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Absorption, Distribution, and Excretion

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Section A

The Toxicological Process

Definition

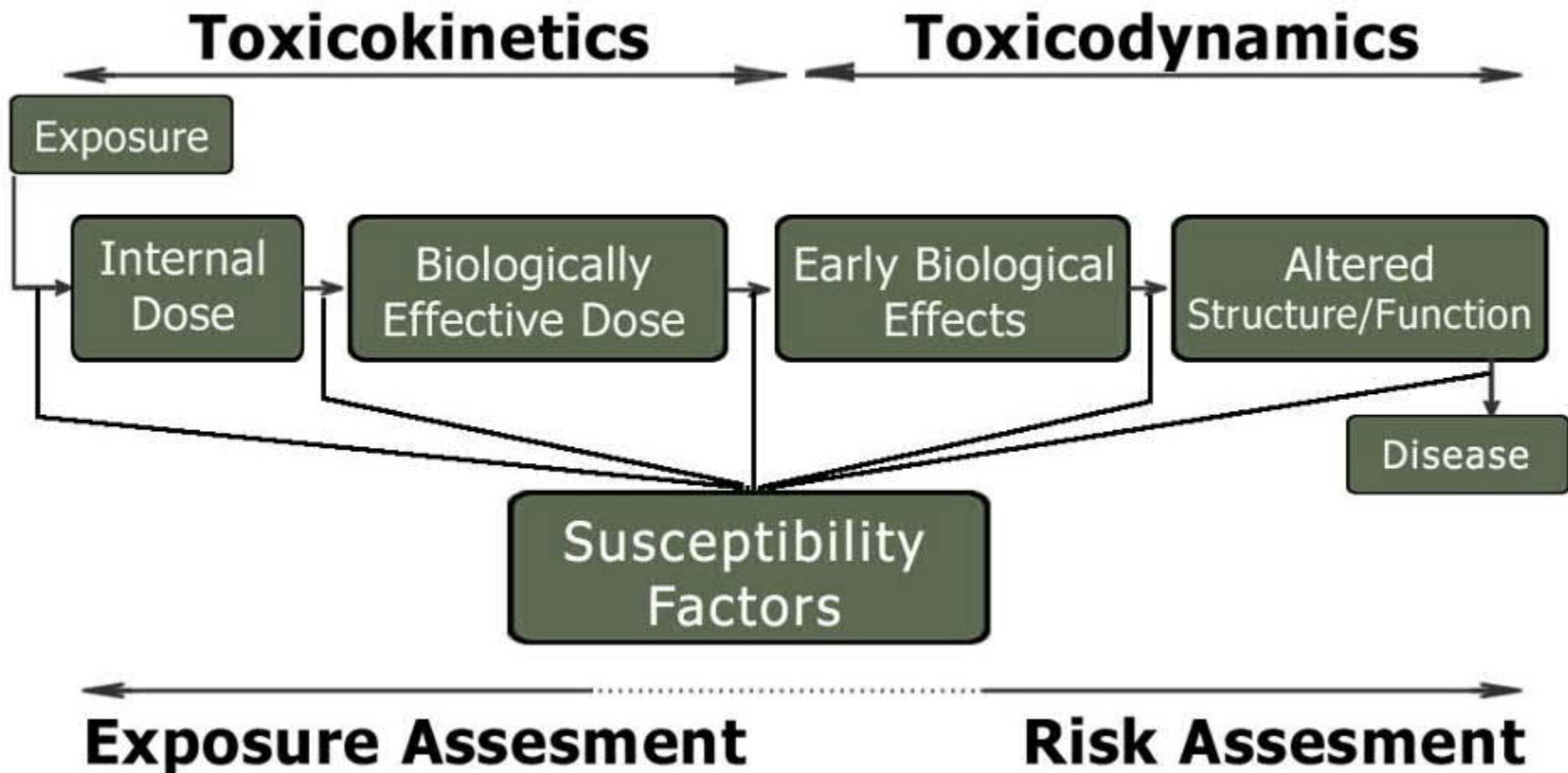
- ◆ **Toxicology** is the study of poisons
- ◆ **Poisons** are chemical/physical agents that produce adverse responses in biological organisms



“What is there that is not poison? All things are poison and nothing without poison. Solely, the dose determines that a thing is not a poison”

Paracelsus (1493-1541)

The Toxicological Paradigm



Toxicokinetics

- ◆ Toxicokinetics is the quantitation of the time course of toxicants in the body during the processes of **absorption, distribution, biotransformation, and excretion** or clearance of toxicants. In other words, toxicokinetics is a reflection of how the body handles toxicants as indicated by the plasma concentration of that xenobiotic at various time points
- ◆ The end result of these toxicokinetic processes is a **biologically effective dose** of the toxicant.

Toxicodynamics

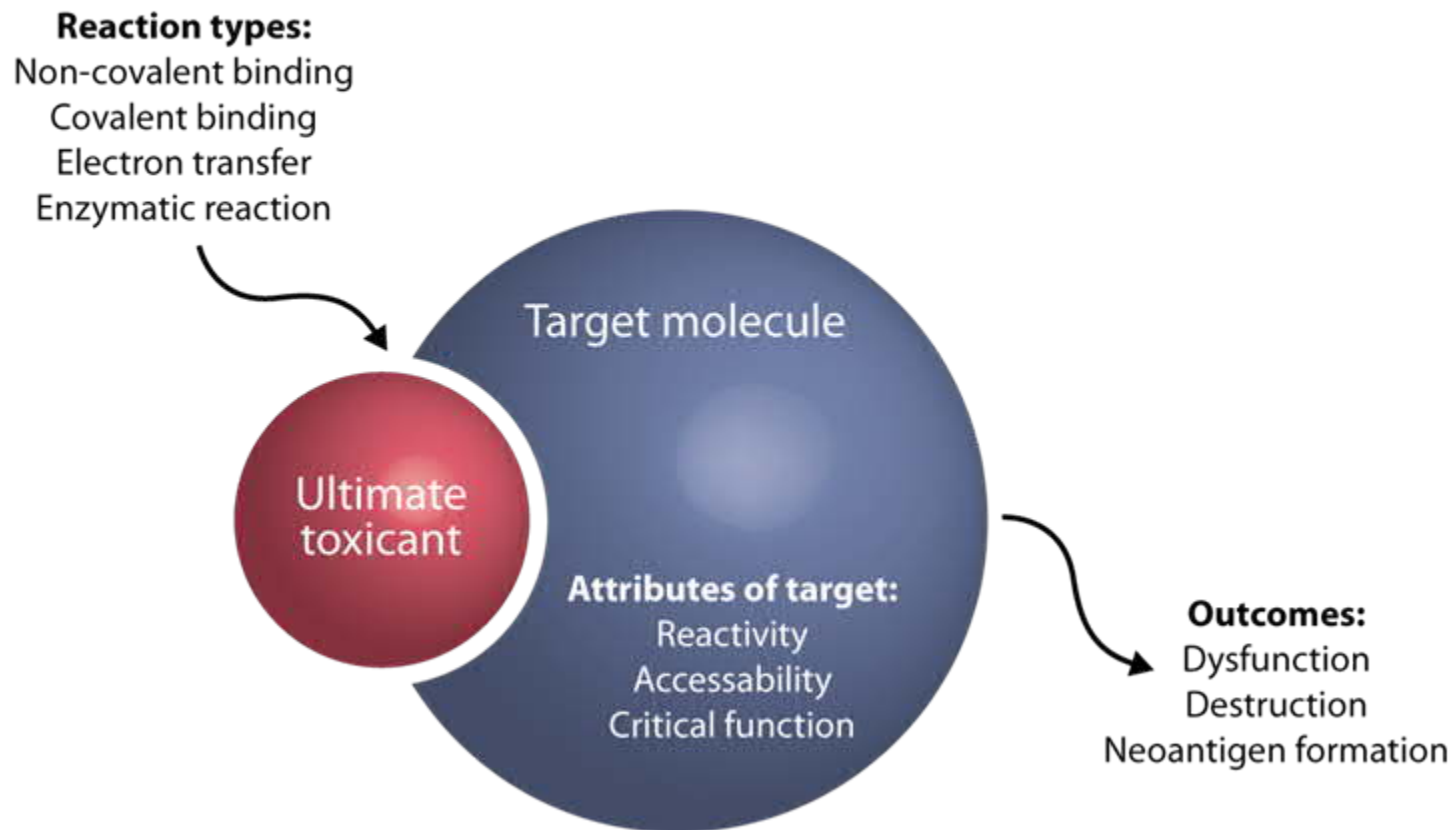
- ◆ Toxicodynamics refers to the molecular, biochemical, and physiological effects of toxicants or their metabolites in biological systems
- ◆ These effects are result of the interaction of the biologically effective dose of the ultimate (active) form of the toxicant with a molecular target

Molecular Targets Concept

- ◆ The toxic action of a chemical is a consequence of the physical/chemical interaction of the **active** form of that chemical with a molecular target within the living organism

Molecular Targets Concept

Molecular Targets Concept



Examples of Molecular Targets

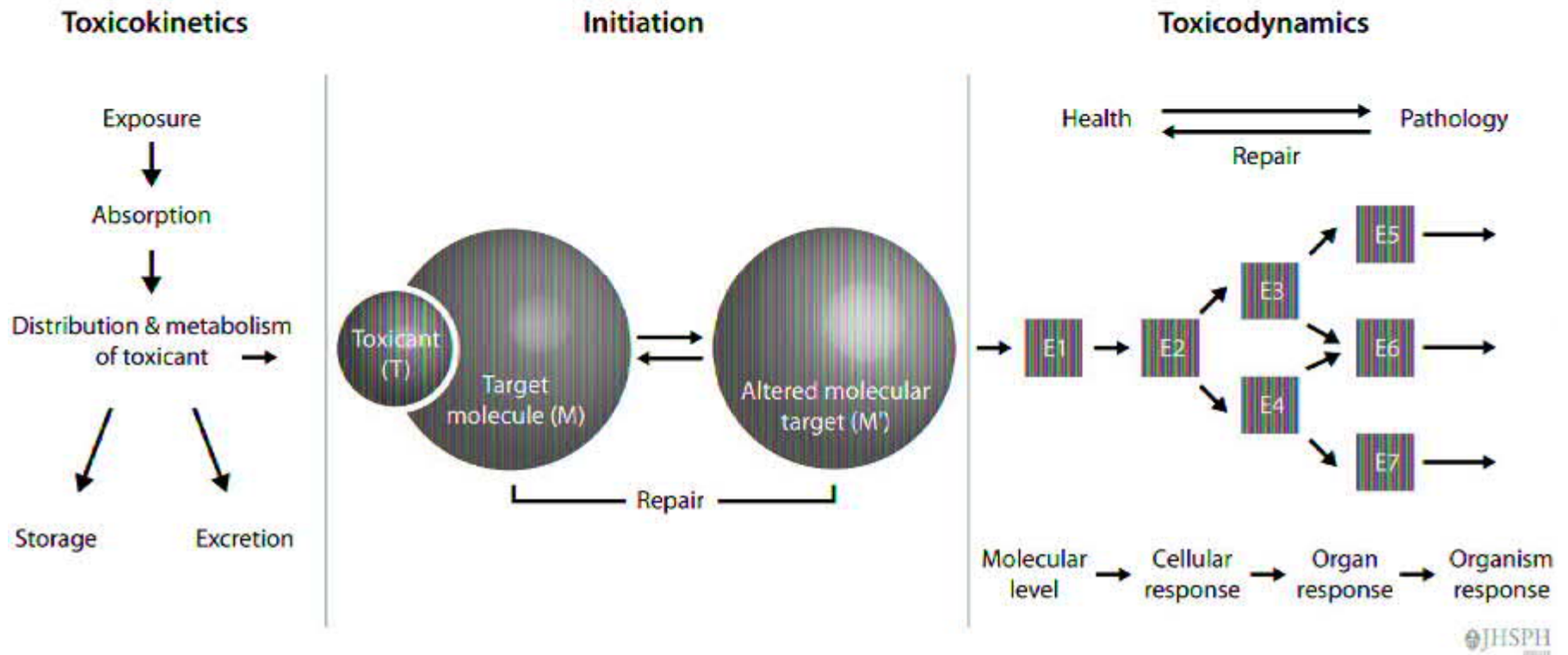
- ◆ Proteins
 - **Aryl**hydrocarbon(Ah) receptor—Dioxin
 - Hemoglobin—CO
- ◆ Lipids—Carbon tetrachloride
- ◆ DNA—Aflatoxin

Dose-Response Concept

- ◆ The magnitude of the toxic effect will be a function of the concentration of altered molecular targets, which in turn is related to the concentration of the active form of the toxicant(biologically effective dose) at the site where the molecular targets are located.

The Toxicological Process

The Toxicological Process



The Toxicological Process

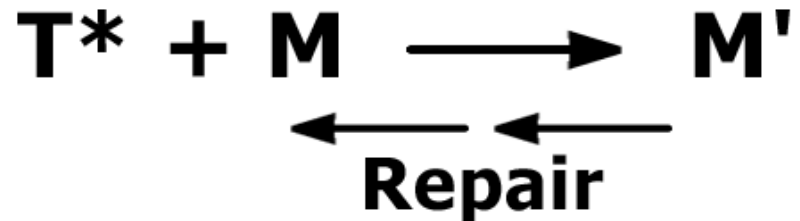
Reversible



Irreversible



**Irreversible
with repair**



T= toxicant; M= molecular target
M'= altered molecular target



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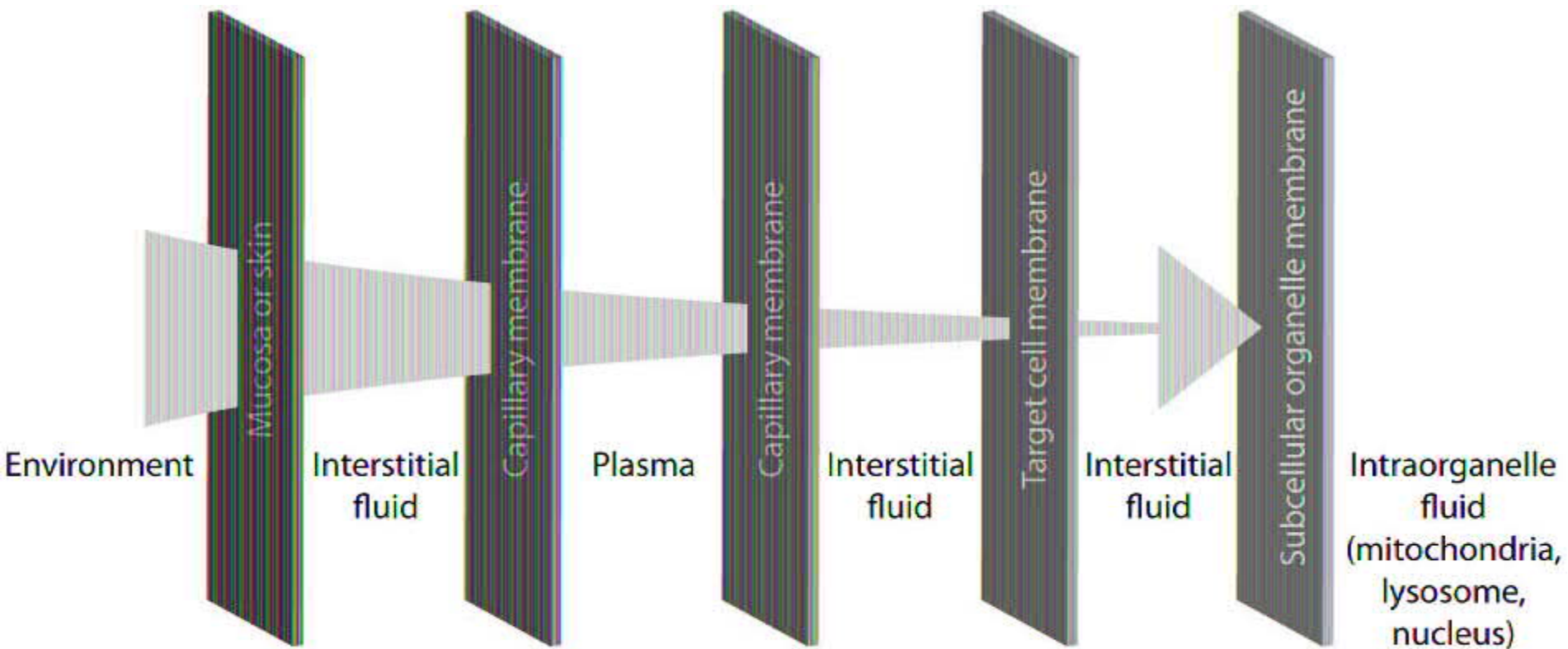
Section B

Transport Process Mechanisms

Membrane Transport of Xenobiotics

- ◆ The absorption, distribution, and excretion of xenobiotics involves passing through various cell and organ membranes.
- ◆ This occurs through various transport mechanisms

Membrane Transport of Xenobiotics



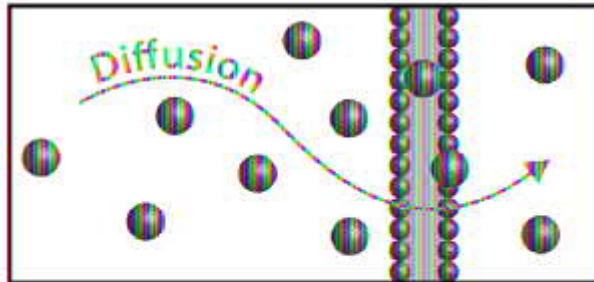
Xenobiotics: Transport Mechanisms

- ◆ Factors affecting membrane transport of chemicals:
 - Molecular weight/shape
 - Charge
 - Lipid solubility
 - Membrane composition
 - Membrane thickness

Types of Transport

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

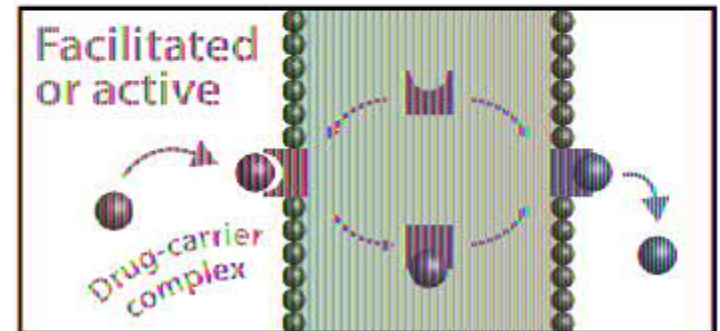
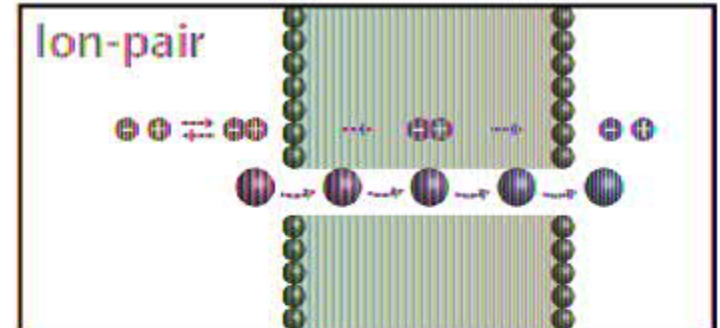
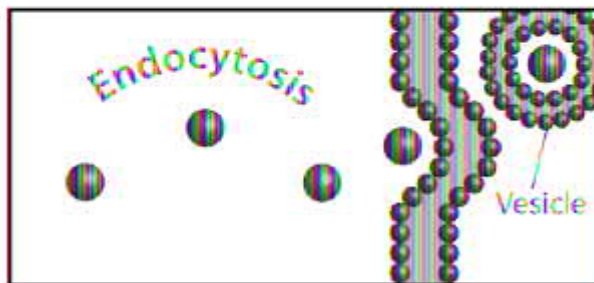
Types of Transport



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



Molecules of
varying sizes

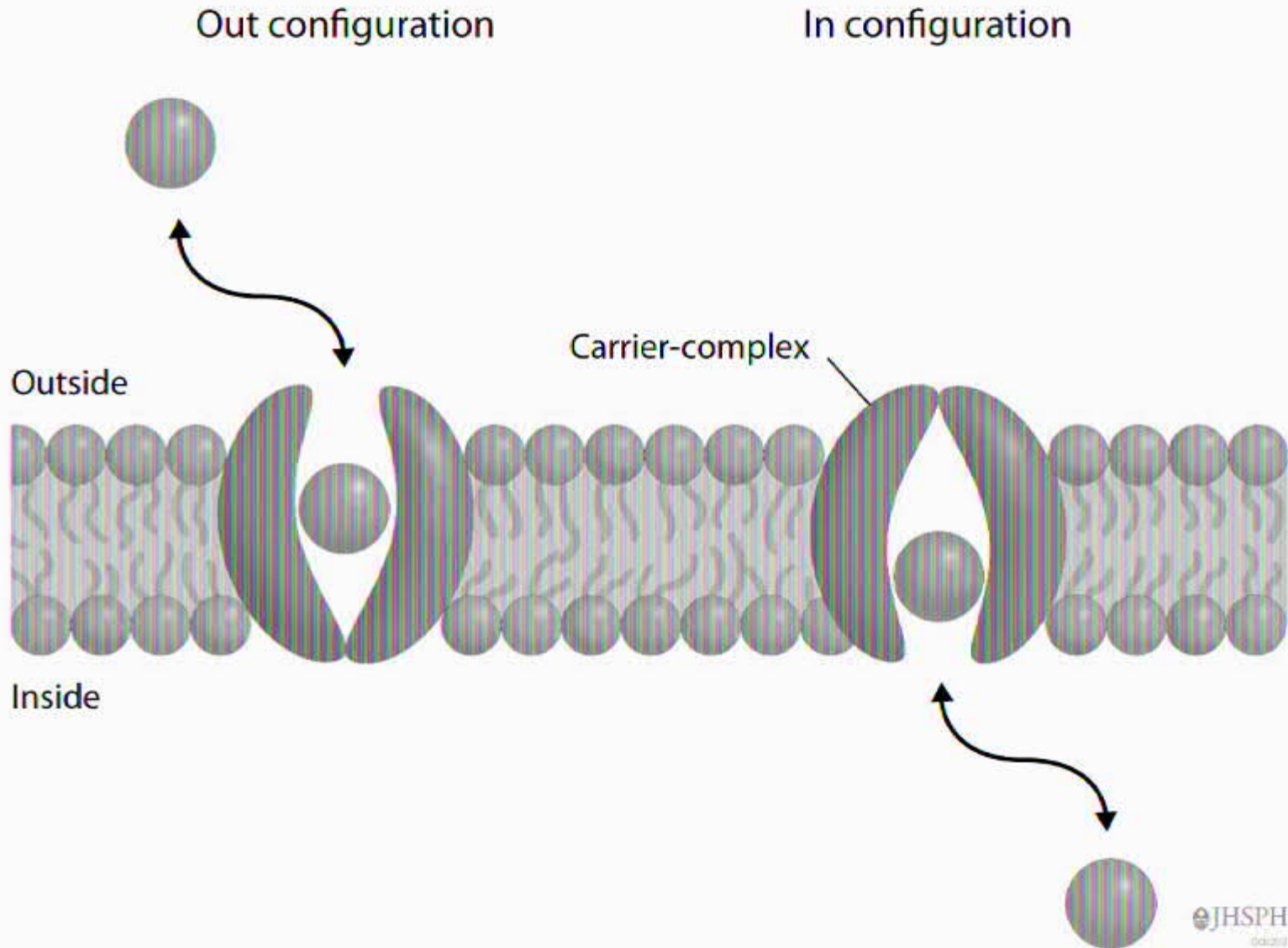


Characteristics of Simple Diffusion

- ◆ Transport proceeds in the direction of the electrochemical potential (concentration) gradient
- ◆ Transport is not saturable at high concentration gradients
- ◆ No structural specificity
- ◆ No energy requirement
- ◆ Inherently symmetrical transport

**BOTH PASSIVE MEDIATED and
ACTIVE MEDIATED TRANSPORT
INVOLVE the USE of CARRIER
PROTEINS**

Carrier-Mediated Transport



Characteristics of Passive Mediated Transport

- ◆ Transport proceeds in the direction of the electrochemical potential (concentration) gradient
- ◆ The process is saturable at high concentration gradients, i.e., there is a maximum rate of transport

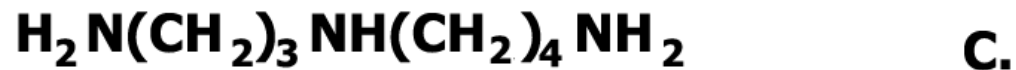
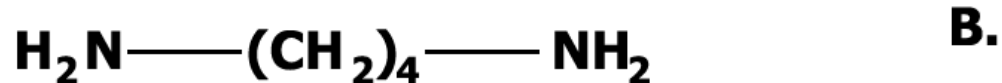
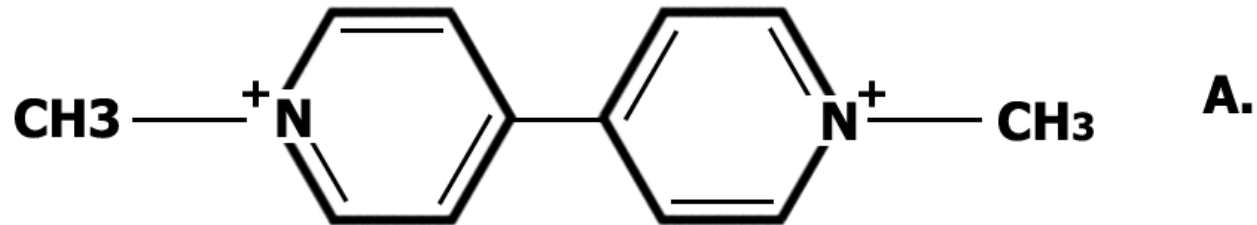
Characteristics of Passive Mediated Transport

- ◆ Structural specificity (specific inhibitors)
- ◆ No energy requirements
- ◆ Inherently symmetrical transport

Characteristics of Active Mediated Transport

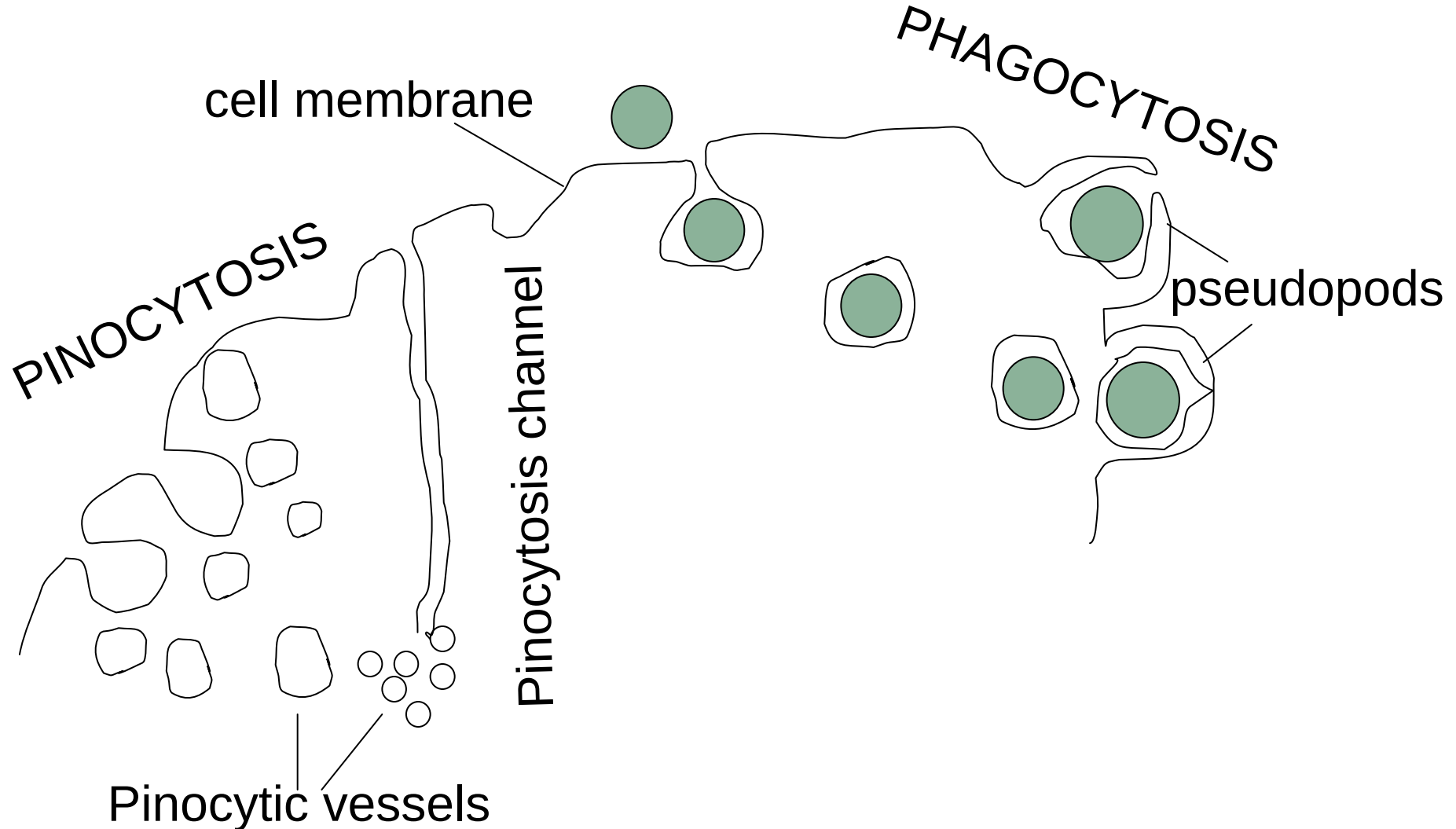
- ◆ Transport can proceed against an electrochemical potential (concentration) gradient
- ◆ The process is saturable at high concentration gradients
- ◆ Structural specificity
- ◆ Requires cellular energy
- ◆ Asymmetrical transport

Active Mediated Transport



- ◆ The structure of the herbicide paraquat (A) and the polyamines putrescine (B) and spermine (C)

Pinocytosis / Phagocytosis / Receptor Mediated Endocytosis



Filtration

- ◆ Transport of solutes as a consequence of bulk flow of fluid (aqueous) phase
- ◆ Glomerulus of kidney is a good example of site where filtration occurs



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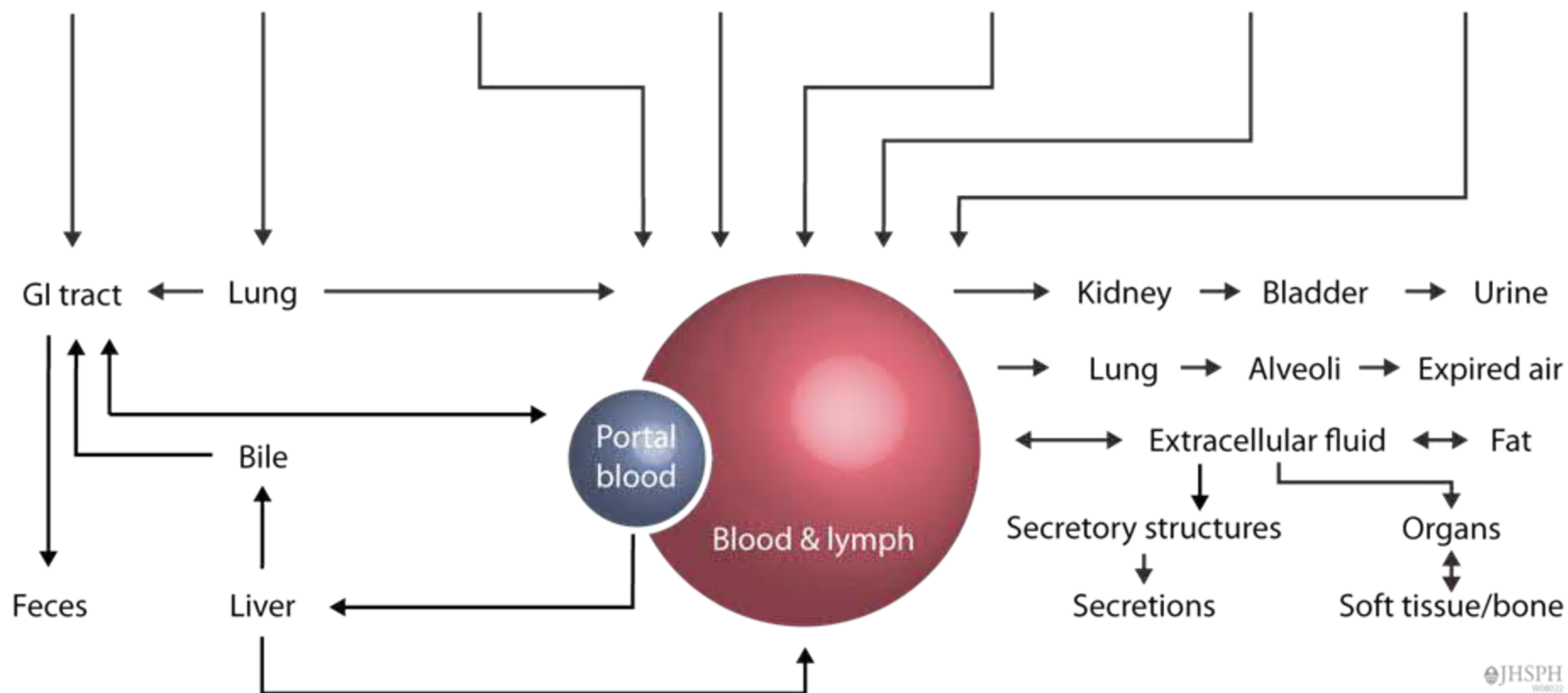
Section C

Toxicokinetics

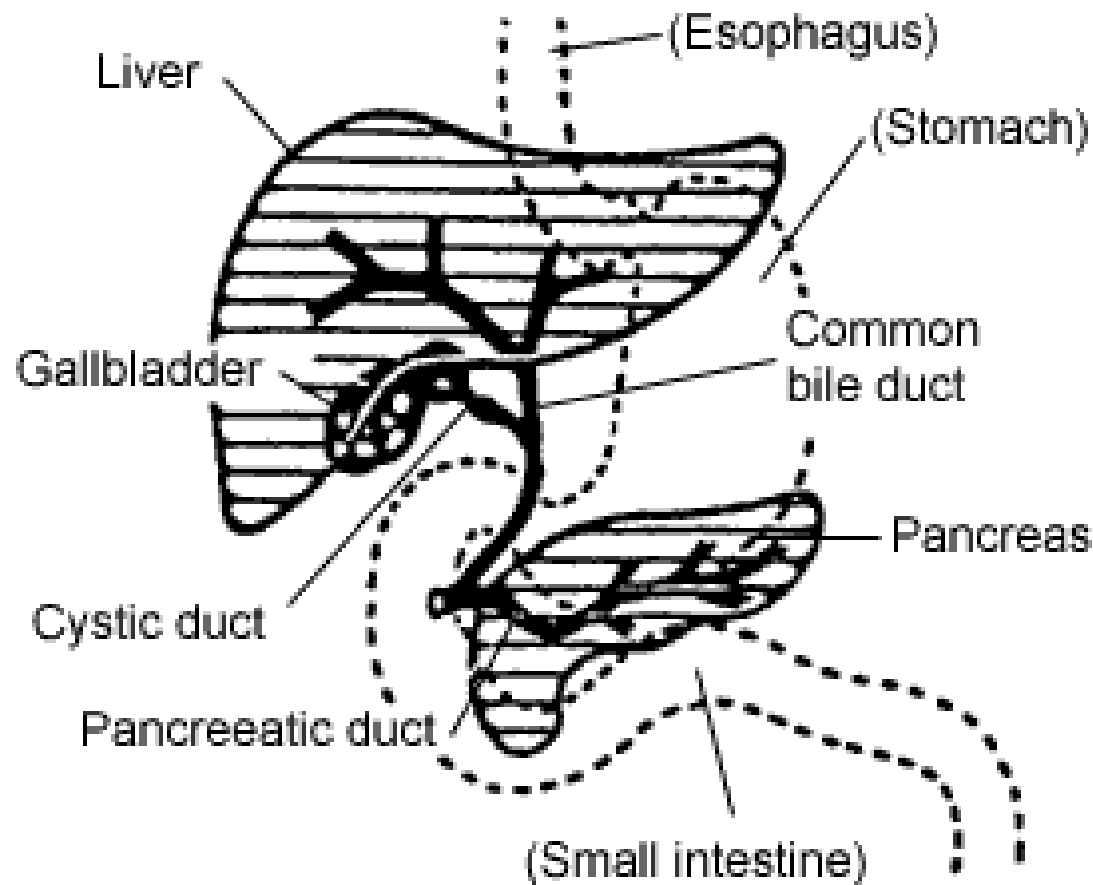
Systemic Kinetics: Outline

- ◆ Physiological basis of toxicokinetics
- ◆ Biliary excretion route for foreign compounds
- ◆ Barriers
- ◆ Major difference between a general (non-neural) and brain capillary
- ◆ Excretion pathways

Ingestion Inhalation Intravenous Intraperitoneal Subcutaneous Intramuscular Dermal



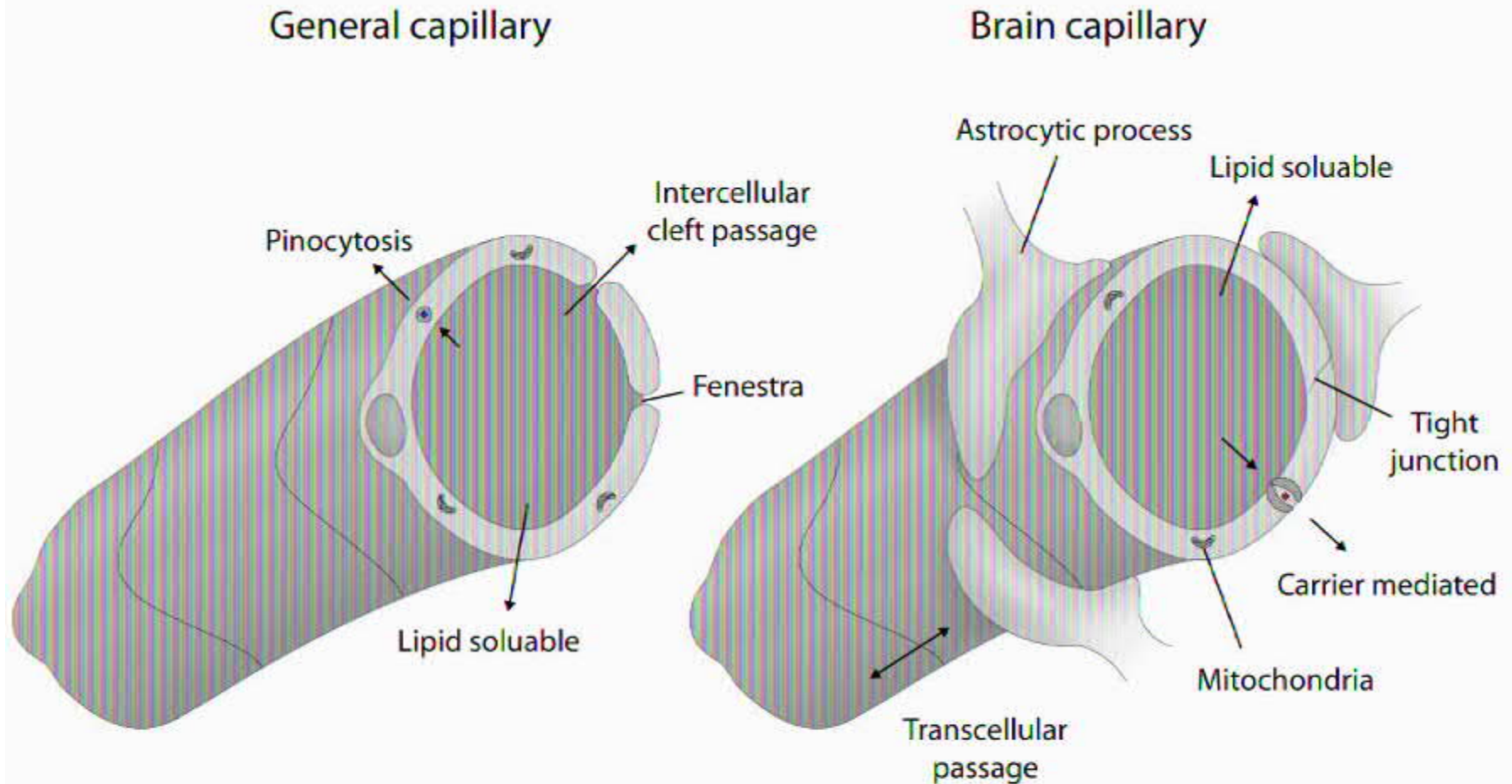
Biliary Excretion Route For Foreign Compounds



Systemic Kinetics: Barriers

- ◆ Blood-brain barrier
- ◆ Placenta
- ◆ Blood-testicular barrier

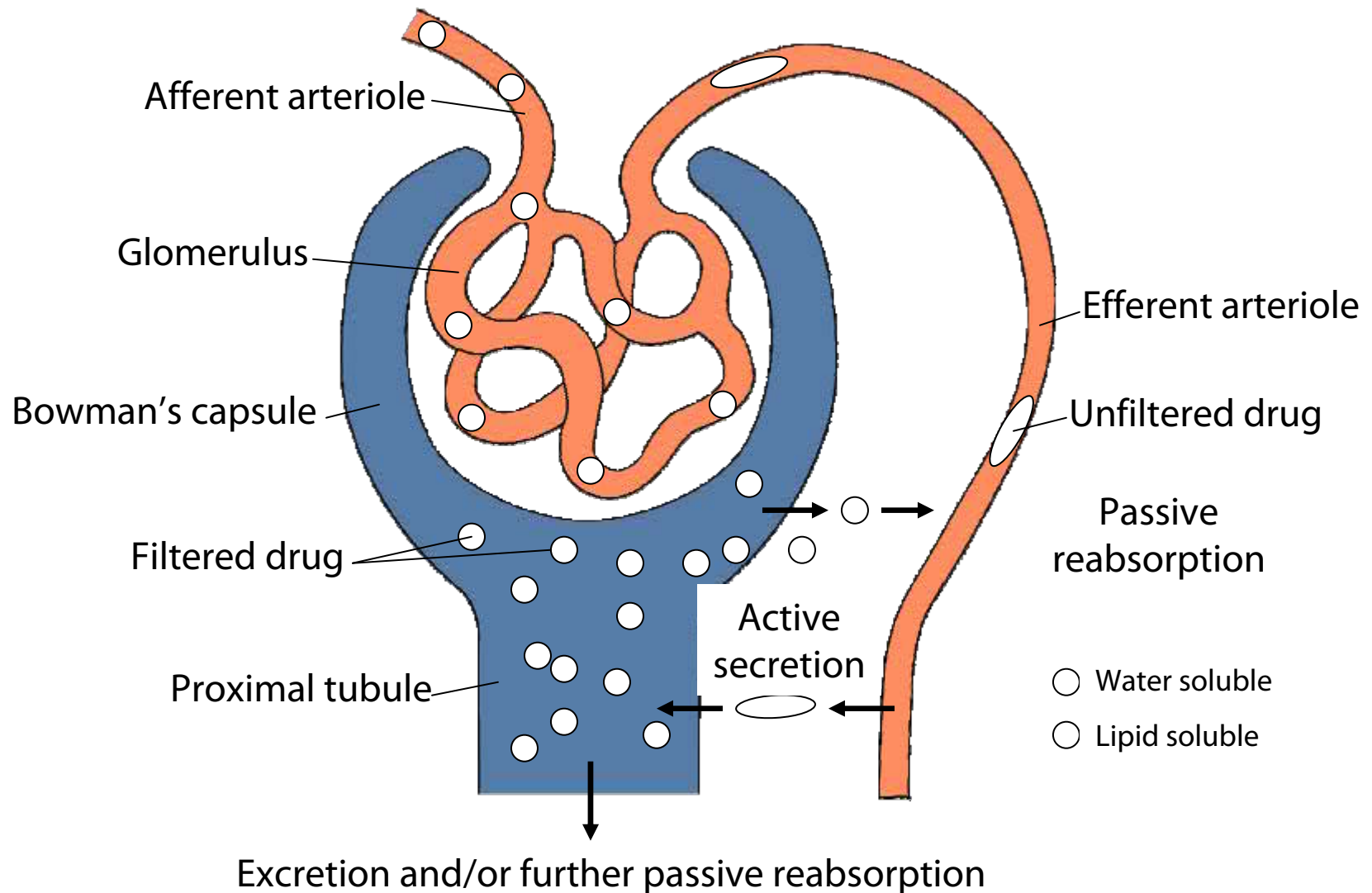
Major Difference between a General (Non-Neural) and a Brain Capillary



Excretion Pathways

- ◆ **Respiratory excretion**
 - Mucocilliary clearance
- ◆ **Gastrointestinal excretion**
 - Biliary excretion
 - Entero-hepatic circulation
- ◆ **Urinary excretion**
 - Glomerular filtration
 - Trans-tubular secretion

Renal Excretion of Chemicals



Other Routes of Excretion

- ◆ Milk
- ◆ Sweat
- ◆ Hair
- ◆ Nails
- ◆ Saliva

Biological Half Life

- ◆ The *biological half-life* ($T_{1/2}$) is the time required for some measure of the amount of a chemical in the body (for example, body burden, tissue concentration) to decrease to 1/2 its value at the beginning of the observational interval



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Section D

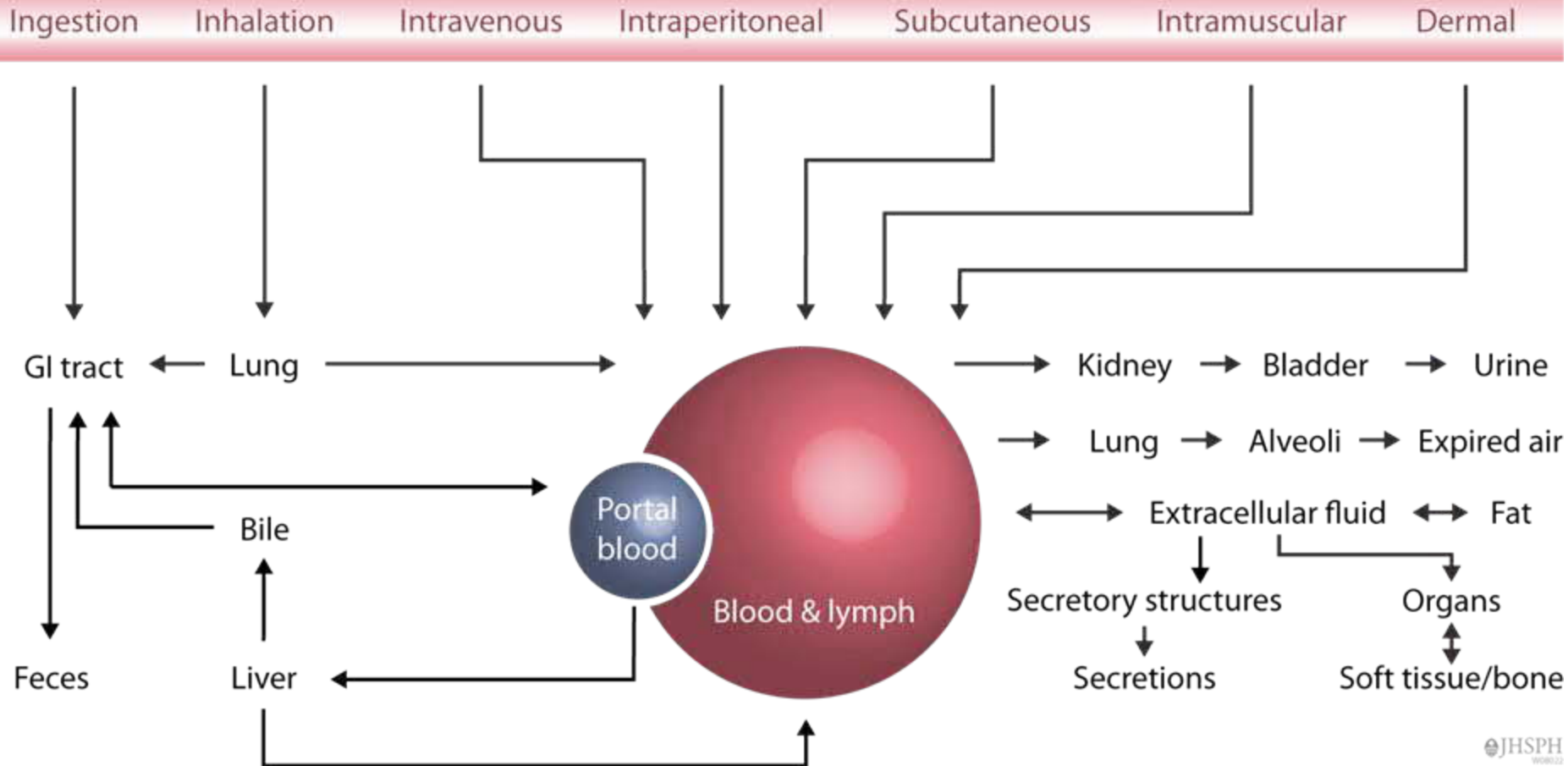
Toxicokinetics and PBK Modeling

PBPK Modeling

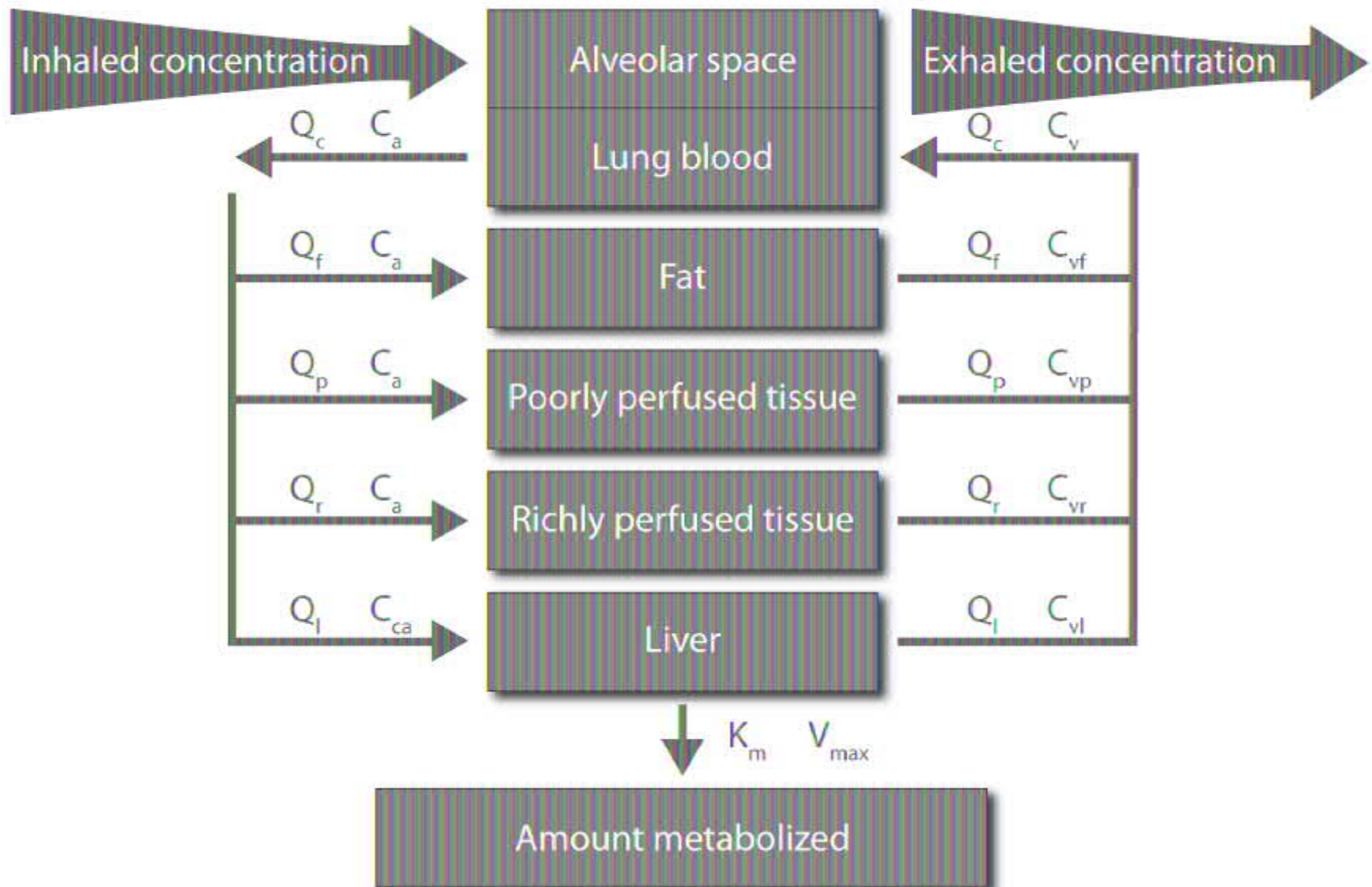
Physiologically Based Pharmacokinetic (Toxicokinetic)

- ◆ Purpose
 - To mathematically model how a substance is absorbed, distributed, and metabolized in the body to reduce uncertainties in determining the estimated dose

PBPK Modeling

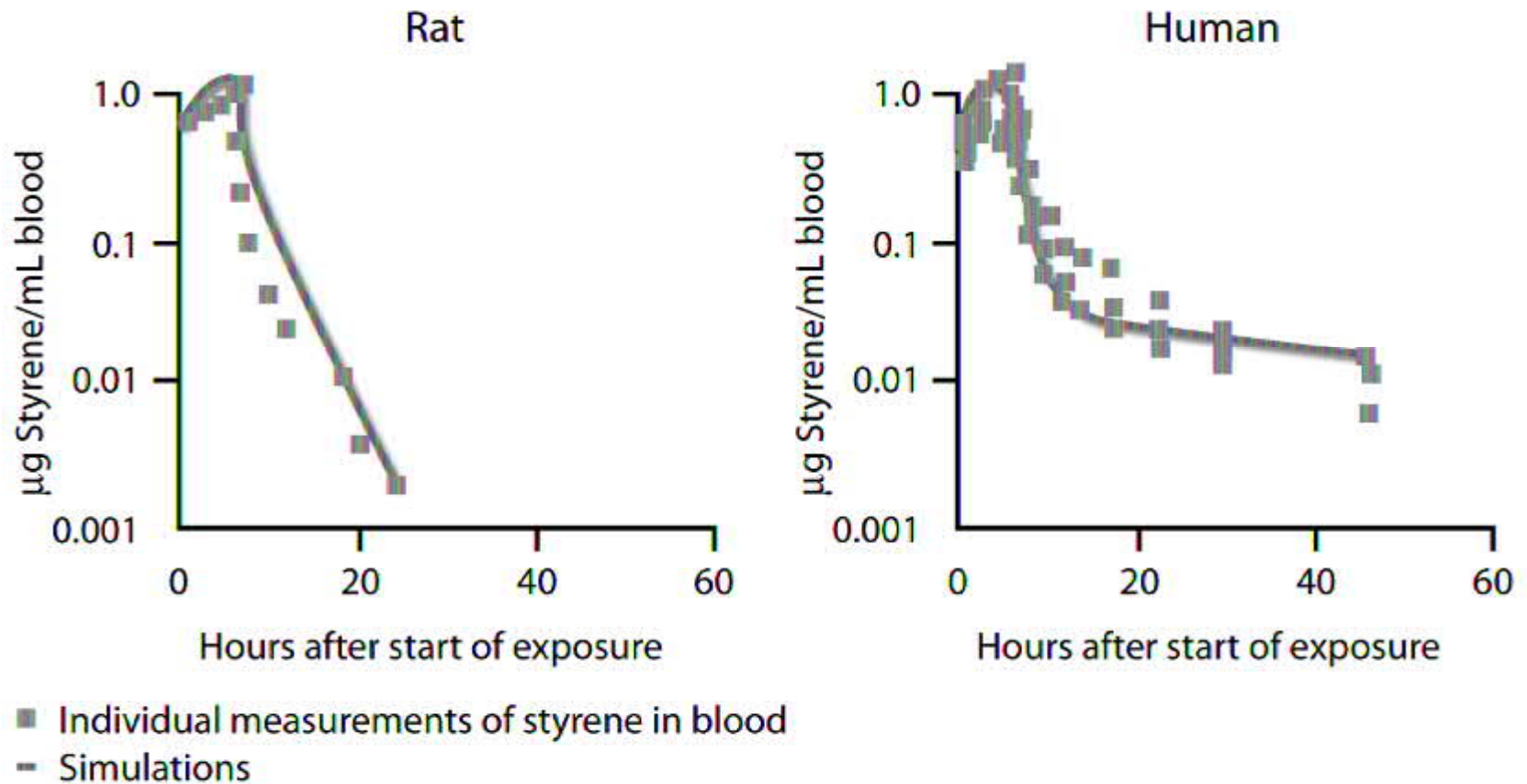


PBPK Modeling: Complex Models



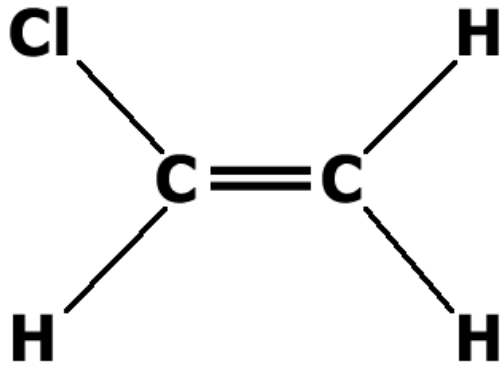
PBPK Modeling

PBPK Modeling
Blood Styrene Levels: Rat vs. Human



Adapted by CTLT from Caserett & Doull, Chap. 7, 1996.

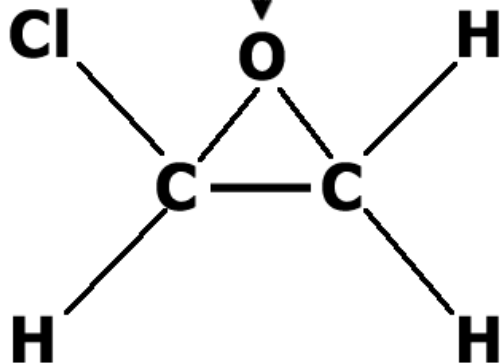
Vinyl Chloride Metabolism



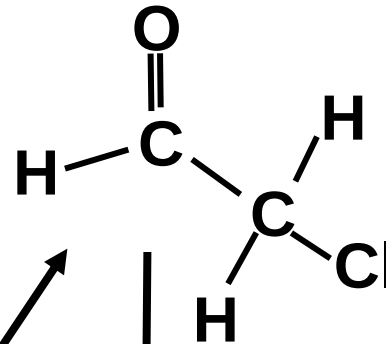
Vinyl Chloride

P450

Metabolism



Vinyl Chloride Epoxide



Chloroacetaldehyde

GSH conjugation

Covalent binding to proteins

Vinyl Chloride – Exposure, Metabolism in Rats & the Incidence of Hepatic Angiosarcoma

Exposure	µg of VC per L of air	µg of VC metabolized/4 hr	Incidence %
50	128	739	2
250	640	2435	7
500	1,280	3413	12
2,500	6,400	5030	22
6,000	15,360	5003	22
10,000	25,600	5521	15