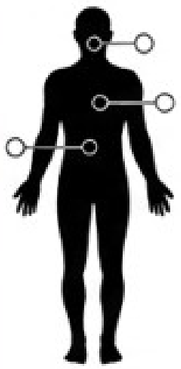
TOXICOKINETIC AND TOXICODYNAMIC

Step 1: Exposure & Absorption



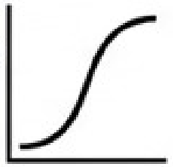
The chemical must reach the target individual and enter via a specific route (Inhalation, Ingestion, Skin, Injection).

Step 2: Toxicokinetics (ADME)



The body attempts to process the chemical, primarily relying on the liver for biotransformation (detoxication vs. activation).

Step 3: Toxicodynamics & Response



The dose reaching the target site determines the biological effect, subject to individual genetic variability and synergistic modifiers.

"The Dose Makes the Poison."

The Exposure Pathway



Inhalation:
Lungs/respiratory tract.



Skin Contact:
Dermal absorption.

In order for a chemical to produce a biological effect, it must reach a target individual, then reach a target site within the body.



Ingestion:
Gastrointestinal tract.



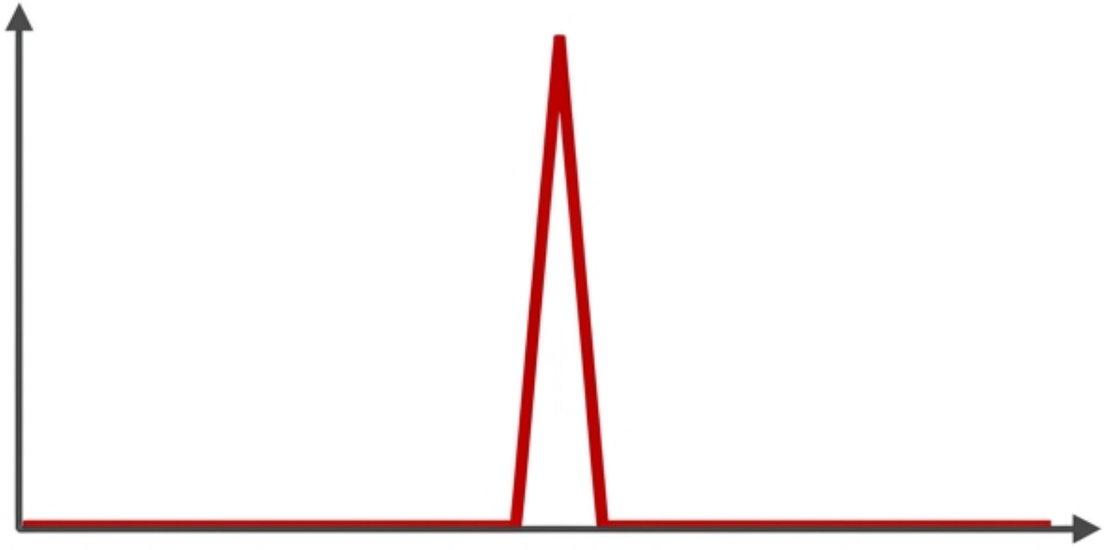
Injection:
Direct bloodstream entry.

The route of exposure determines if toxic effects will be local or systemic.

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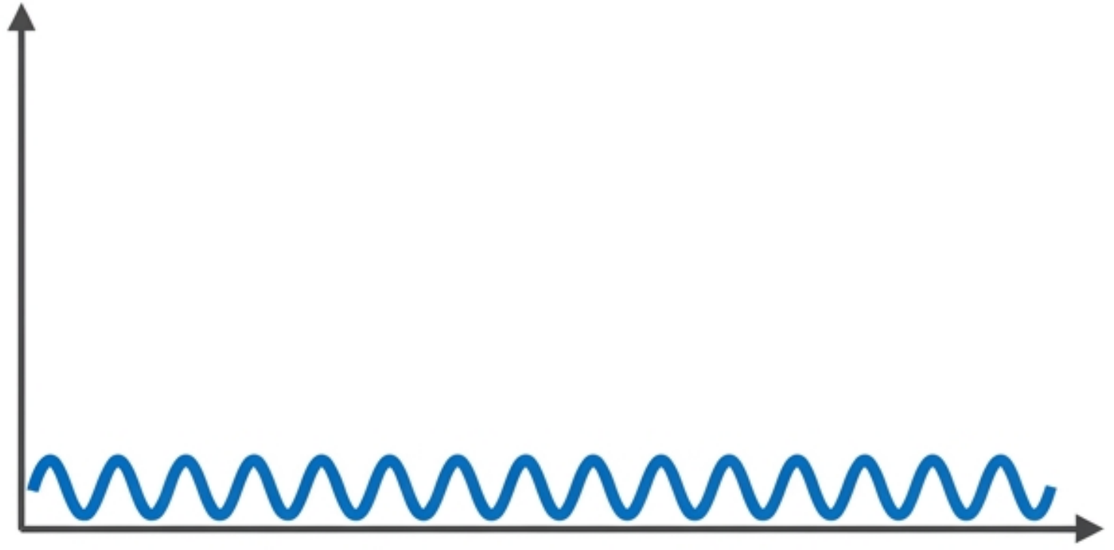
Time Dynamics: Acute vs. Chronic

ACUTE



Nature: A one-time event.
Mechanics: Rapid absorption; sudden & severe exposure.
Outcome: Critical period for death/survival.

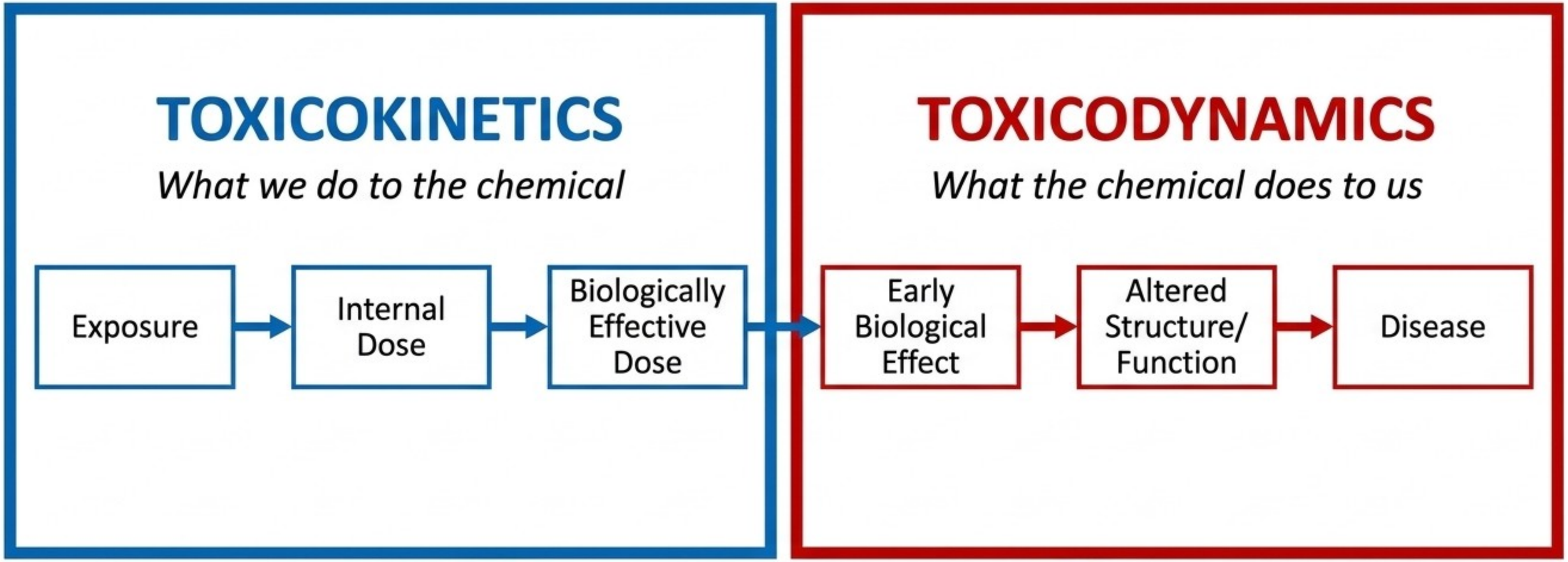
CHRONIC



Nature: Multiple exposures over time.
Mechanics: Rate of intake > rate of elimination. Small doses.
Outcome: Material remains in tissue; progressive injury.

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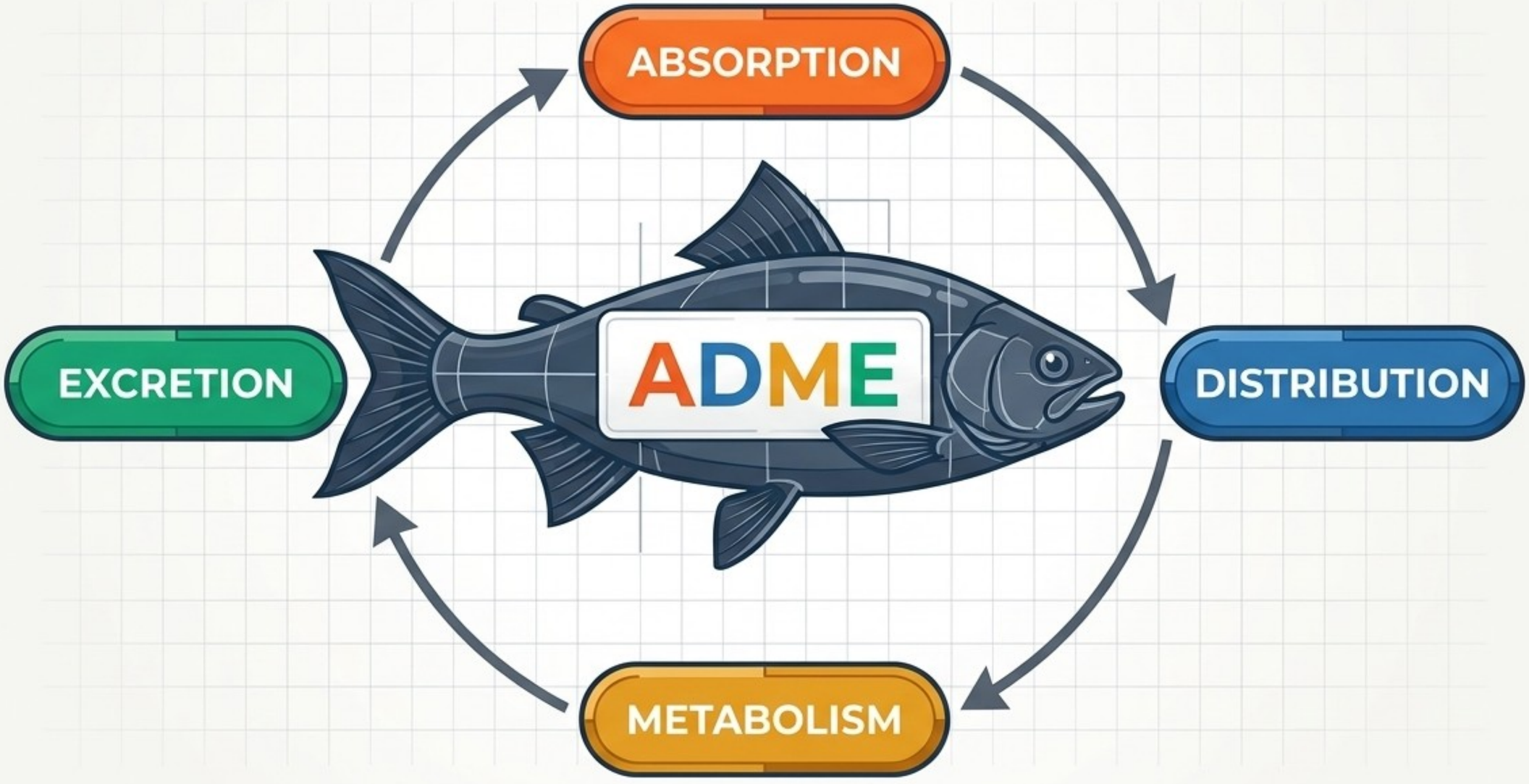
The Toxicological Paradigm



Modifying Factors: Both sides are influenced by **Susceptibility** (Genetics and Nutritional Status).

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The ADME Cycle in Biological Models



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ADME

Dose becomes concentration through ADME

1. **Absorption**

   Moves a chemical into the body from its exposure route.

2. **Distribution**

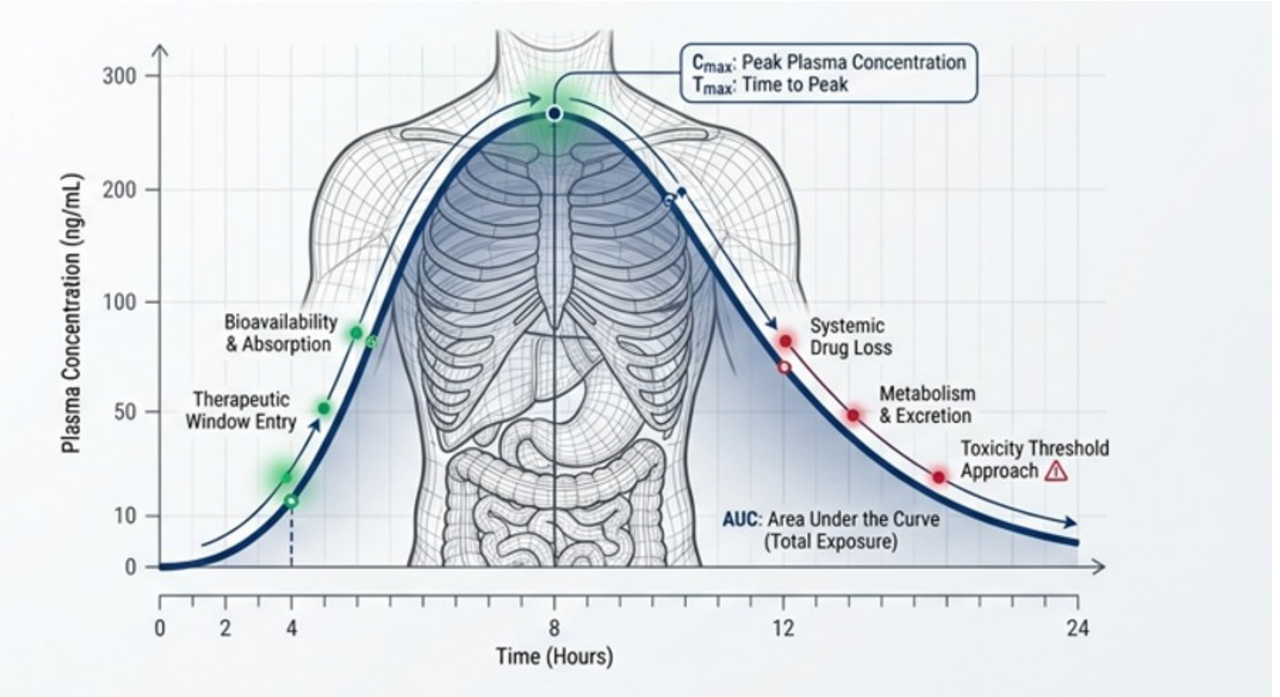
   Carries it through blood to organs and tissues.

3. **Metabolism**

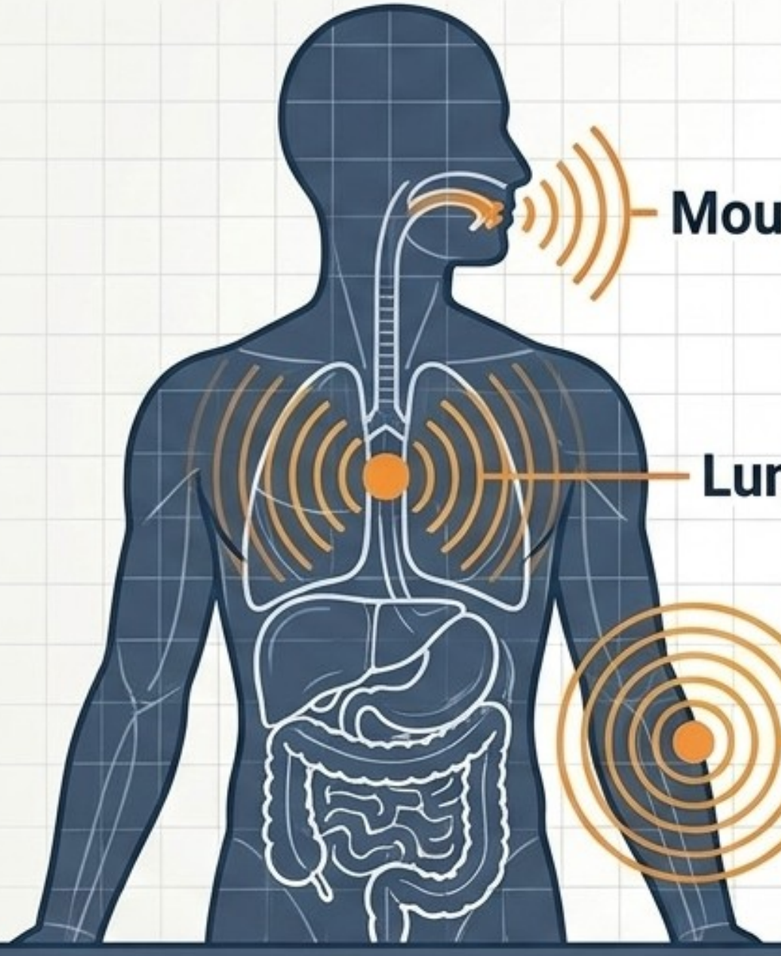
   Transforms the parent compound into products.

4. **Excretion**

   Removes parent compound or metabolites in urine, bile, feces, or expired air.



Route of Exposure Dictates the Threat



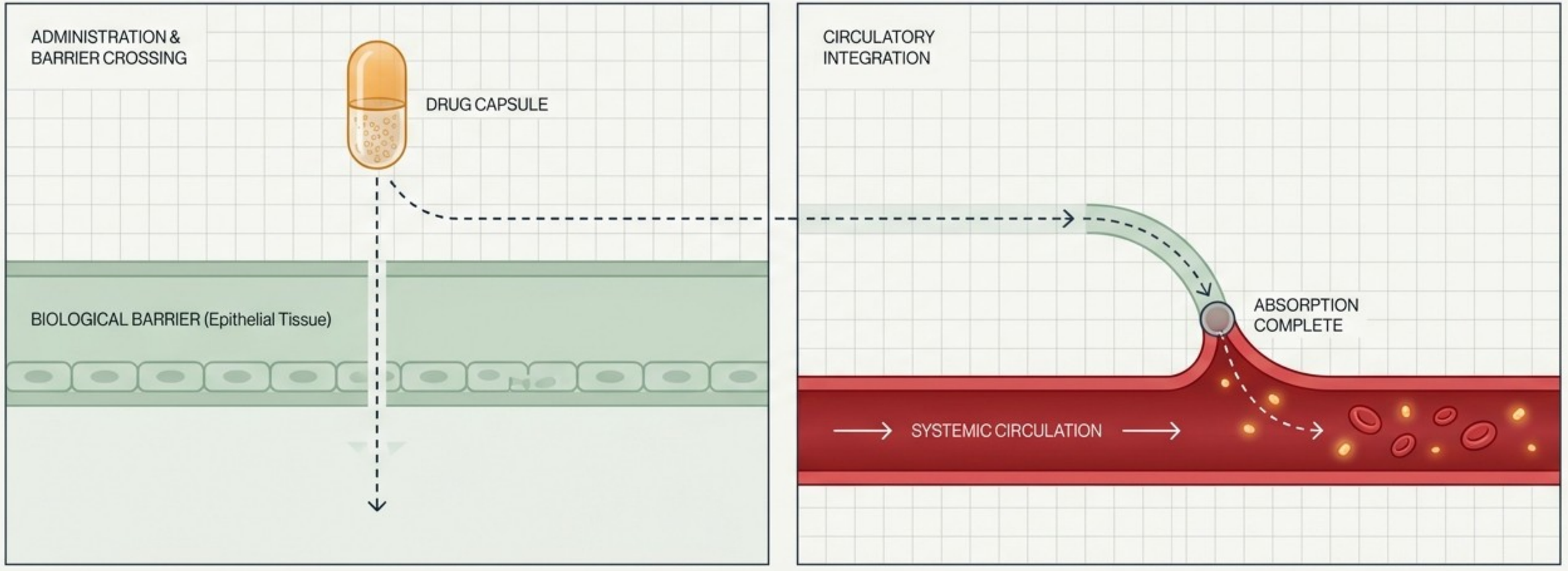
Volume: Determines exactly how much of the substance is successfully absorbed into the systemic circulation.

Trajectory: Dictates which specific organs are exposed to the highest initial concentrations before the body has a chance to mount a metabolic defense.

Absorption is the biological gateway; without it, systemic toxicity cannot initiate.

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Absorption: The Journey to Circulation



The Process

Absorption is the physiological process and chronological journey of a drug from its initial site of administration across biological barriers.

The Ultimate Goal

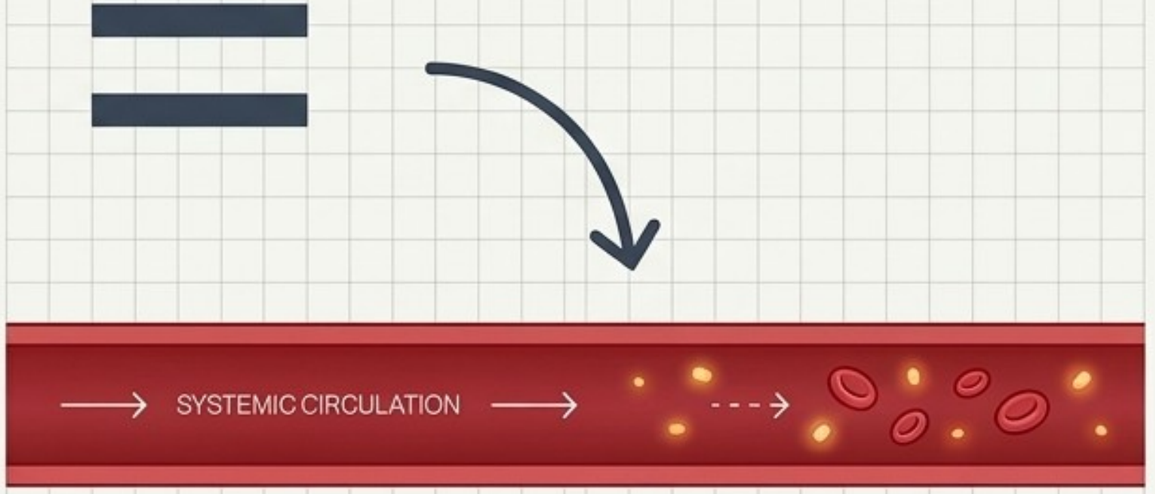
Regardless of how a drug is administered, the primary objective is to deliver active molecules into the systemic circulation for systemic distribution.

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Measuring Survival: Bioavailability

Fraction of unchanged drug

Administered Dose



Definition:

Bioavailability is the specific fraction of an administered dose that successfully reaches the systemic circulation in a completely unchanged and active state.

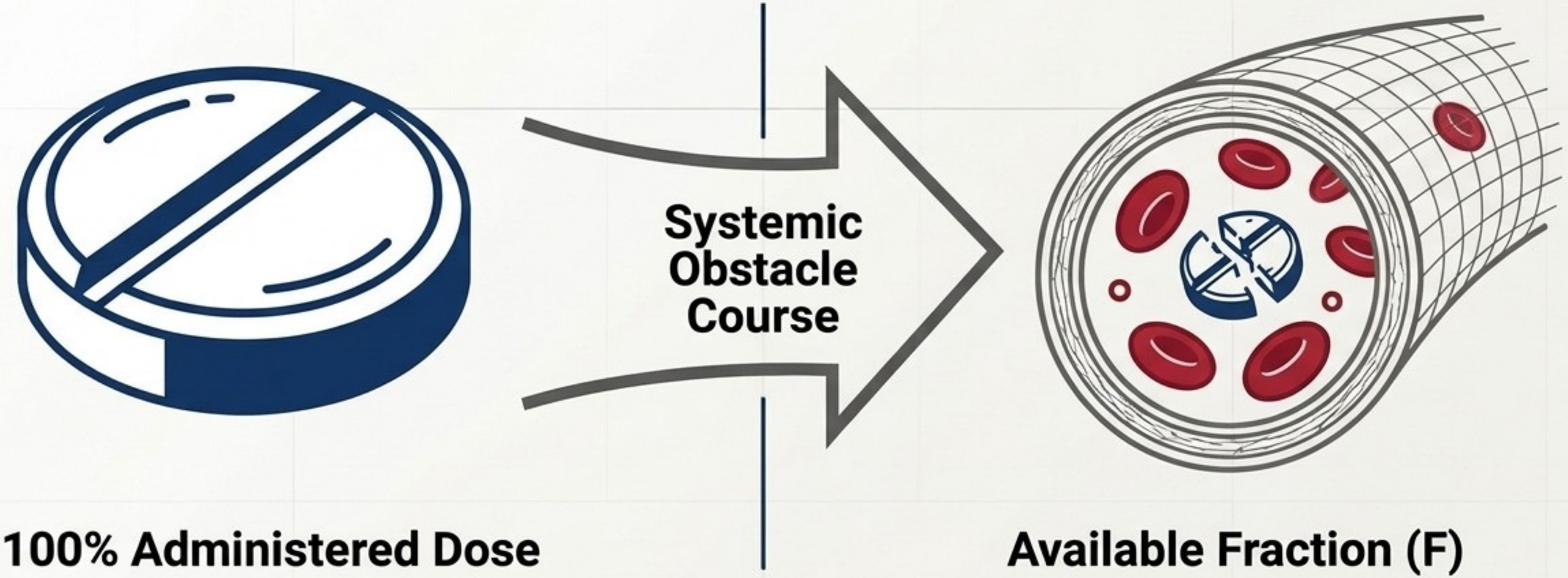
The Baseline Rule:

A drug administered intravenously has 100% bioavailability. All other routes result in fractional bioavailability due to anatomical obstacles.

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Defining Bioavailability (F) as the Surviving Fraction

Bioavailability (F) is defined as the exact fraction of an administered dose of unchanged drug that successfully reaches the systemic circulation. It is the ultimate measure of delivery efficiency.

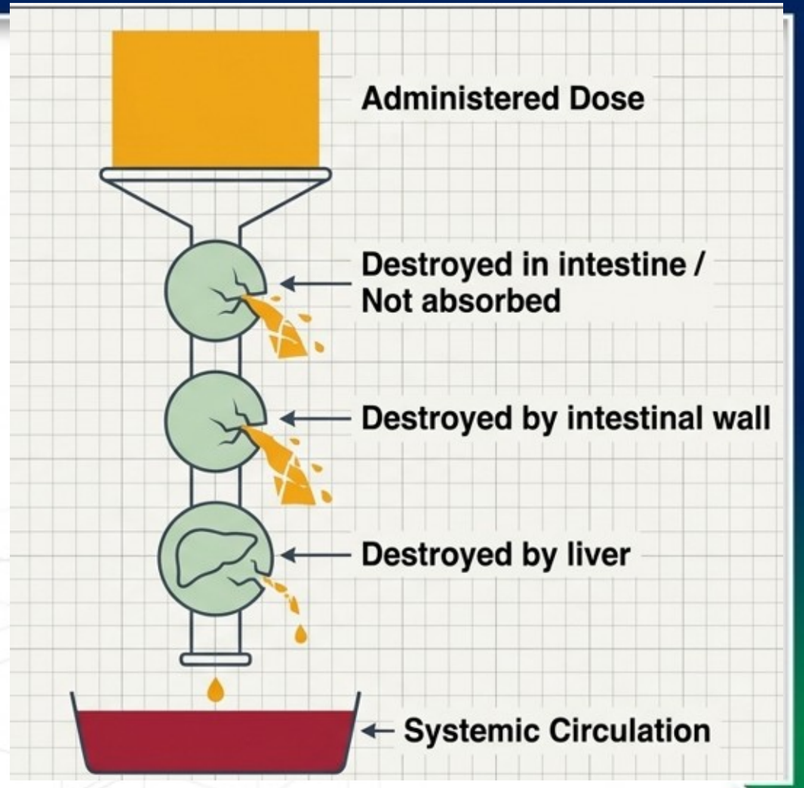


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The Systemic Cascade of Fraction Loss

A drug's journey from ingestion to circulation is a sequence of diminishing returns.
At each anatomical checkpoint, a specific percentage of the dose is **permanently lost.**

Administered Dose (100%)



Destroyed in or not absorbed by the intestine

Destroyed by the intestinal wall

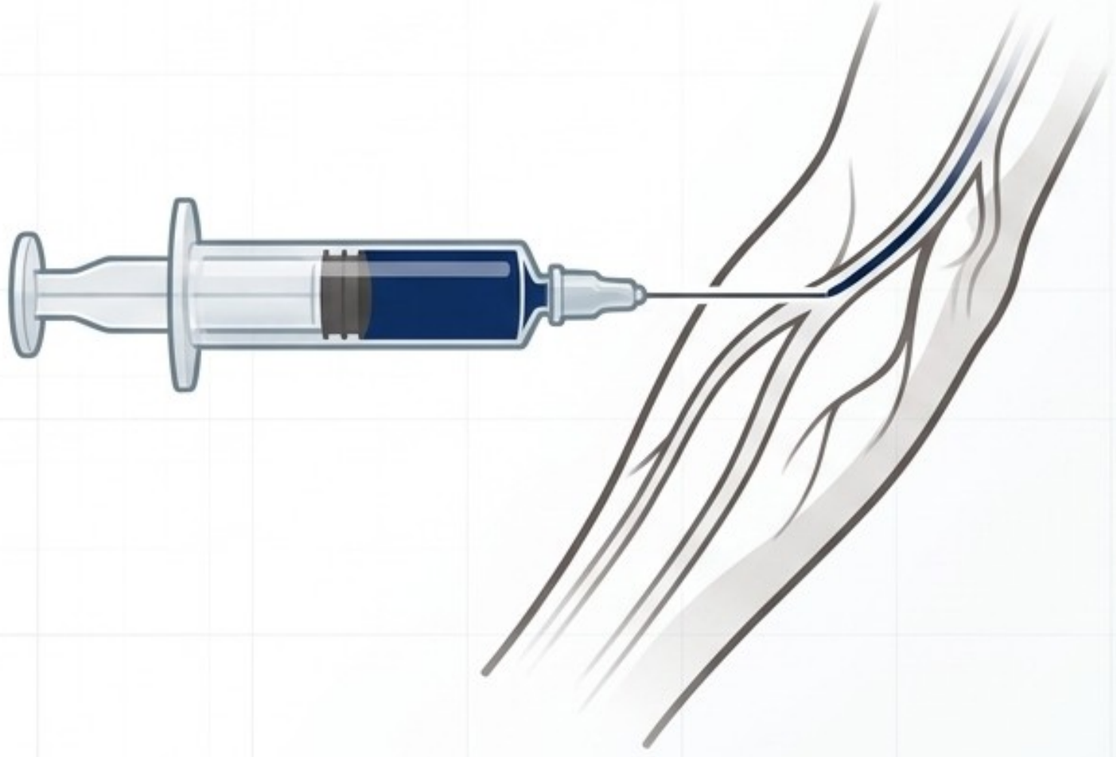
Destroyed by the liver (Hepatic First-Pass)

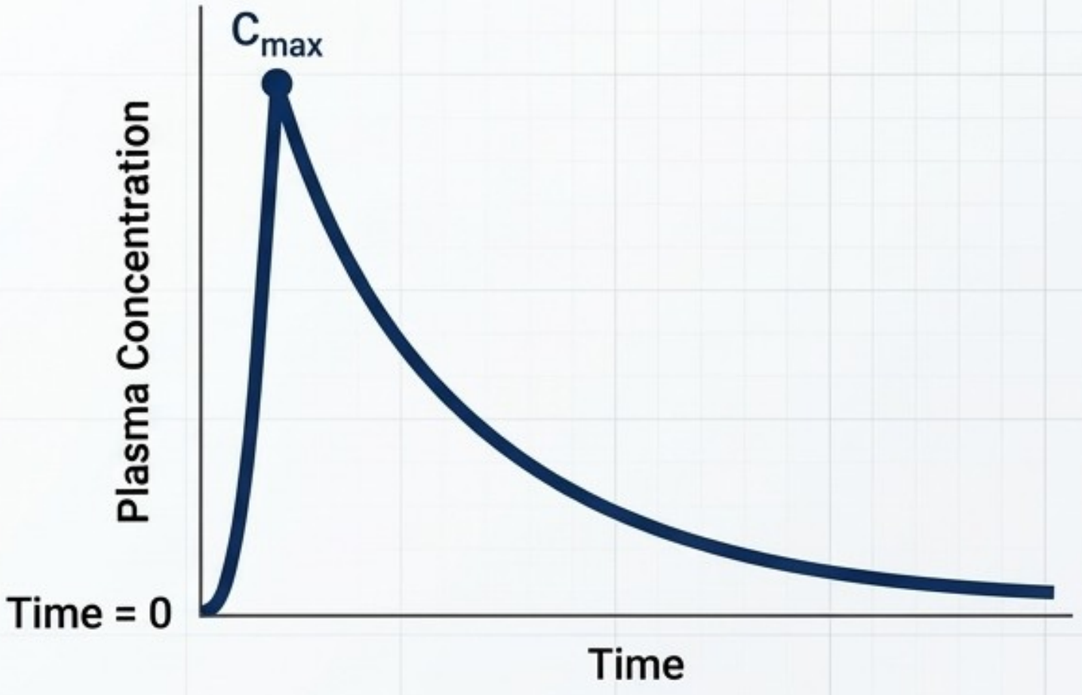
Systemic Circulation (Bioavailability F)

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The Intravenous Baseline Guarantees 100% Bioavailability

By bypassing the gastrointestinal tract entirely, intravenous (IV) administration experiences zero anatomical loss. The active drug is deposited directly into the systemic circulation, resulting in an absolute bioavailability where F = 1.0.





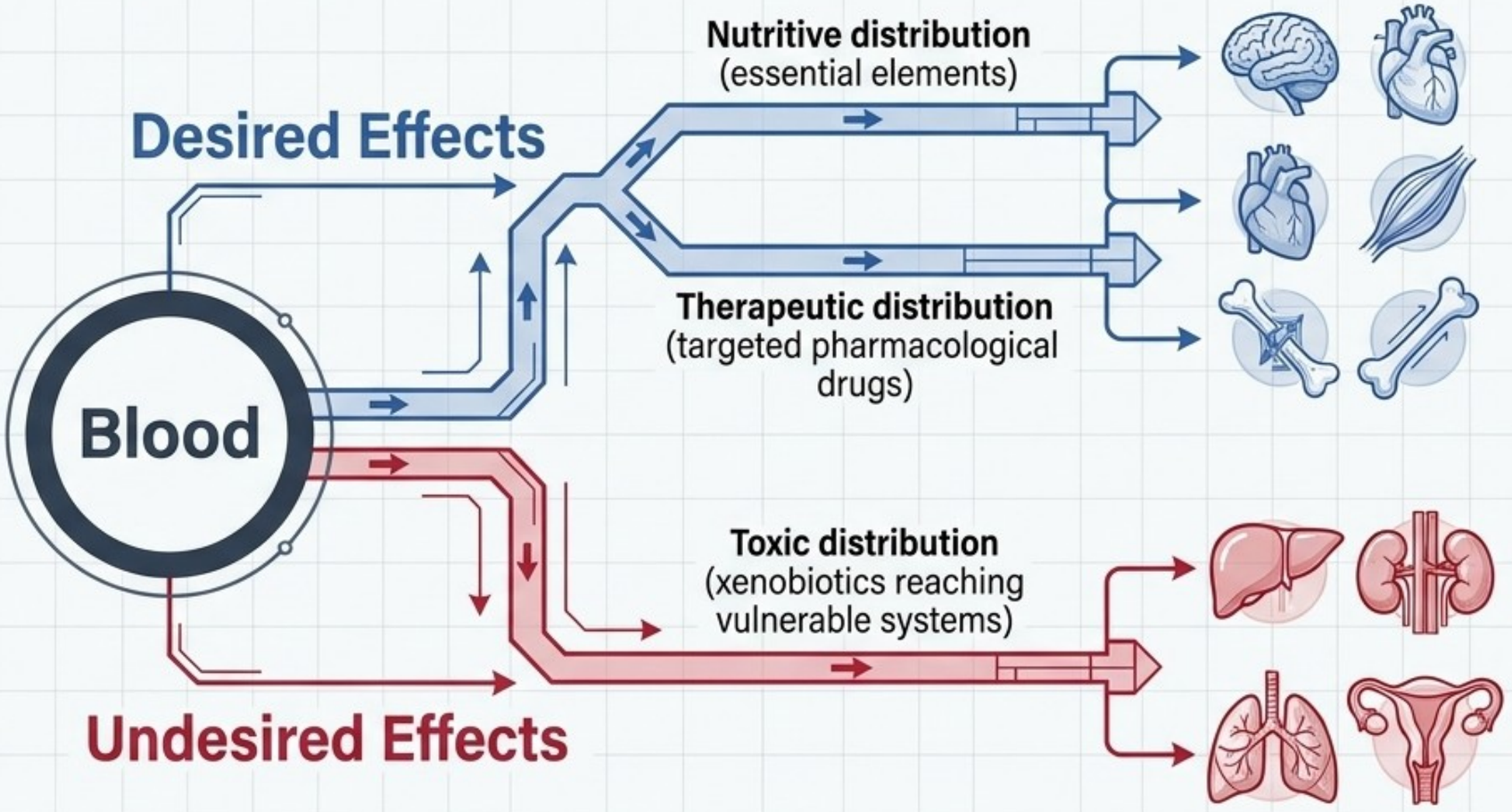
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- The same drug administered via different routes presents completely different bioavailability.
- Notice the tails of the curves: They share the exact same elimination rate, but have entirely different absorption rates.

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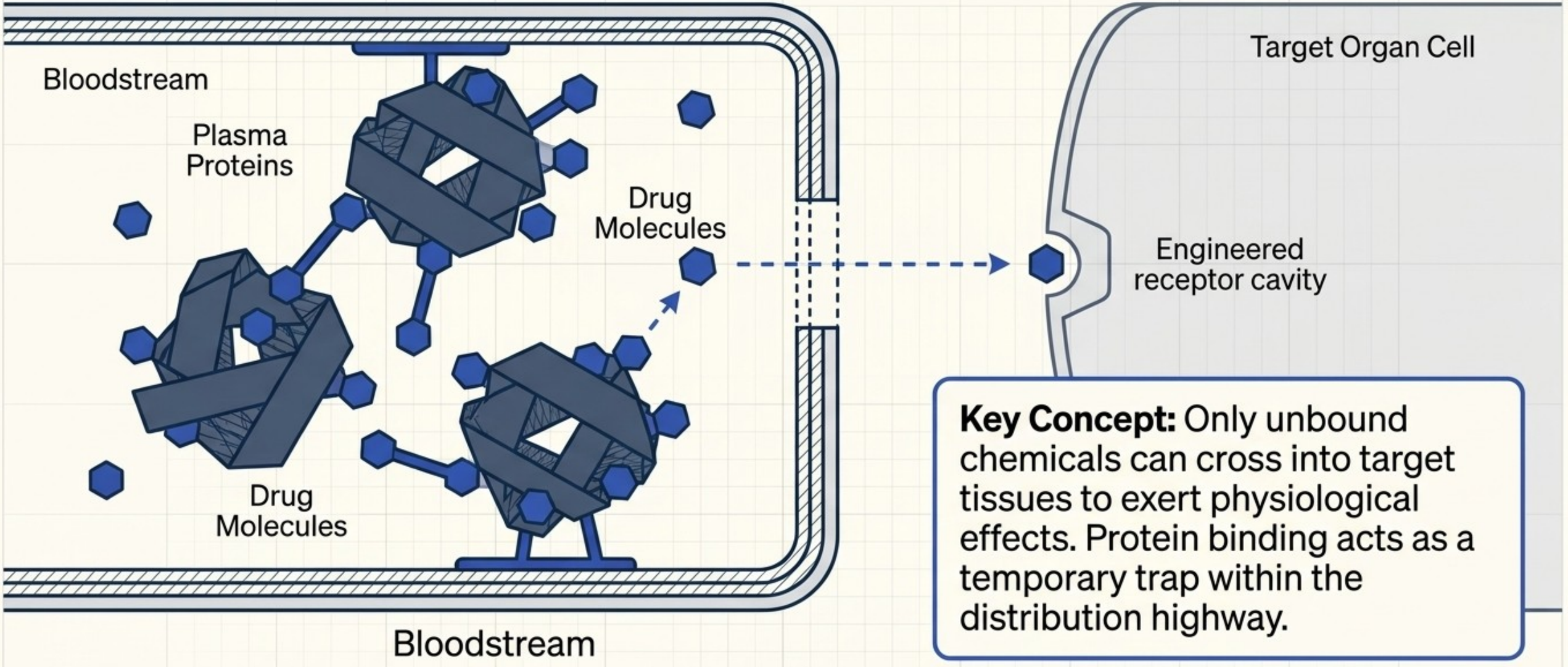
Distribution Along the Blood Highway



Organs respond to circulating chemicals in vastly different ways based on their specific cellular receptors and biological functions.

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The Plasma Protein Tether

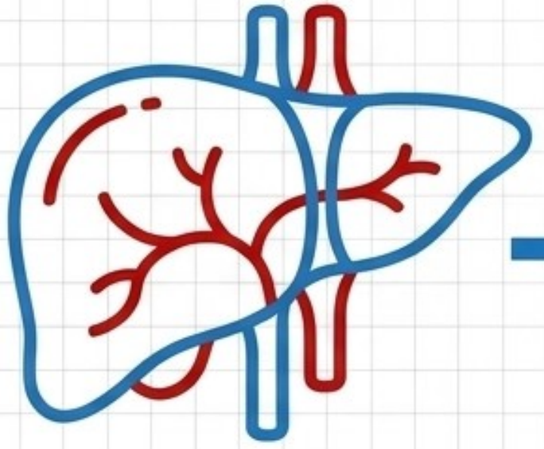


Key Concept: Only unbound chemicals can cross into target tissues to exert physiological effects. Protein binding acts as a temporary trap within the distribution highway.

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The Dual Role of Metabolism

The Liver is the primary site of biotransformation—the most important determinant of duration and intensity of the toxic response.



Activation → Yields a MORE toxic metabolic product (e.g., Parathion converting to Paraoxon). → ***Increases Cellular Damage***

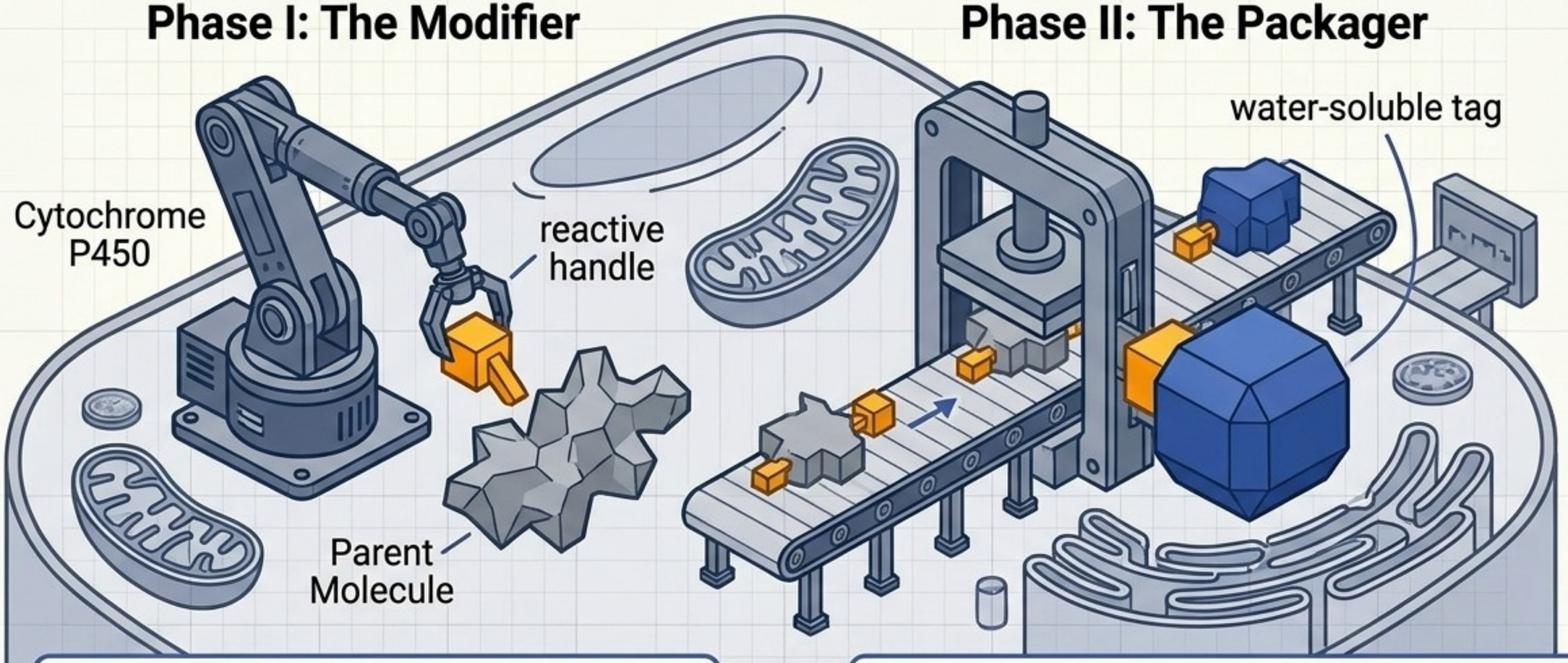
Detoxication → Yields a less toxic metabolic product. → Aids Excretion

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The Cytochrome P450 Assembly Line

Phase I: The Modifier

Phase II: The Packager



Phase I: CYP450 modifies the chemical, adding functional groups to make it chemically reactive.

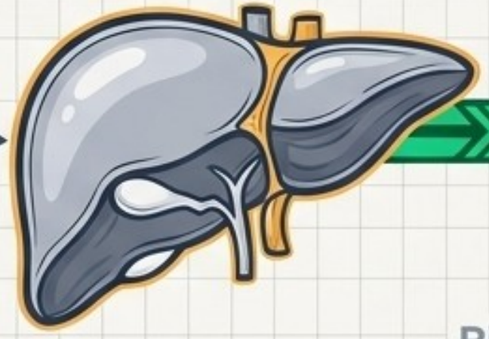
Phase II: Enzymes attach large, **water-soluble tags**, neutralizing the threat and preparing it for immediate physical excretion.

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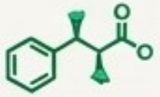
The Metabolism Fork: Detoxication

Parent Substance

Liver



Biotransformation
(Detoxication)



Converted into a Less Toxic Metabolic Product

Safely routed to Excretion channels
(Urine, Feces, Expired Air)



Bioactivation
(Toxification)

Reactive/Toxic Intermediate

Cellular Damage/Toxicity

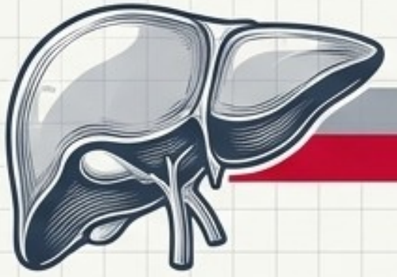
The body's **primary defense mechanism** working as intended: **transforming** a lipophilic threat into a **hydrophilic, excretable waste product**.

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The Metabolism Fork: Lethal Activation

Parent Substance

Liver



Biotransformation
(Detoxication)

Converted into a Less Toxic Metabolic Product

Safely routed to Excretion channels
(Urine, Feces, Expired Air)



The Parathion Misfire: The relatively mild insecticide Parathion enters the liver and is accidentally converted through activation into Paraoxon—a highly potent and deadly neurotoxin.

Clinical Example

Biotransformation Misfire
(Activation)

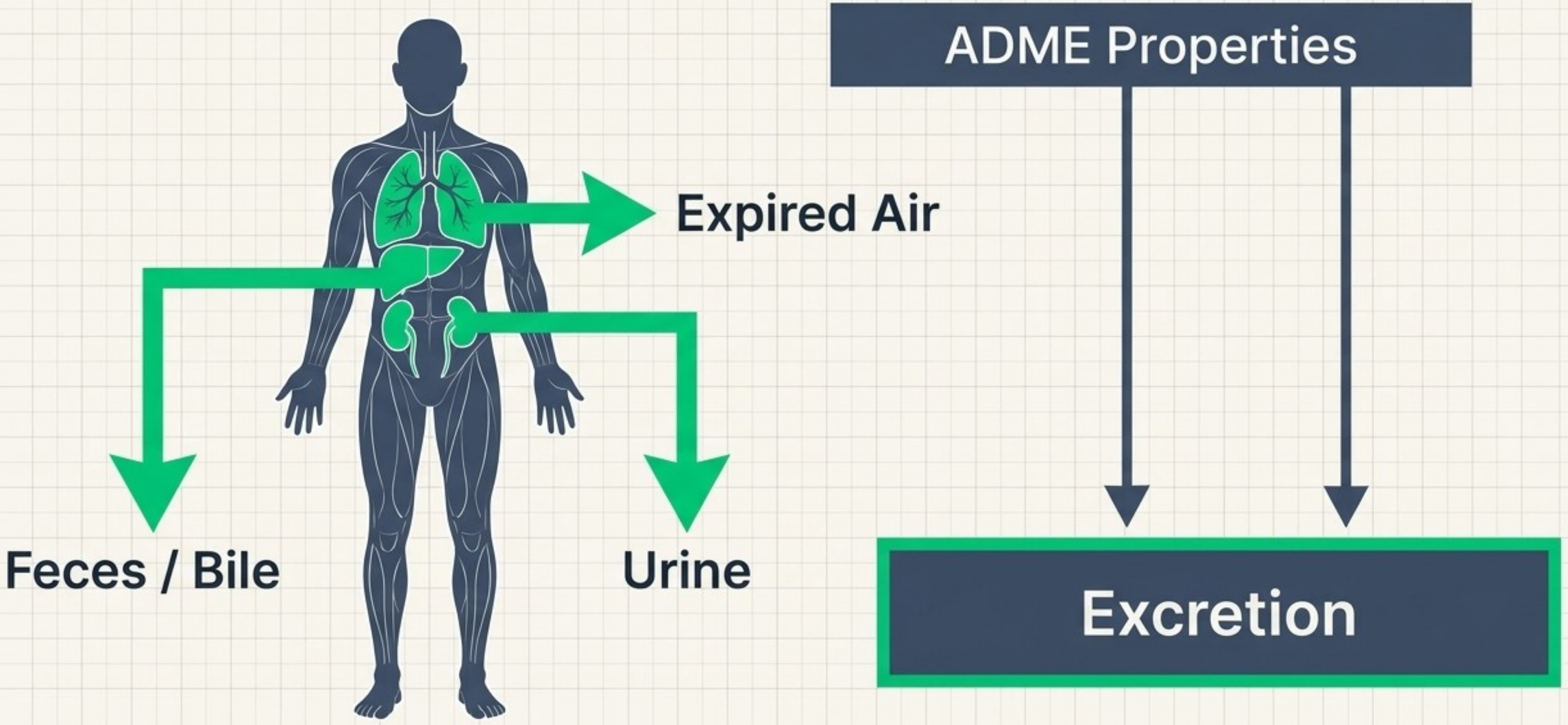
Converted into a More Toxic Metabolic Product



Cellular Damage/Toxicity

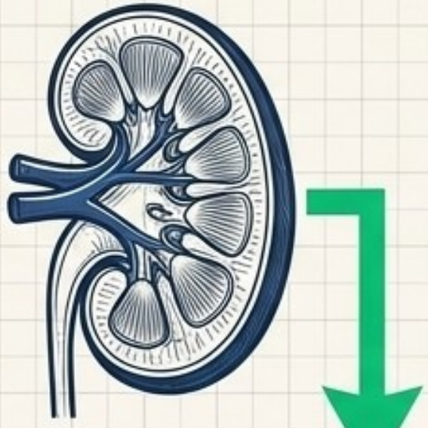
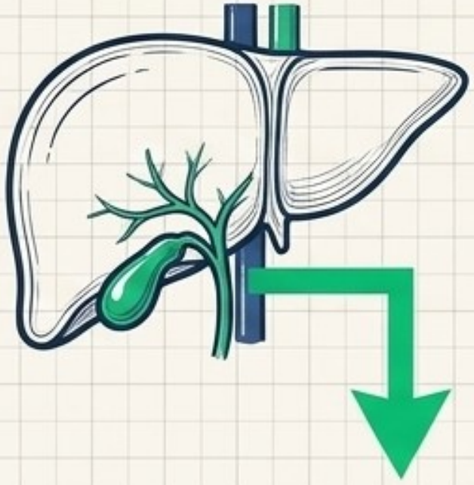
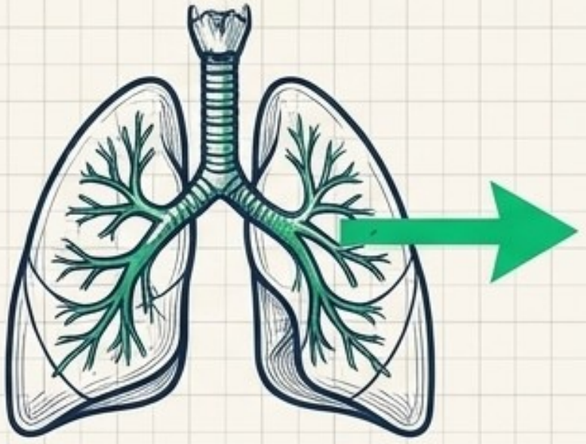
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Excretion: The Physical Exit Routes



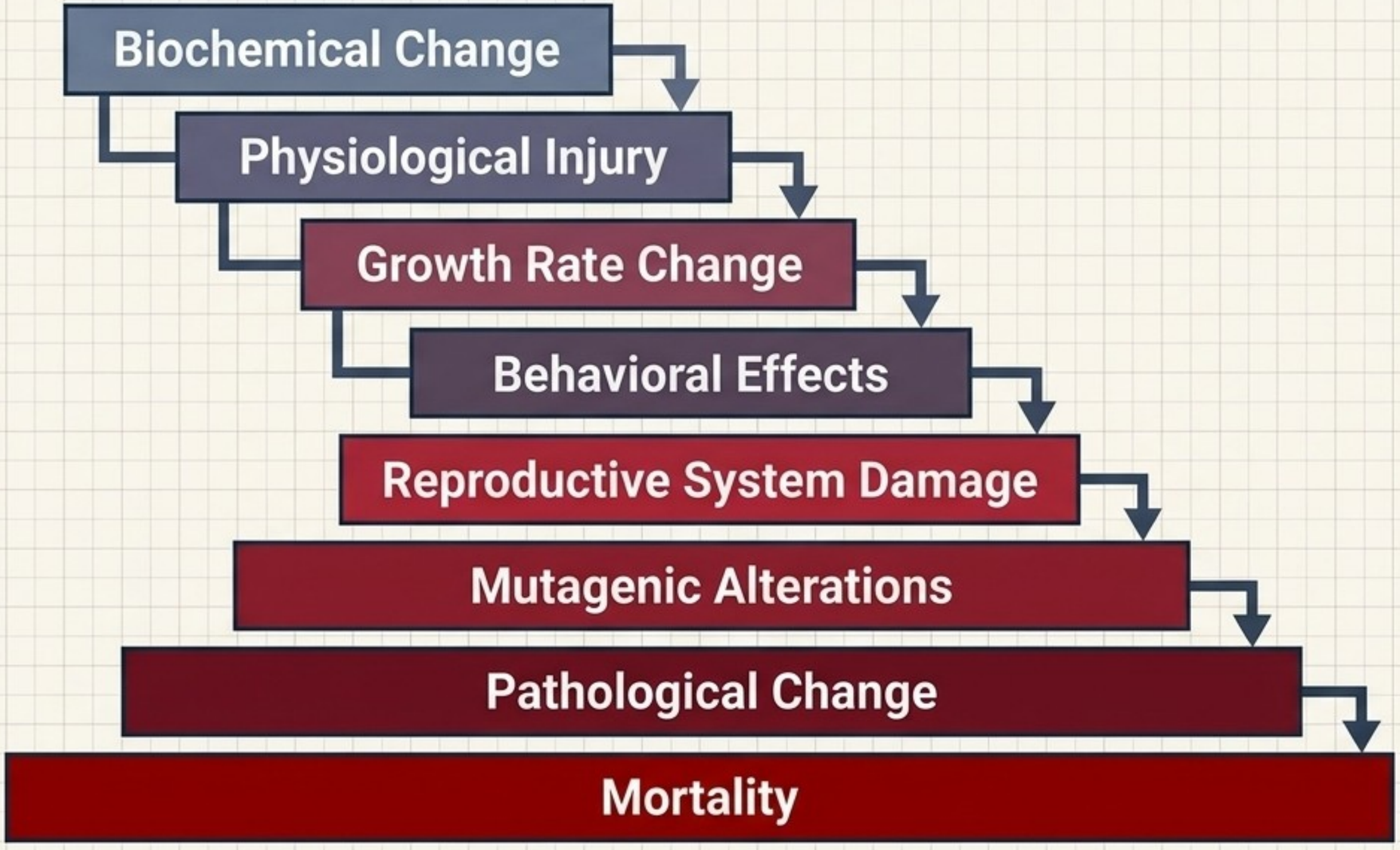
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Routes of Elimination Diagnostic Matrix

Renal Excretion	Biliary Excretion	Pulmonary Excretion
Primary Organ: Kidney	**Primary Organ: Liver**	**Primary Organ: Lung**
		
Exit Medium: Urine	**Exit Medium: Feces / Bile**	**Exit Medium: Expired Air**
Mechanism Notes: The dominant pathway for water-soluble products resulting from Phase II biotransformation.	**Mechanism Notes:** Primarily for large, heavy molecules processed directly by the liver that cannot pass through the renal filters.	**Mechanism Notes:** Specialized route for volatile liquids and toxic gases (e.g., anesthetics, asphyxiants).

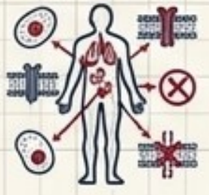
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The Anatomy of Toxicity



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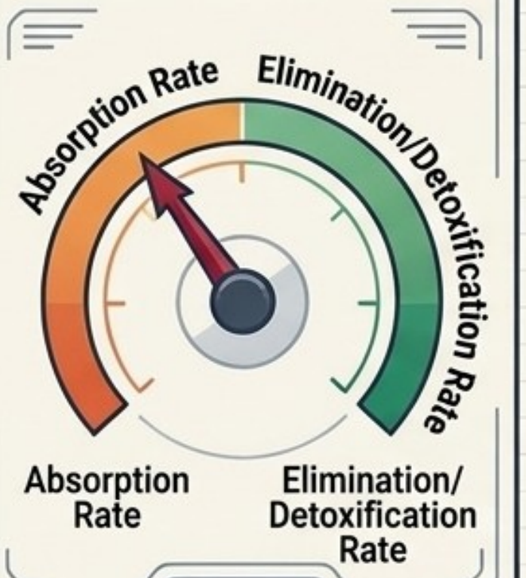
Target Organ Toxicity Map

Clinical Classifications	Target Systems
Hepatotoxic	 Liver Damage
Nephrotoxic	 Kidney Dysfunction
Neurotoxic	 Central/Peripheral Nervous System Damage
Pulmonary	 Lung & Respiratory Tract Injury
Irritant / Asphyxiant / Anesthetic	 Systemic / Membrane / Receptor Disruption

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Factors Influencing Intensity

Rate of Exposure



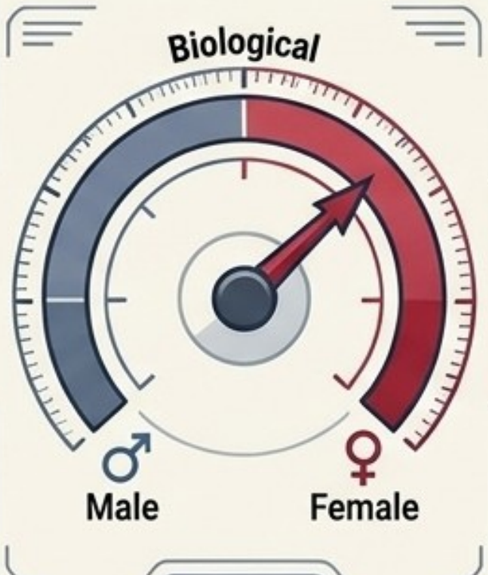
The tug-of-war between the rate of absorption versus the rate of elimination/detoxification.

Age of Host



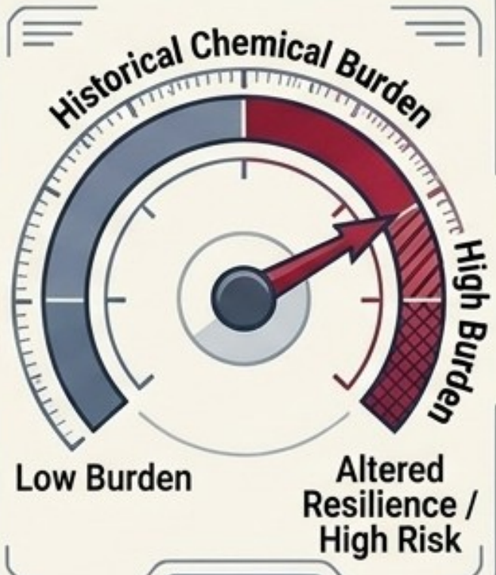
Extreme sensitivity at the biological margins (babies and older populations).

Gender



Biological variations resulting in certain substances being highly toxic to one gender over another.

Prior Exposure

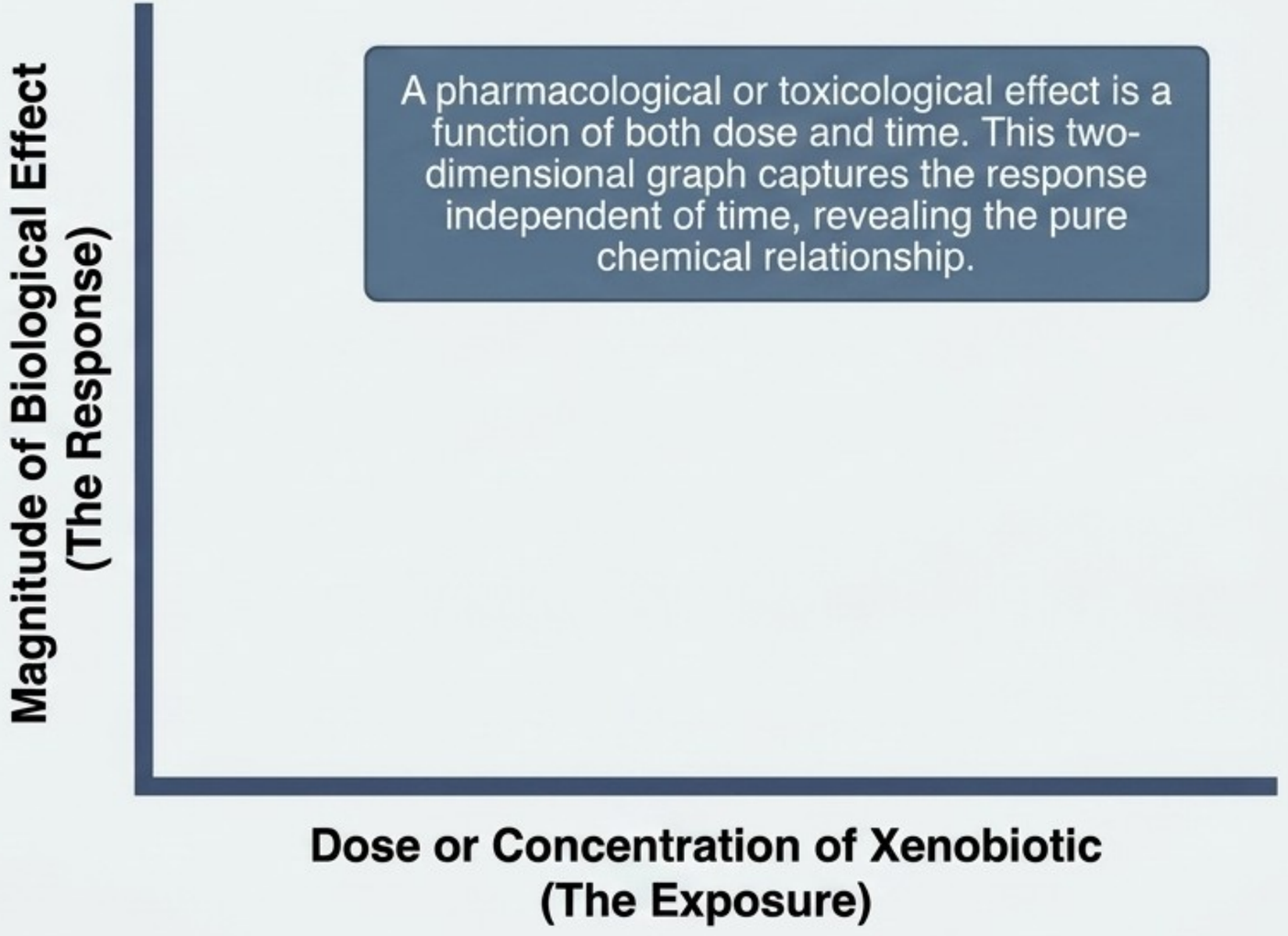


Historical chemical burden altering current system resilience.

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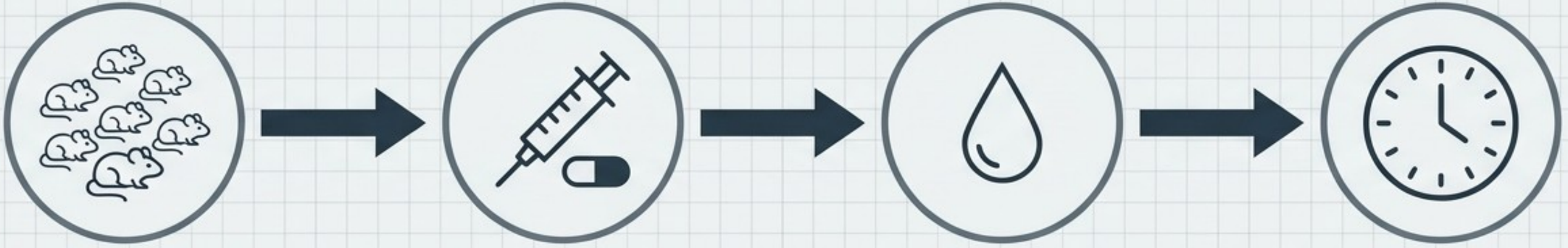
ACUTE TOXICITY

The Architecture of the Relationship



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Experimental Pipeline



1. Cohort Selection

Specify exact species, strain, and sex to ensure a homogeneous biological baseline.

2. Administration Route

Specify entry method (Oral, IV, Inhalation) as absorption drastically alters toxicity.

3. Exposure

Exposure must be a single, acute dose.

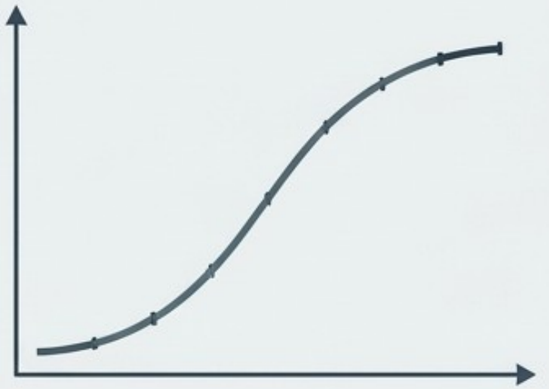
4. Observation Window

By strict convention, lethality is tracked over exactly 24 hours.

LD50 (Median Lethal Dose): The statistically derived single dose of a substance expected to cause death in 50% of the tested animal population.

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Graded Response (Individual)



Measures the continuous intensity of an effect within a single biological system (e.g., blood pressure, organ weight).

Quantal Response (Population)



An “All-or-None” response. Measures the frequency of a specific binary outcome across a population.

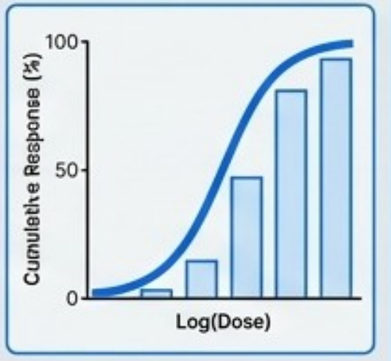
Lethality is the ultimate quantal response. An individual is either alive or dead. Therefore, toxicity must be mapped as a percentage of a population responding at specific doses.

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Graded Response
(The Individual)

Nature	Continuous scale.
Measurement	Measures the intensity of a response in a single biological system as dose increases (e.g., organ weight, blood glucose).
Concept	How severe is the effect in this one subject?

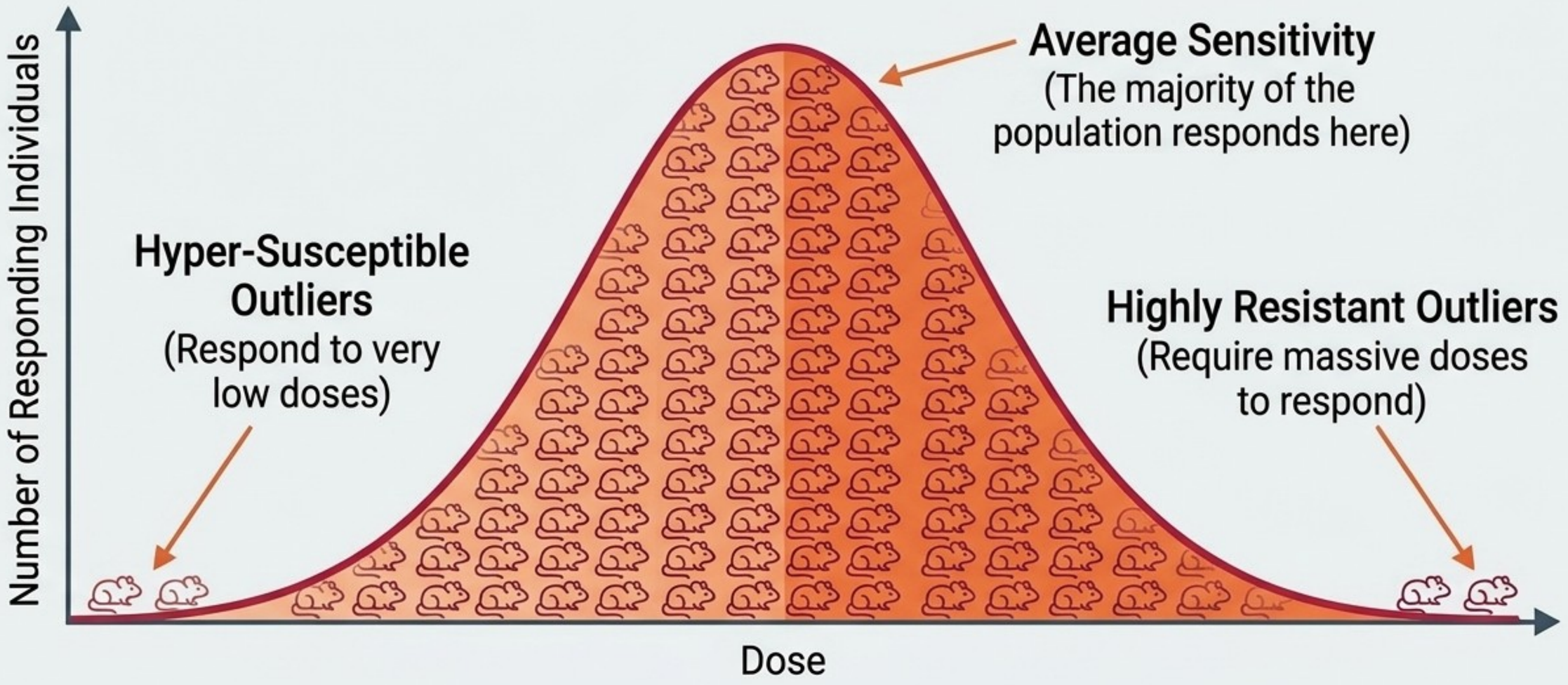
Quantal Response
(The Population)



Nature	All-or-nothing scale.
Measurement	Measures the frequency of a specific binary response across a group (e.g., mortality, tumor appearance).
Concept	What percentage of the population shows the effect?

Synthesis Note: Though distinct in methodology, plotting cumulative Quantal responses yields the identical sigmoidal curve used for Graded individual responses.

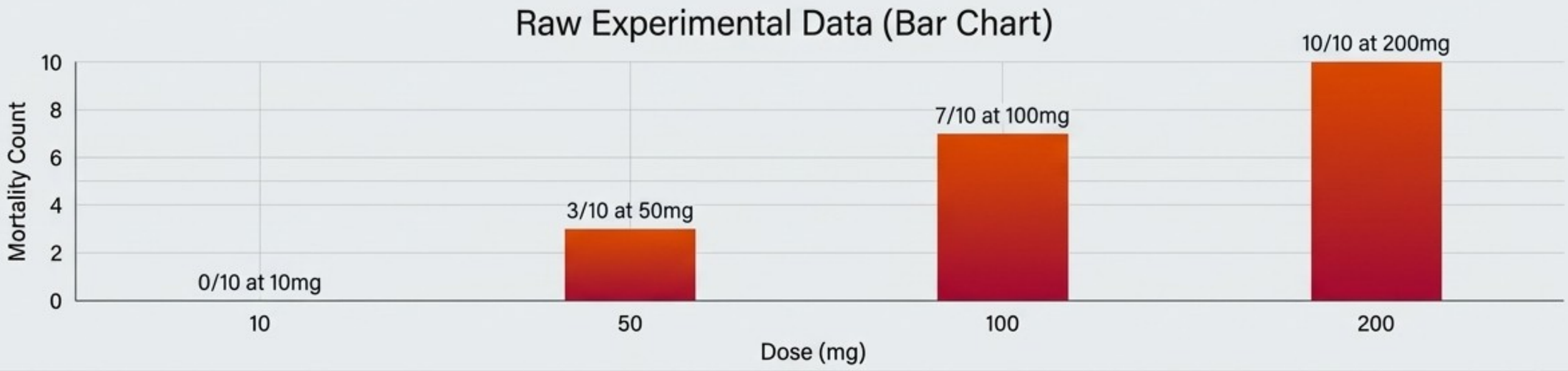
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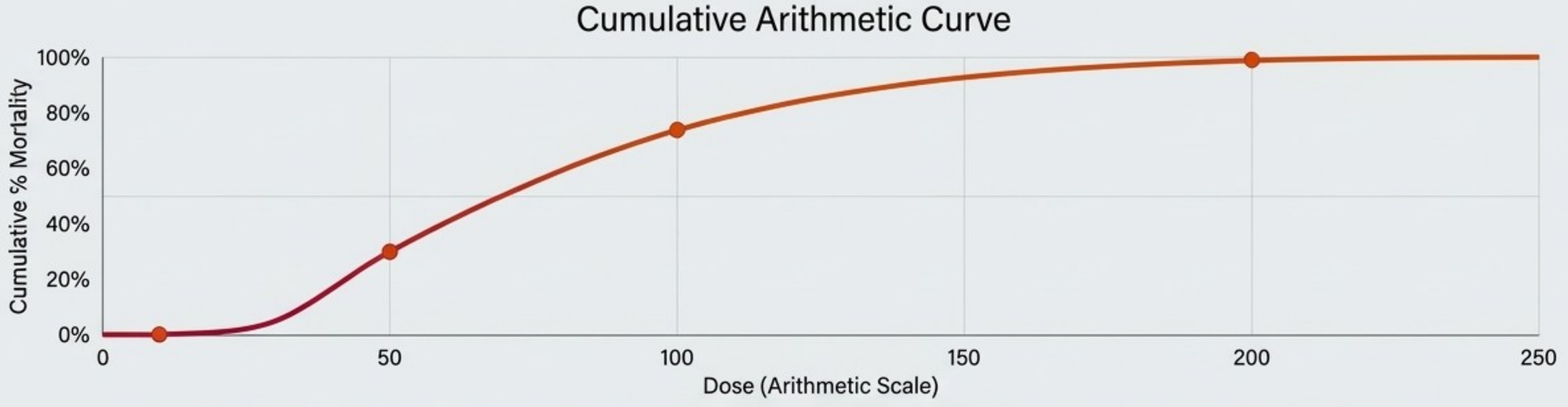


Biological variance dictates that to find the true average toxicity, we must plot the cumulative response of the entire spectrum of individuals.

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Data Translation: Raw Data to Cumulative Arithmetic Curve

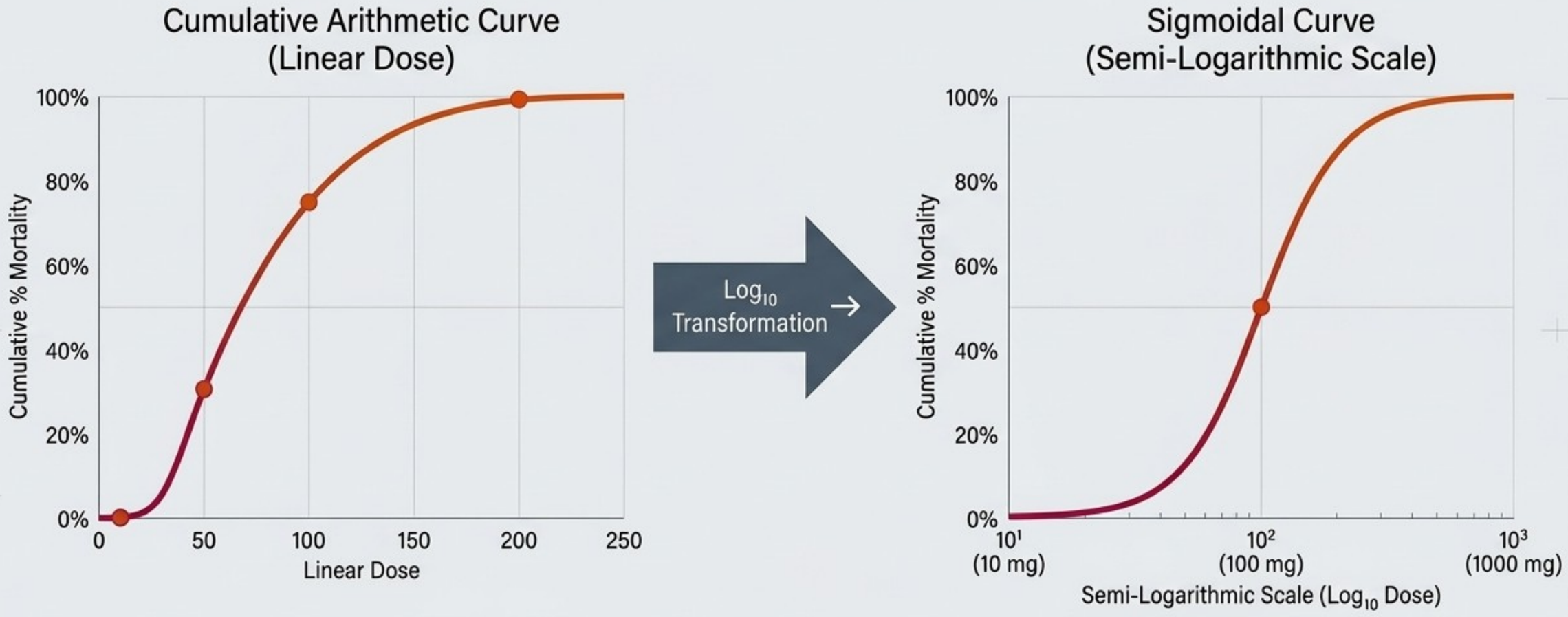




Adding the individual frequencies together creates a Cumulative Percent Mortality curve. However, on an arithmetic scale, the low-dose responses are compressed, making exact mid-point derivation mathematically difficult.

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Data Transformation: Linear to Semi-Logarithmic Scale

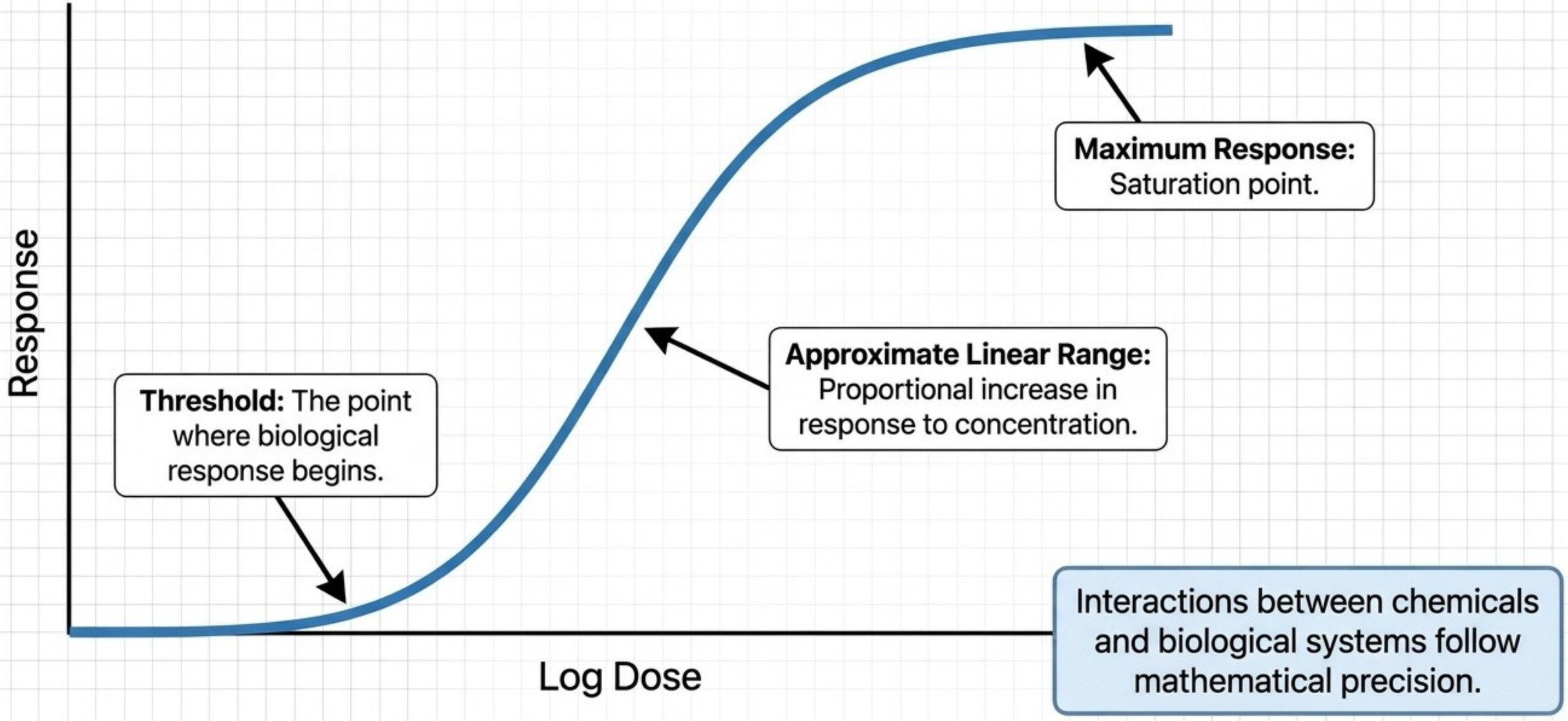


Why Logarithmic?

It stretches out the critical low-dose region and compresses the less relevant high-dose region, transforming the data into a perfectly symmetrical mathematical model.

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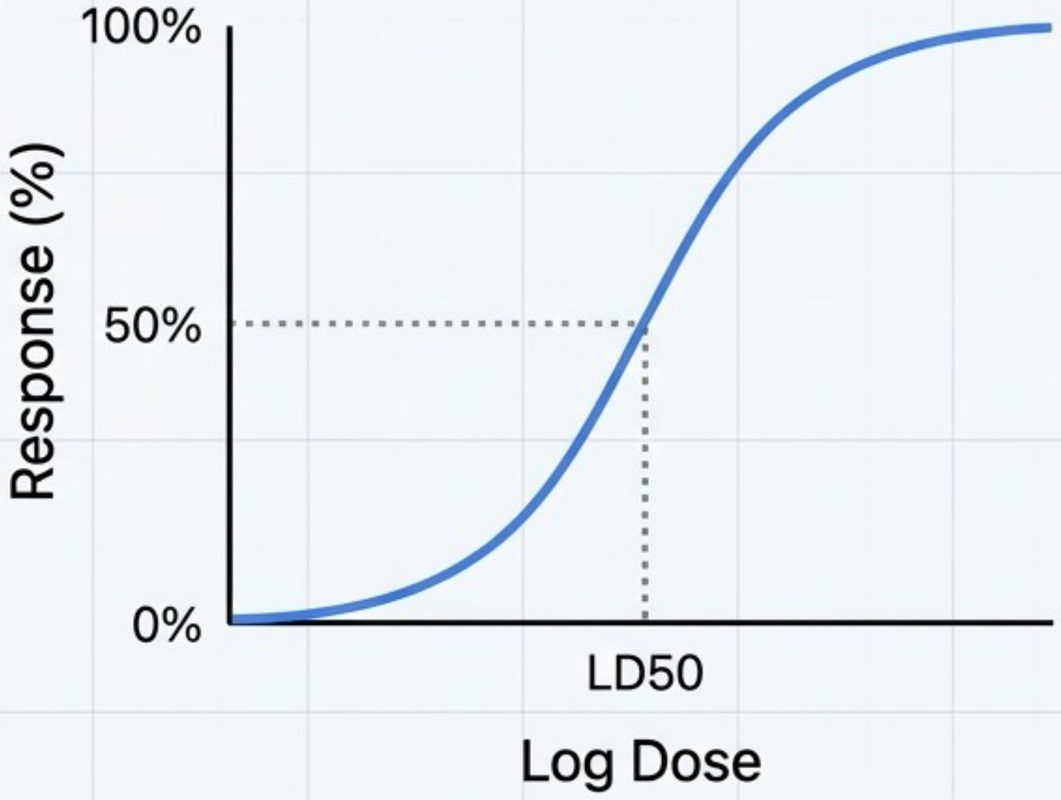
Toxicodynamics: Anatomy of the Dose-Response Curve



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Quantifying Toxicity: ED50 & LD50

- **ED50:** Effective Dose in 50% of the population.
- **LD50: Median Lethal Dose** (kills 50% of test population).

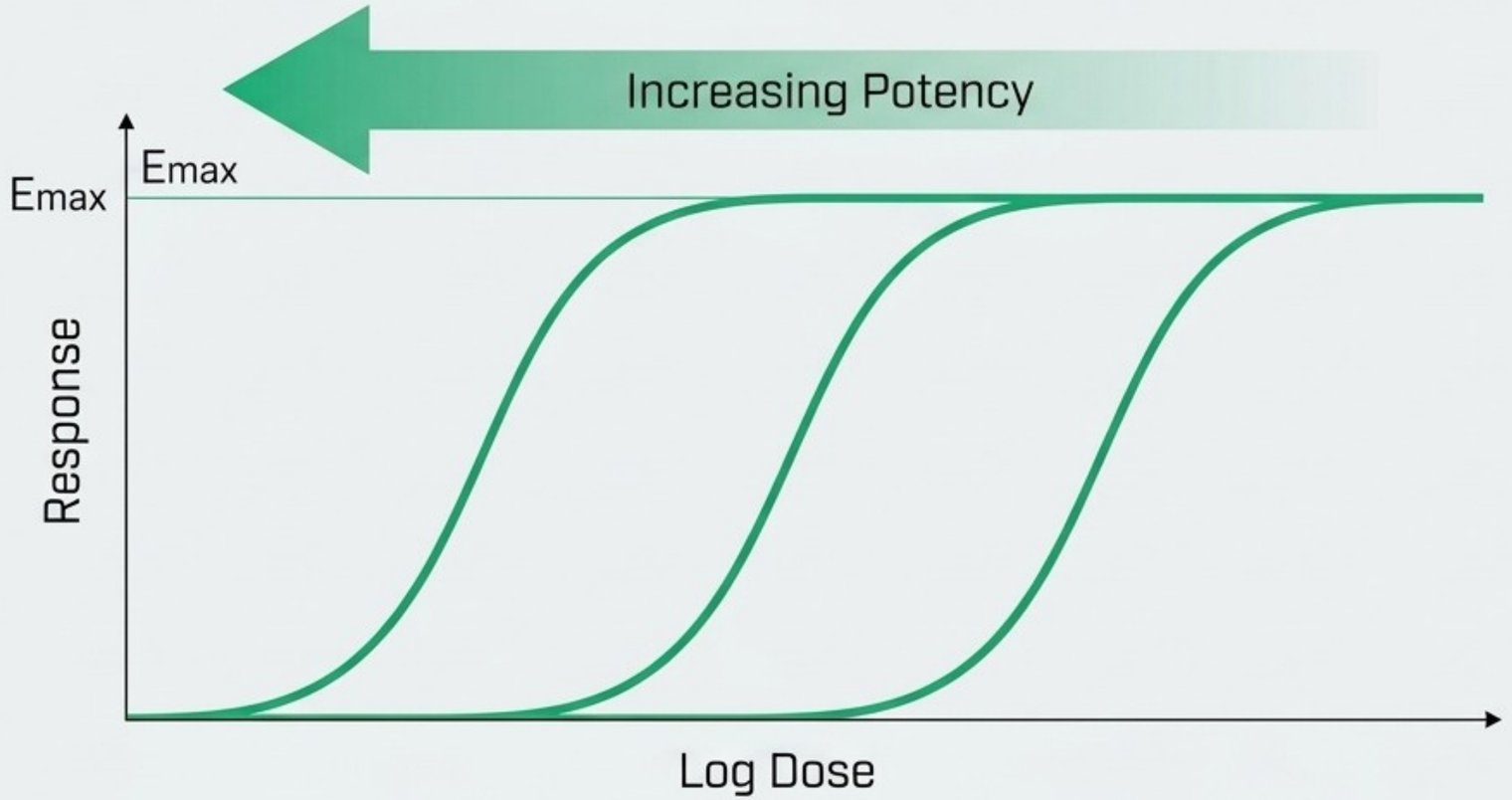


Toxicity Level (by LD50 / kg body weight)

≤ 1mg	Extremely Toxic (e.g., Botulinum toxin at 100ng)
1 - 50mg	Highly Toxic
50 - 500mg	Moderately Toxic (e.g., Caffeine at 200mg)
> 500mg	Non Toxic (e.g., Sodium chloride at 40g)

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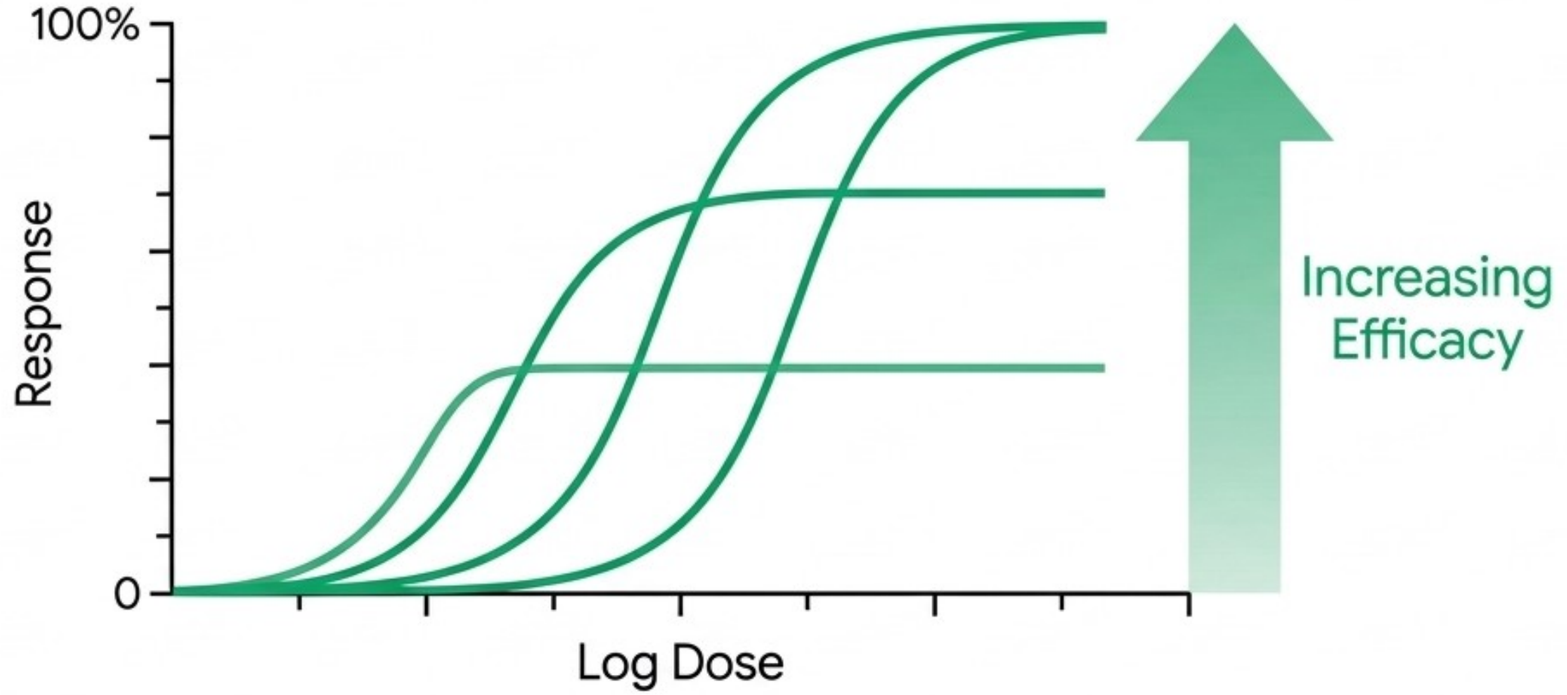
Chemical Dynamics: Potency



Potency describes the affinity a drug has for a receptor. When a curve shifts to the left, a lower concentration is required to reach the ED_{50}. The substance on the far left is the most potent.

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Chemical Dynamics: Efficacy

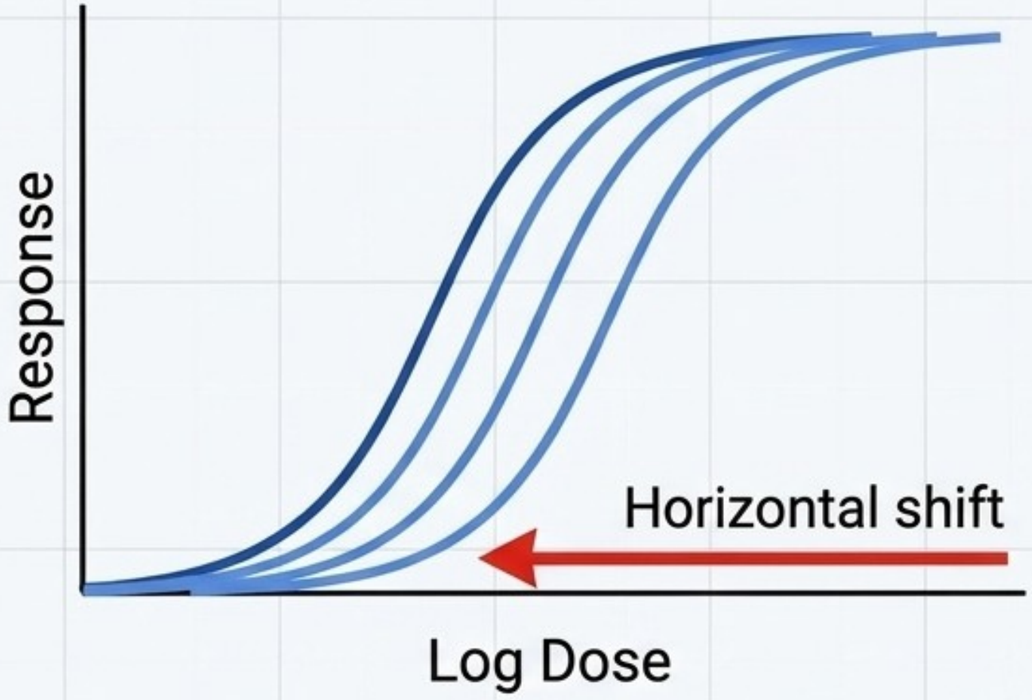


Efficacy dictates the maximum biological response (E_{max}) achievable. Even at infinite doses, a drug with lower efficacy cannot achieve the maximum effect of a superior agonist because it cannot trigger the same degree of receptor activation.

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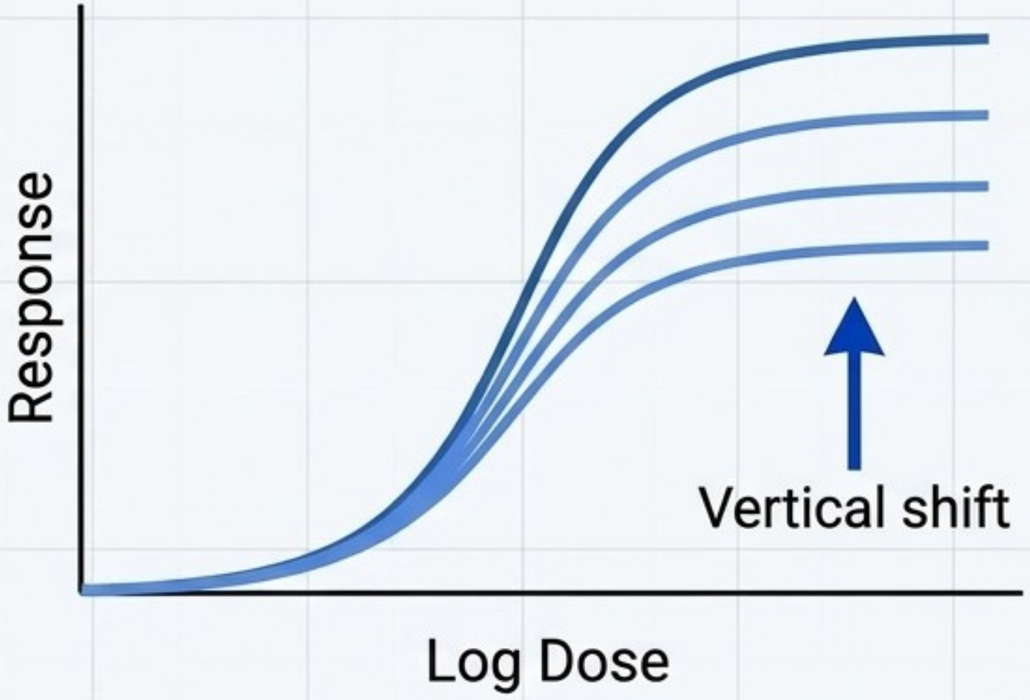
Diagnostic Matrix: Potency vs. Efficacy

POTENCY



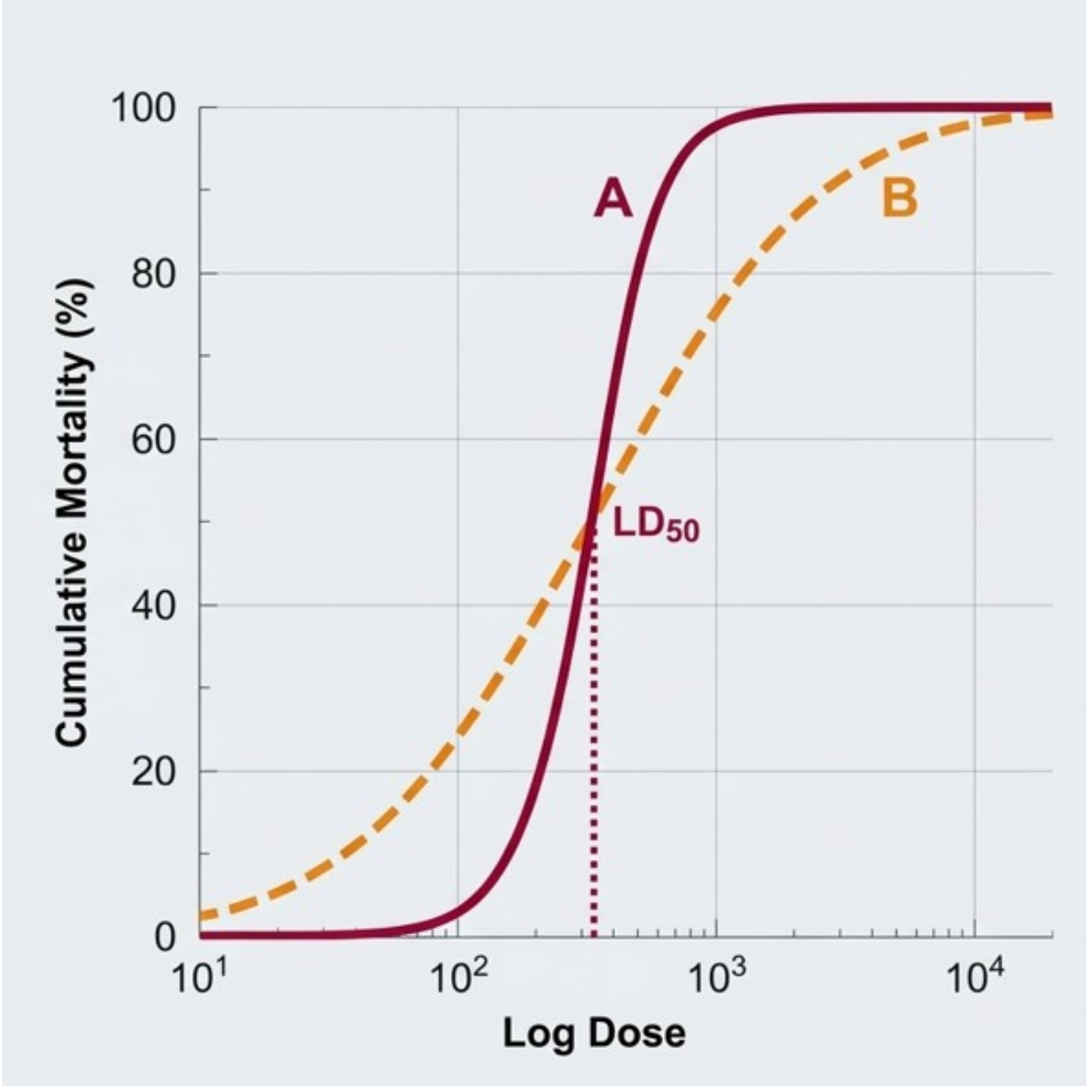
The lower the EC_{50}, the higher the drug potency (requires less drug to obtain the effect).

EFFICACY



The higher the E_{max}, the higher the efficacy (maximum achievable biological response).

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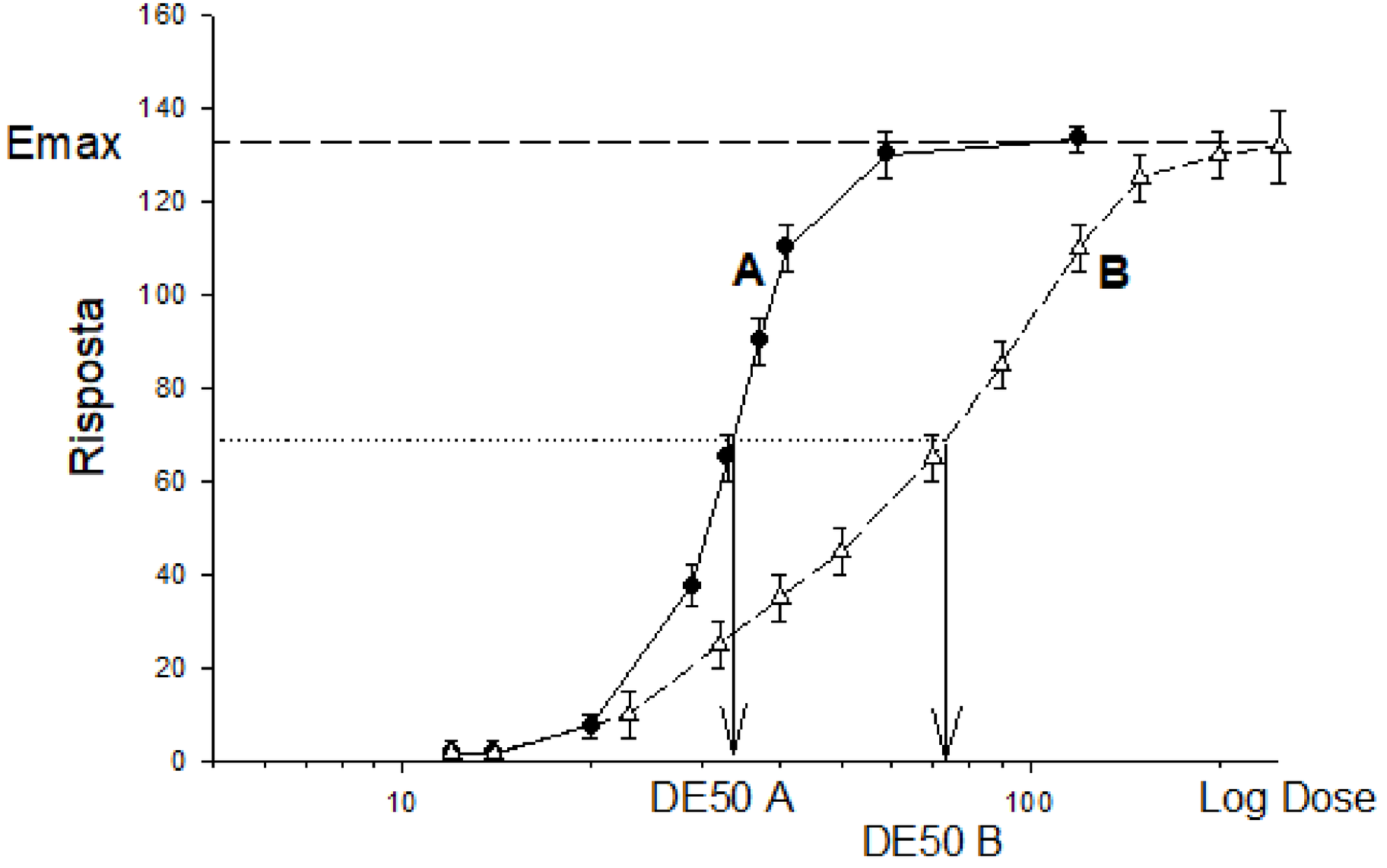
The Danger of Averages

Both chemicals share the exact same LD50.

However, Chemical B (shallow slope) represents a **significant hazard even at very low doses,** causing early casualties.

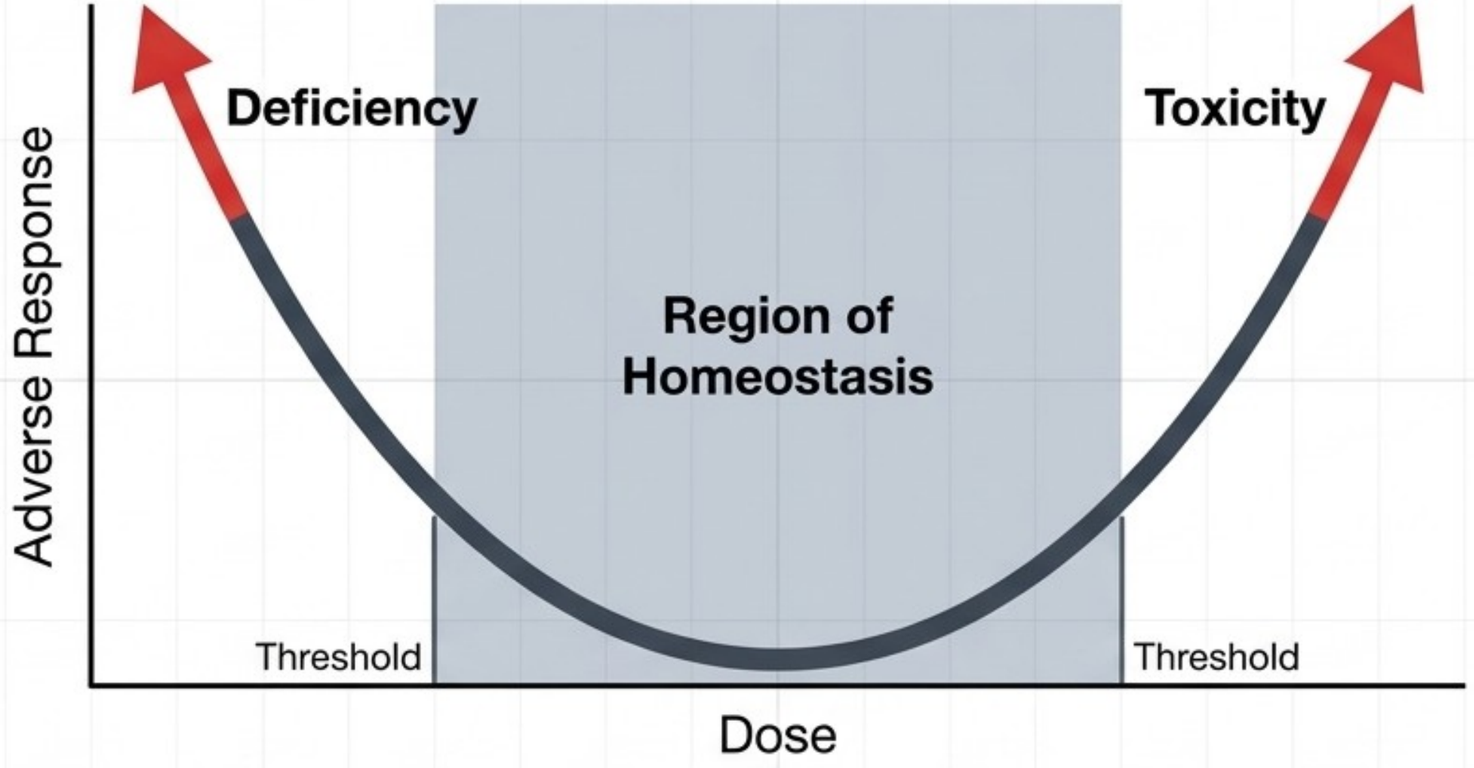
Chemical A **(steep slope) is entirely safe at low doses, but becomes rapidly lethal with tiny concentration increases once the threshold is crossed.**

Slope determines predictability.


160
140
120
100
80
60
40
20
0
Emax
Risposta
A
B
10
100
DE50 A
DE50 B
Log Dose

The Exception: Essential Nutrients

Some chemicals have both therapeutic and toxic effects based on a U-shaped dose-response.



Example: Vitamin A	
Deficiency: Blindness, dry skin, increased infections.	**Toxicity:** Anorexia, joint pain, liver damage.

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