	6	178	80	39
Nicotine	0.02	Miscible	18	23	71	83

Data of Shah *et al.* (1981) *Toxicol. Appl. Pharmacol.*, 59, 414 and Ahdaya *et al.* (1981) *Pestic. Biochem. Physiol.*, 16, 38 from Hodgson and Levi (1987) *A Textbook of Modern Toxicology* (New York: Elsevier).

MUNI PHARM

Gastrointestinal tract (GIT)

- Main site for absorption
- Good blood flow
- Large surface area
- Various pH
- Intestinal bacteria
- Various transport processes
- Effect of food

MUNI
PHARM

Lungs

- Huge surface area (50-100 m^2)
- Well supplied with blood
- Easily permeable

MUNI
PHARM

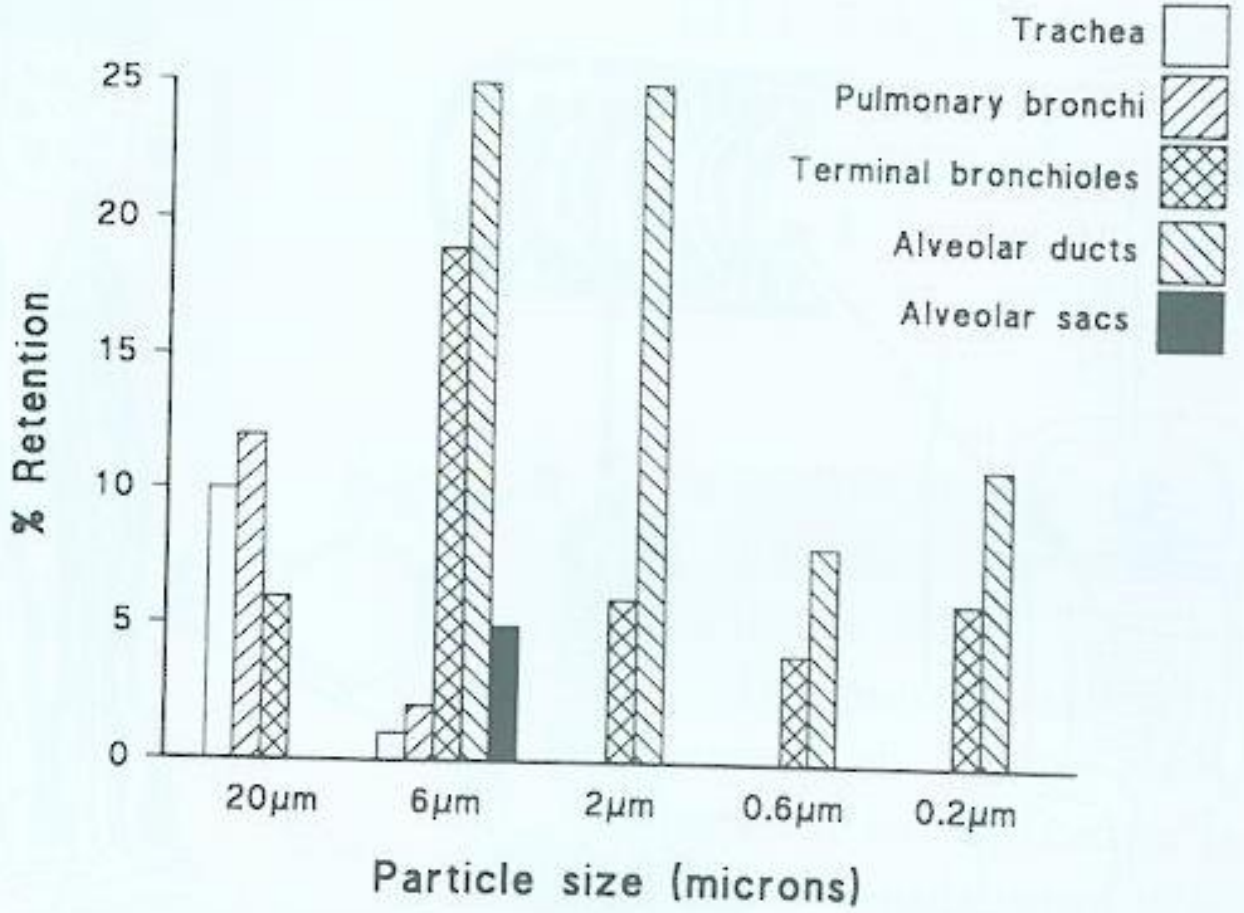


FIGURE 3.11 *The retention of inhaled particles in various regions of the human respiratory tract in relation to size. Data from Hatch and Gross,* Pulmonary Deposition and Retention of Inhaled Aerosols. *New York: Academic Press, 1964.*

MUNI PHARM

Distribution

- Limited by binding substance on the blood protein

  - bonds - ionic, hydrophobic, oxygen, Van der Waals (lipophilic DDT binds to the hydrophobic proteins - lipoproteins)

- Consequences:

  - saturation
  - competitive inhibition
  - displacement

MUNI PHARM

- **SATURATION** – at higher doses, limited number of specif. binding sites leads to saturation and subsequent release of toxic substances from binding ⇒ TOXIC THRESHOLD

- **DISPLACEMENT** – between 2 foreign substances
  – between foreign and endogenous substance
  ⇒ TOXIC EFFECT

Eg.: sulfisoxazol in preterm infants displace bilirubin from its binding to plasma proteins ⟶ toxic levels of bilirubin enter the brain

MUNI PHARM

Excretion

- Rapid excretion decreases the probability of toxic effects and duration of action

- It may goes through:
  - kidney (solid and non-volatile substances)
  - liver by bile (large polar and amphiphilic substances)
  - lungs by exspiration (volatile and gaseous substances)
  - secretion into GIT, milk, saliva, sweat, tears, semen

MUNI PHARM

TABLE 3.4 *Effect of molecular weight on the route of excretion of biphenyls by the rat*

Compound	Molecular weight	Percent of total excretion	
		Urine	Faeces
Biphenyl	154	80	20
4-Monochlorobiphenyl	188	50	50
4,4′-Dichlorobiphenyl	223	34	66
2,4,5,2′,5′-Pentachlorobiphenyl	326	11	89
2,3,6,2′,3′,6′-Hexachlorobiphenyl	361	1	99

Data from Matthews, H. B. (1980) In *Introduction to Biochemical Toxicology*, edited by E. Hodgson and F. E. Guthrie (New York: Elsevier-North Holland).

MUNI PHARM

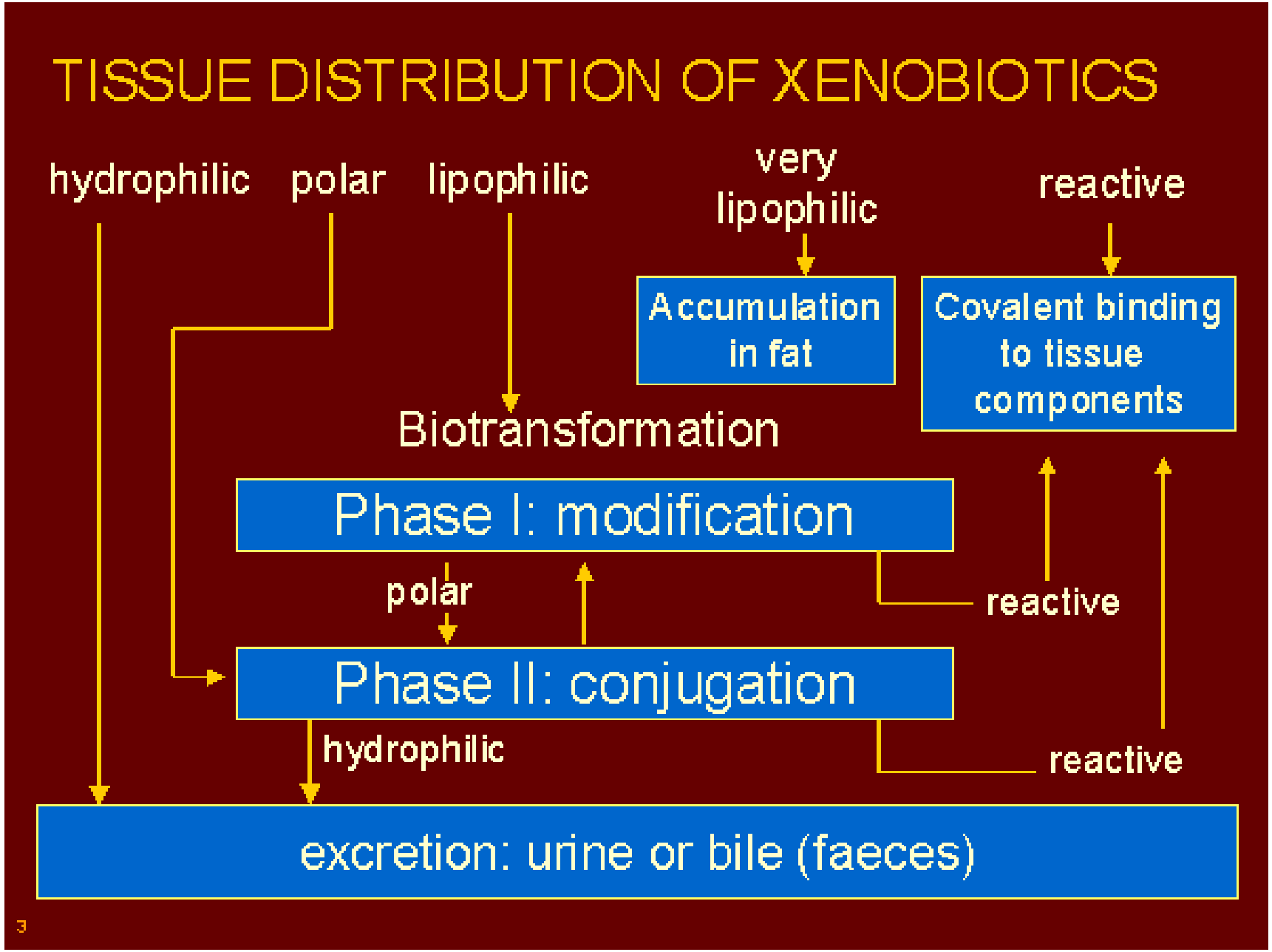
3. Factors influencing the toxic response: metabolism

- Biotransformation increases the polarity, size, and MW

   increased excretion

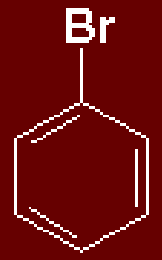
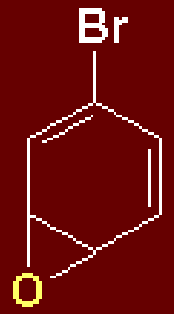
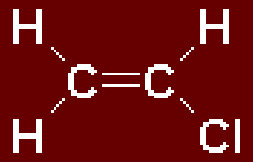
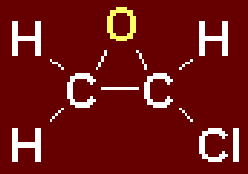
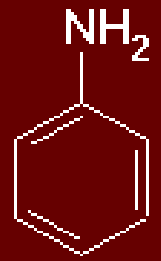
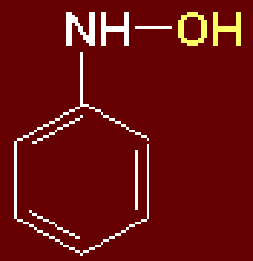
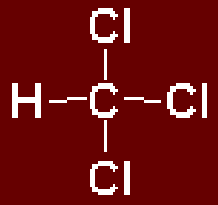
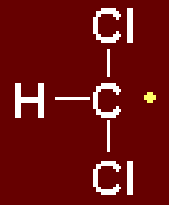
- Biotransformation may lead to toxic substances from less-or non-toxic compounds

MUNI PHARM


TISSUE DISTRIBUTION OF XENOBIOTICS
hydrophilic
polar
lipophilic
very lipophilic
reactive
Accumulation in fat
Covalent binding to tissue components
Biotransformation
Phase I: modification
polar
reactive
Phase II: conjugation
hydrophilic
reactive
excretion: urine or bile (faeces)
3

MUNI PHARM

PHASE I METABOLIC ACTIVATION

Compound	Reactive metabolite		Toxic effect
bromobenzene			Liver necrosis
vinylchloride			Liver cancer
aniline			Methemoglo-binemia
chloroform			Liver/kidney necrosis

MUNI PHARM

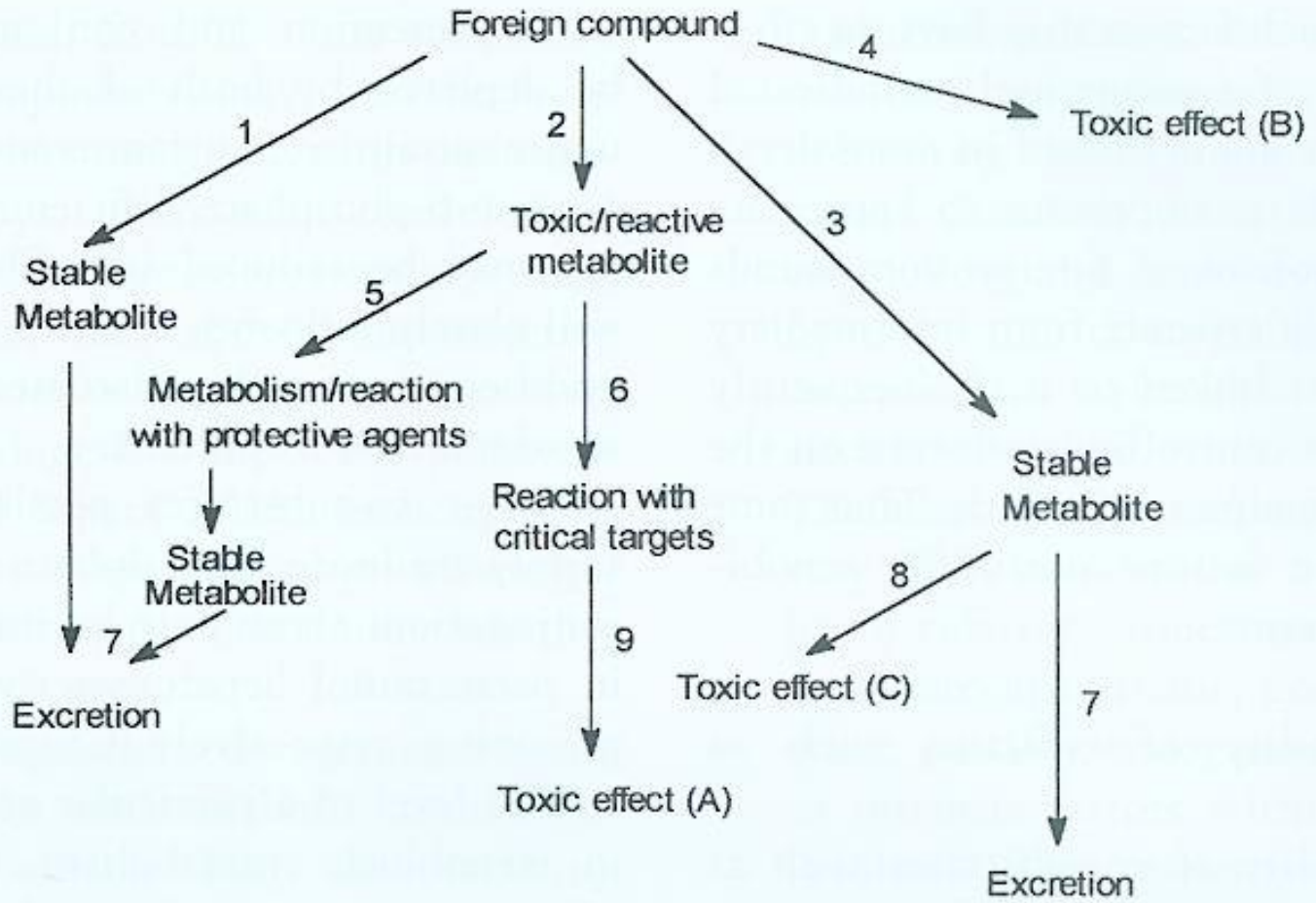


FIGURE 4.67 *The various possible consequences of metabolism of a foreign compound. The compound may undergo detoxication (1); metabolic activation (2); formation of a stable metabolite (3) which may cause a toxic effect (C) or (4) cause a direct toxic effect (B). The reactive metabolite may be detoxified (5/7) or (6/9) cause a toxic effect (A).*

MUNI
PHARM

4. Factors affecting the distribution and MTB of toxic substances

- **Physico-chemical factors**

  - lipophility
  - size
  - polarity pKa
  - chirality

(Eg.: benzopyrene – is metabolized to the *trans*-epoxide, which is more mutagenic than other enantiomers)

MUNI PHARM

Biological factors

- gender (parathion is 2x more toxic in F than in M)
- genetic factors (idiosyncrasies, polymorphisms)
- diet
- age (higher permeability of BBB in newborns – neurotoxicity of morphine, Pb)
- disease
- dose
- tissue specificity (uptake by organs such as thyroid gland or lungs – paraquat)
- enzymatic induction and inhibition

MUNI
PHARM

5. Reaction of organism to toxic substances

- Direct toxic reactions: tissue damage
- Pharmacological, physiological or biochemical effects
- Teratogenity
- Immunotoxicity
- Mutagenity
- Carcinogenity

Reaction could be as follows:

- *all-or-none* type (death, presence / absence of damage)
- graded (biochemical / physiological changes)

MUNI
PHARM

Same teratogen administered at different times has different toxicity

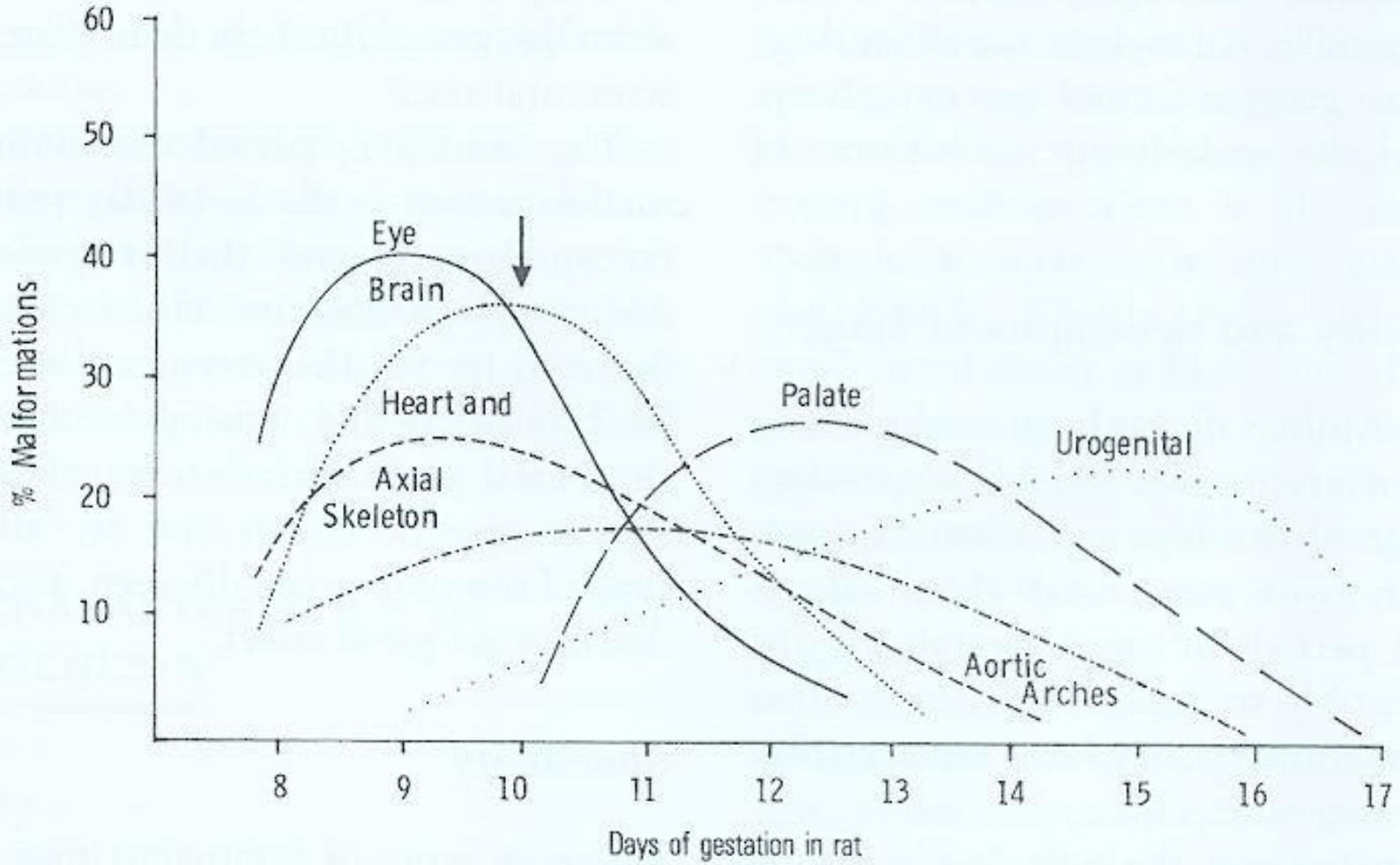


FIGURE 6.14 *Periods of peak sensitivity to teratogens in the rat. A teratogen administered at the time shown by the arrow would cause a mixture of malformations. It would particularly damage the eyes and brain but would have little or no effect on the palate. Adapted from Wilson, J. G. (1973)* Environment and Birth Defects *(New York: Academic Press.)*

MUNI PHARM

Thank you
for your attention

MUNI PHARM