CHAPTER 2

TOXICOKINETICS AND TOXICODYNAMICS

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Abstract

The knowledge about how the toxic substances enter, distribute through, transform within, and exit the body is fundamental to predicting, preventing, and treating poisonings. Toxicokinetics is the study about absorption of xenobiotics through gastrointestinal, dermal, pulmonary, and parenteral routes, each with distinct characteristics affecting the rate and extent of entry into circulation. Once absorbed, distribution is influenced by factors including protein binding, lipid solubility, and specialized barriers such as the blood-brain and placental interfaces. Metabolism, primarily occurring in the liver, encompasses Phase I (functionalization) and Phase II (conjugation) reactions that can either detoxify harmful substances or bioactivate relatively innocuous compounds into toxic metabolites. Excretion pathways—renal, biliary, pulmonary, and others—complete the ADME process, with parameters like half-life and clearance rate determining how long toxins persist. Toxicodynamics addresses mechanisms by which substances produce adverse effects, including receptor interactions, enzyme inhibition, protein and DNA adduct formation, oxidative stress, and disruption of cellular homeostasis. These principles provide the mechanistic foundation for clinical toxicology, explaining why certain exposures produce specific symptoms and guiding the development of targeted therapeutic interventions.

Keywords: *Toxicokinetics, Toxicodynamics, Biotransformation, Bioactivation, Xenobiotic Metabolism, Cellular Toxicity*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Differentiate between toxicokinetic and toxicodynamic processes and explain their interrelationship in determining toxic responses.
- Compare the absorption characteristics of toxic substances across different routes of exposure and identify factors that enhance or inhibit absorption.
- Analyze how distribution factors including protein binding, tissue affinity, and specialized barriers affect the toxicity of substances.
- Explain the role of Phase I and Phase II metabolic pathways in both detoxification and bioactivation of xenobiotics.
- Evaluate the primary excretion mechanisms for toxic substances and calculate parameters such as half-life and clearance rates.
- Identify the major cellular and molecular mechanisms of toxicity and relate them to specific clinical manifestations of poisoning

ABSORPTION

The entry of toxicants into the body initiates the toxicokinetic process, with absorption dynamics significantly influencing the ultimate toxic impact. Various routes of exposure present distinct absorption profiles that determine the bioavailability of toxicants and their subsequent systemic effects.

Gastrointestinal Absorption

Gastrointestinal absorption represents the most common route for toxicant entry, whether through intentional ingestion, accidental exposure, or contaminated food and water. The complex physiology of the gastrointestinal tract creates variable absorption environments throughout its length. Gastric absorption occurs primarily with weak acids that remain predominantly in their non-ionized form in the acidic environment of the stomach (pH 1-3), allowing passive diffusion across the gastric mucosa. The small intestine, with its extensive surface area enhanced by villi and microvilli, serves as the principal site of absorption for most toxicants. Its relatively alkaline environment (pH 5-7) favors absorption of weakly basic compounds that become non-ionized in this milieu. The specialized enterocytes lining the intestinal wall employ multiple transport mechanisms, including passive diffusion, facilitated diffusion, active transport, and pinocytosis, depending on the physicochemical properties of the toxicant.

Several factors modulate gastrointestinal absorption. Food presence generally delays gastric emptying, potentially reducing absorption rates of concurrent toxicants, though high-fat meals may enhance absorption of lipophilic compounds.

Remember

Absorption varies significantly by route of exposure, with inhalation typically providing the most rapid systemic exposure, followed by intravenous, intramuscular, subcutaneous, oral, and dermal routes.

Gastrointestinal motility alterations, whether accelerated or decreased, significantly impact toxicant transit time and absorption opportunity. Pathological conditions affecting mucosal integrity, such as inflammatory bowel disease or celiac disease, may enhance absorption of compounds normally restricted by intact epithelial barriers. First-pass metabolism, particularly in the liver, can substantially reduce bioavailability of orally ingested toxicants through biotransformation before they reach systemic circulation.

Table 2.1: Factors Affecting Toxicant Absorption

Route	**Major Factors**	**Examples of Modifying Factors**
Oral	Gastric pH, food presence, formulation	Antacids increase lead absorption
	First-pass metabolism, gastric emptying	Alcohol accelerates chloral hydrate absorption
Dermal	Molecular weight, lipid solubility	Solvents enhance pesticide absorption
	Skin integrity, anatomical location	Damaged skin increases all absorption
Inhalation	Particle size, solubility	Exercise increases respiratory absorption
	Respiratory rate, airway pathology	Asthma enhances inhaled toxin absorption
Parenteral	Tissue vascularity, injection site	IV administration bypasses absorption barriers
	Formulation (solution vs. suspension)	IM depot formulations delay absorption

Pulmonary Absorption

The respiratory system provides an extensive absorption surface with immediate access to the bloodstream, bypassing hepatic first-pass metabolism. Gases, vapors, and fine particulates can reach the alveolar surfaces, where the extremely thin alveolar-capillary membrane (0.2-0.5 µm) facilitates rapid exchange. Gaseous toxicants dissolve in the alveolar lining fluid before diffusing into pulmonary circulation, with more soluble compounds generally achieving higher blood concentrations. Particle size fundamentally determines the deposition site within the respiratory tract: large particles (>10 µm) typically deposit in the upper airways, medium particles (2.5-10 µm) reach the tracheobronchial region, while fine (<2.5 µm) and ultrafine (<0.1 µm) particles can penetrate to alveolar spaces.

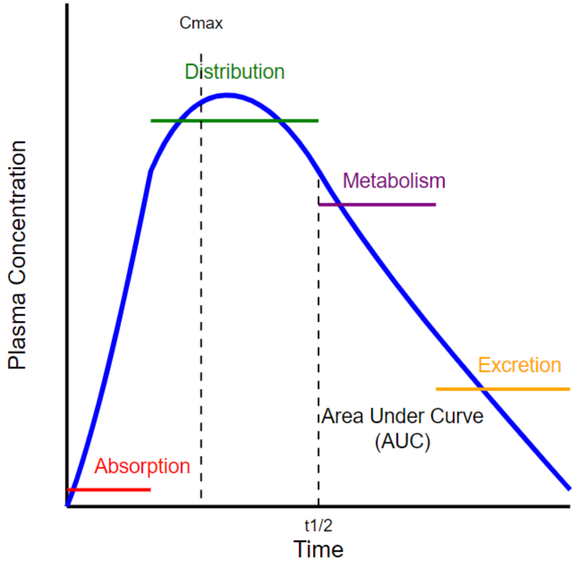

Figure 2.1 Various Phases in Toxicokinetics

Ventilation rate significantly influences absorption kinetics, with increased respiratory rate and depth during physical exertion enhancing toxic exposure. Pre-existing pulmonary conditions, such as chronic obstructive pulmonary disease or asthma, may alter airflow patterns and deposition of inhaled toxicants. The pulmonary epithelium contains specialized defense mechanisms, including ciliated cells and mucus secretion, which can trap and eliminate particles through mucociliary clearance, though these defenses may become overwhelmed with high-concentration exposures or compromised by concurrent respiratory conditions.

Dermal Absorption

The skin, while serving as a protective barrier, permits absorption of certain toxicants, particularly lipophilic compounds. The stratum corneum, composed of dead keratinocytes embedded in a lipid matrix, represents the rate-limiting barrier to percutaneous absorption. Toxicants must traverse this hydrophobic layer before reaching viable epidermis and ultimately dermal blood vessels. The physicochemical properties of compounds significantly determine their skin penetration potential, with molecular weight under 500 Da, moderate lipophilicity (log P between 1-3), and adequate water solubility favoring absorption.

Regional variations in skin thickness and composition create different absorption potentials across the body. Thin-skinned areas with rich vascularization, such as the face, scrotum, and forehead, demonstrate enhanced absorption compared to thicker regions like the palms and soles. Skin condition dramatically affects barrier function, with abrasions, lacerations, inflammation, or diseases like psoriasis or eczema potentially increasing absorption rates by orders of magnitude. Environmental conditions, particularly increased temperature and humidity, enhance percutaneous absorption by increasing blood flow, hydrating the stratum corneum, and potentially expanding intercellular channels. Occlusion, whether from clothing, gloves, or specialized transdermal delivery systems, creates a microenvironment of increased hydration and temperature that can significantly enhance absorption.

Other Absorption Routes

Several specialized absorption routes present unique toxicological considerations. Parenteral administration bypasses absorption barriers, with intravenous injection delivering toxicants directly to systemic circulation, while intramuscular and subcutaneous routes provide slower absorption through tissue diffusion before reaching bloodstream. Ocular exposure permits absorption through the cornea and conjunctiva, with lipophilic substances penetrating the corneal epithelium and hydrophilic compounds traversing conjunctival blood vessels. The blood-brain barrier generally restricts direct central nervous system absorption, though lipophilic toxicants and compounds utilizing specific transporters can cross this specialized interface. Transplacental transfer occurs primarily via passive diffusion, active transport, or facilitated diffusion, with lipophilic, low-molecular-weight, un-ionized compounds most readily crossing the placental barrier and potentially affecting fetal development.

DISTRIBUTION

Following absorption, toxicants undergo distribution throughout the body, a process governed by physiological and physicochemical factors that determine tissue concentrations and potential sites of toxic action.

Physiological Determinants of Distribution

Blood flow fundamentally influences toxicant distribution, with highly perfused organs like the brain, liver, and kidneys receiving disproportionately large fractions of cardiac output and consequently experiencing initial high toxicant concentrations.

> **Remember**
>
> **Distribution of toxins depends on factors including protein binding, lipid solubility, volume of distribution, and specialized barriers such as the blood-brain and placental barriers.**

Plasma protein binding significantly affects distribution patterns, as only unbound (free) fractions of toxicants can traverse capillary membranes and interact with target tissues. Albumin primarily binds acidic compounds, while $\alpha 1$-acid glycoprotein preferentially binds basic substances. Binding affinity varies substantially between compounds, from negligible to exceeding 99% of circulating toxicant. Competition for binding sites can occur when multiple toxicants or medications simultaneously occupy circulation, potentially increasing free concentrations of displaced substances.

Tissue permeability barriers selectively restrict toxicant distribution to protected compartments. The blood-brain barrier, formed by tight junctions between cerebrovascular endothelial cells and astrocyte foot processes, limits penetration to lipophilic compounds, small uncharged molecules, and substances utilizing specific transporters. Similarly, the blood-testis barrier protects germinal epithelium, while the placental barrier offers partial protection to developing fetuses, though many toxicants can traverse these specialized interfaces to varying degrees. Body fluid compartments influence distribution patterns, with water-soluble toxicants primarily distributing within extracellular fluids, while lipophilic compounds may extensively penetrate cell membranes and distribute throughout total body water.

Table 2.2: Toxicant Distribution Determinants and Clinical Implications

Factor	Description	Clinical Example
Protein binding	Binding to albumin and other proteins reduces active toxin	Highly protein-bound drugs (warfarin) displaced by competitors
Volume of distribution	Apparent space in which toxin distributes	Lipophilic substances (TCAs) with large Vd resist removal
Blood flow	Rate of delivery to tissues	Shock reduces peripheral tissue distribution
Lipid solubility	Ability to cross membranes and enter tissues	Lipophilic toxins (organophosphates) penetrate CNS rapidly
pKa and pH	Ionization affects membrane crossing	Alkalization "traps" salicylates in blood, enhancing elimination
Tissue affinity	Selective concentration in specific organs	Lead stored in bone creates ongoing exposure source
Barriers	Blood-brain, placental, other selective barriers	Lipophilic substances cross BBB, causing neurotoxicity

Physicochemical Aspects of Distribution

Lipophilicity represents a critical determinant of distribution patterns. Highly lipophilic toxicants readily cross cell membranes and tend to accumulate in adipose tissue, creating potential reservoirs for prolonged release and extended toxic effects. Ionization state significantly affects distribution, as ionized molecules generally demonstrate reduced membrane permeability compared to their un-ionized counterparts. The pH partition theory explains how weakly acidic toxicants accumulate in relatively alkaline compartments, while weakly basic compounds concentrate in more acidic environments, creating potential ion trapping in specific tissues. Molecular size influences distribution capabilities, with smaller molecules (<500 Da) generally exhibiting broader distribution compared to larger compounds that may face restricted passage across certain biological membranes.

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