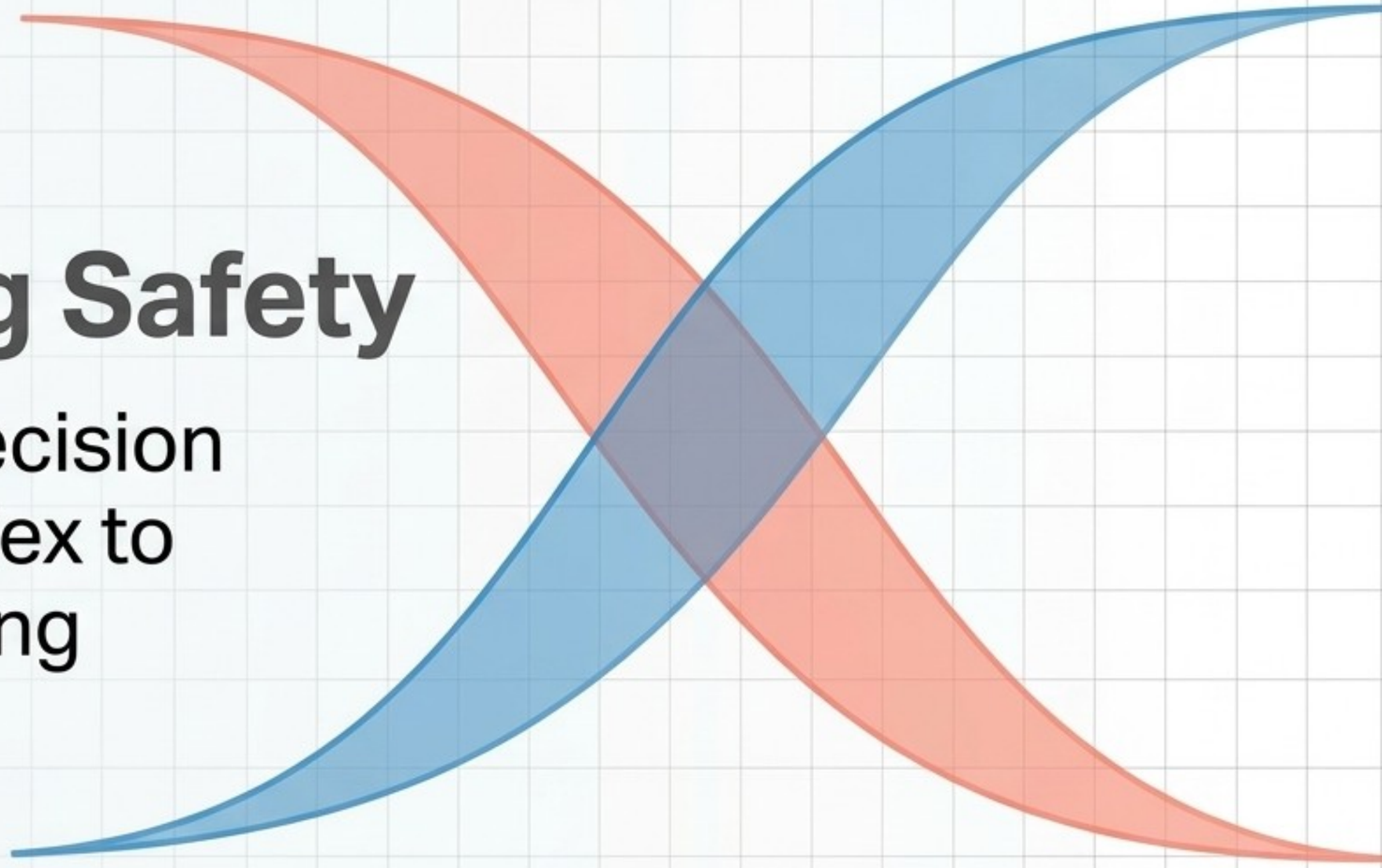
Quantifying Drug Safety

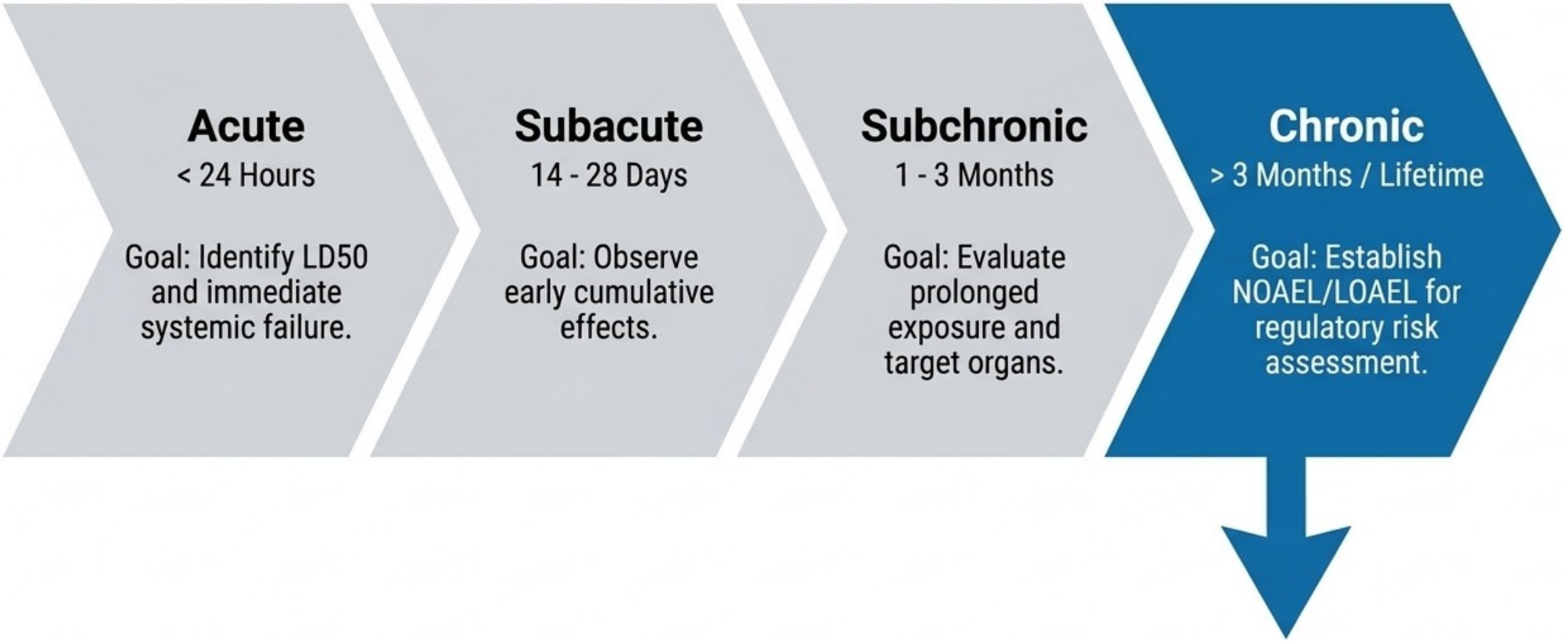
Tracing the pursuit of precision from the Therapeutic Index to Benchmark Dose Modeling



University Lecture Series | Pharmacology & Toxicology

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Empirical Toxicity Testing

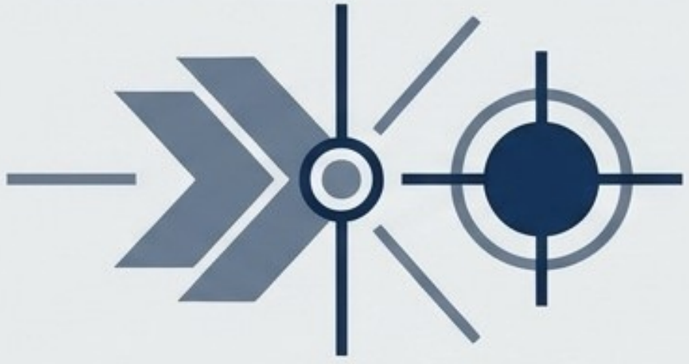


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Transition to Risk Assessment

The goals of toxicological animal studies.

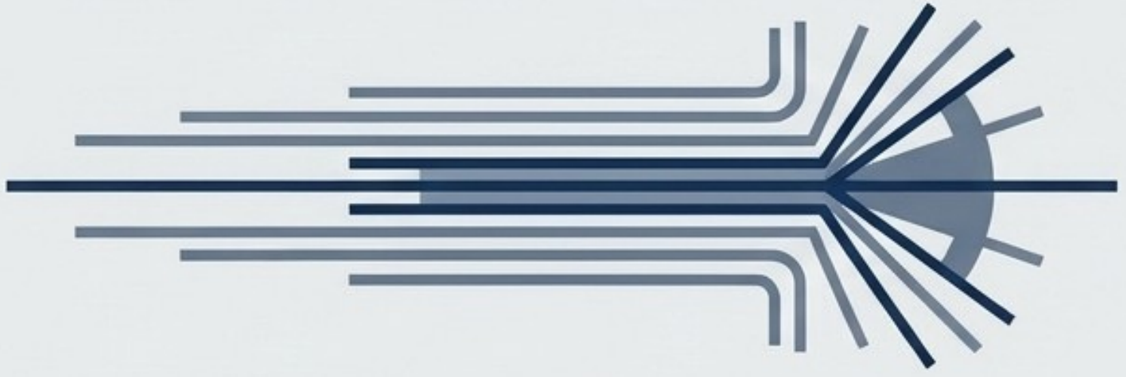
Acute/Subacute Studies



Goal: Determine lenethirum.

- **Goal:** Determine lethality thresholds.
- **Key Output:** LD50 and LC50.

Subchronic/Chronic Studies



- **Goal:** Evaluate long-term safety, cumulative effects, and establish non-carcinogenic safety thresholds.
- **Key Output:** Identification of NOEL, NOAEL, LOEL, and LOAEL to calculate the Acceptable Daily Intake (ADI), NOAEL, LOEL, and LOAEL to calculate the Acceptable Daily Intake (ADI).

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Designing Chronic Toxicity Tests

Lifetime Simulation

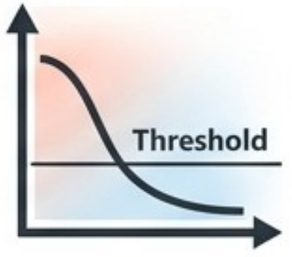
Tests run from 6 months up to 2 years, simulating lifetime exposure to identify late-onset pathologies or cumulative damage.

Continuous Dosing

Animals receive the agent daily, mimicking continuous human pharmaceutical usage or environmental exposure.

Endpoint Monitoring

Continuous tracking of behavior, organ weights, hematology, and ultimate histopathology.



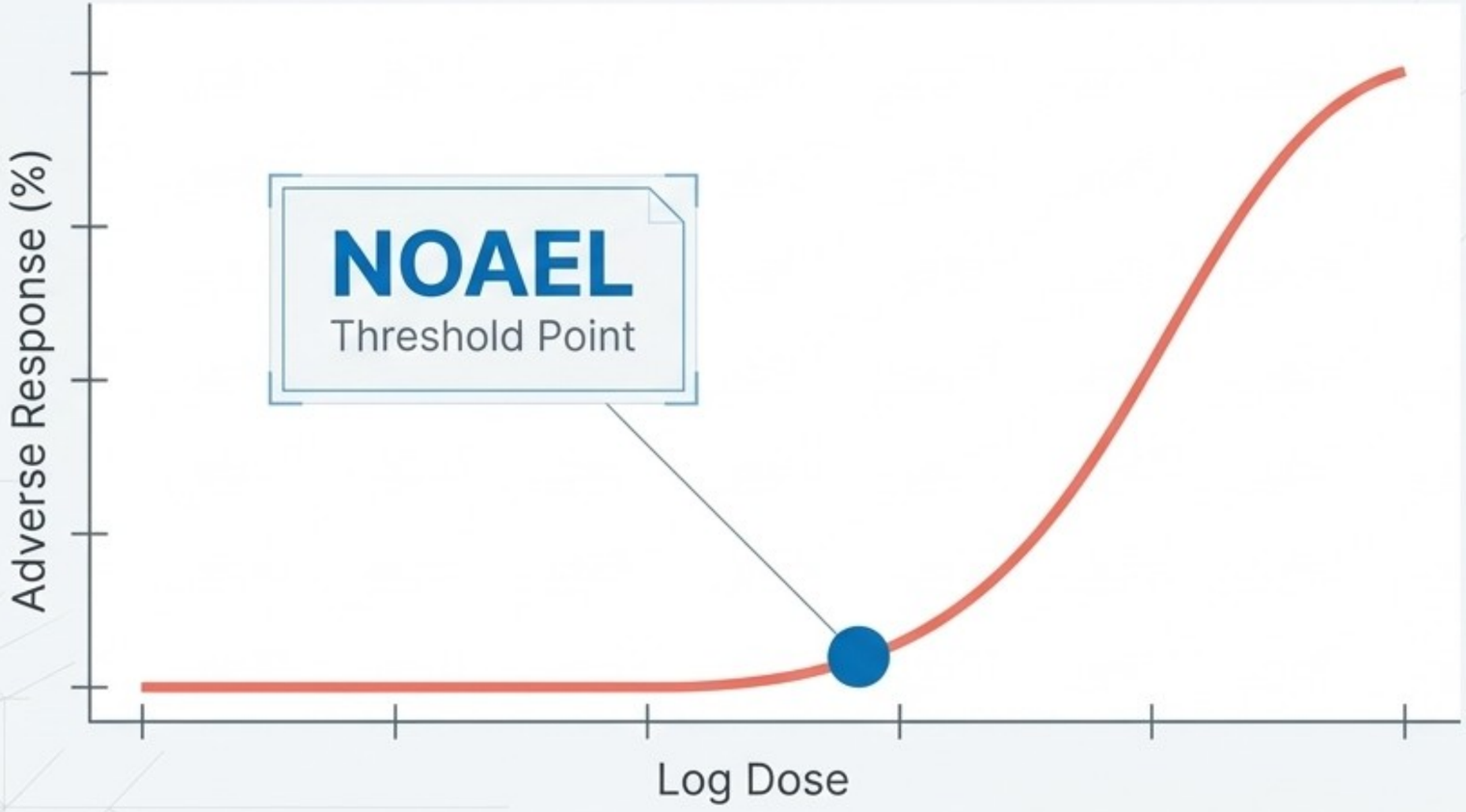
Threshold Identification

The primary objective is to systematically lower the dose until zero adverse effects are observed.

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Establishing the Universal Starting Block

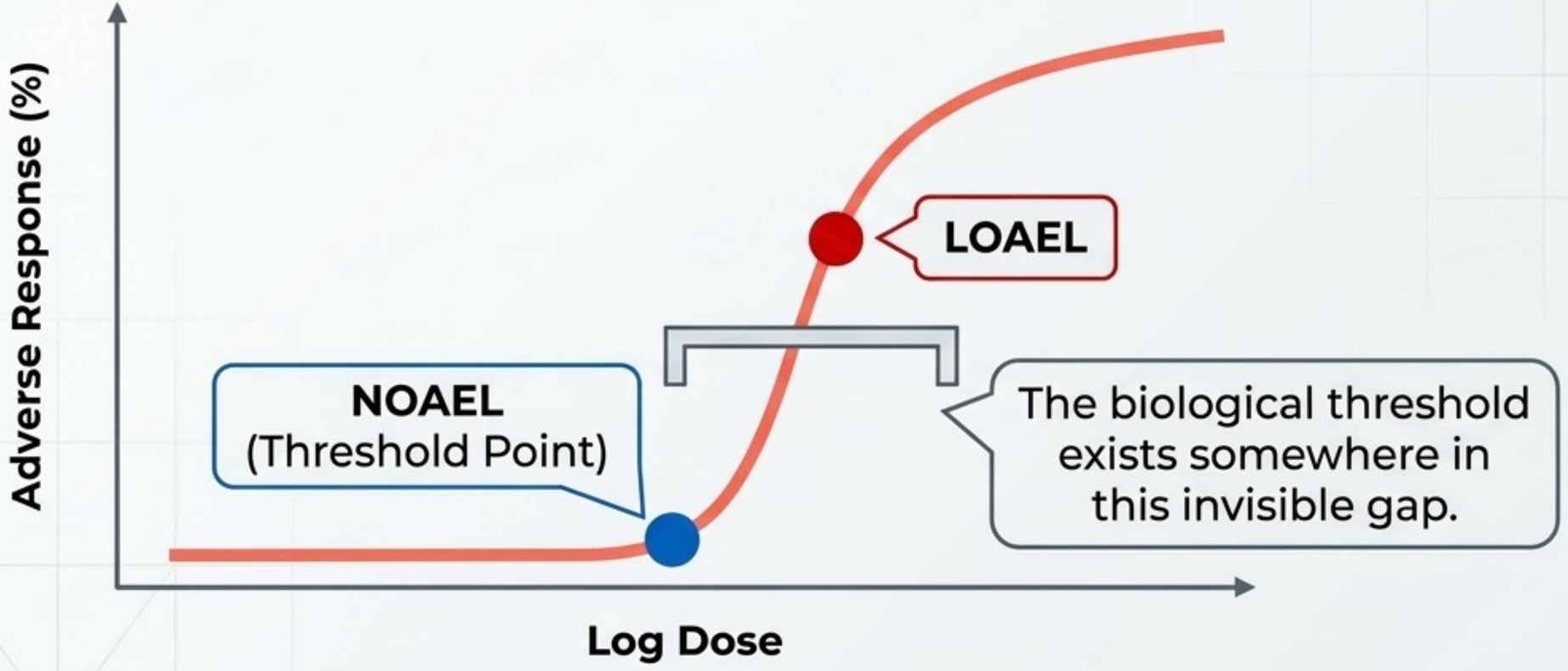
NOAEL (No-Observed-Adverse-Effect Level): The highest experimentally tested dose where zero biologically adverse alterations are observed. This specific empirical data point is the universal foundation for all human safety extrapolation.



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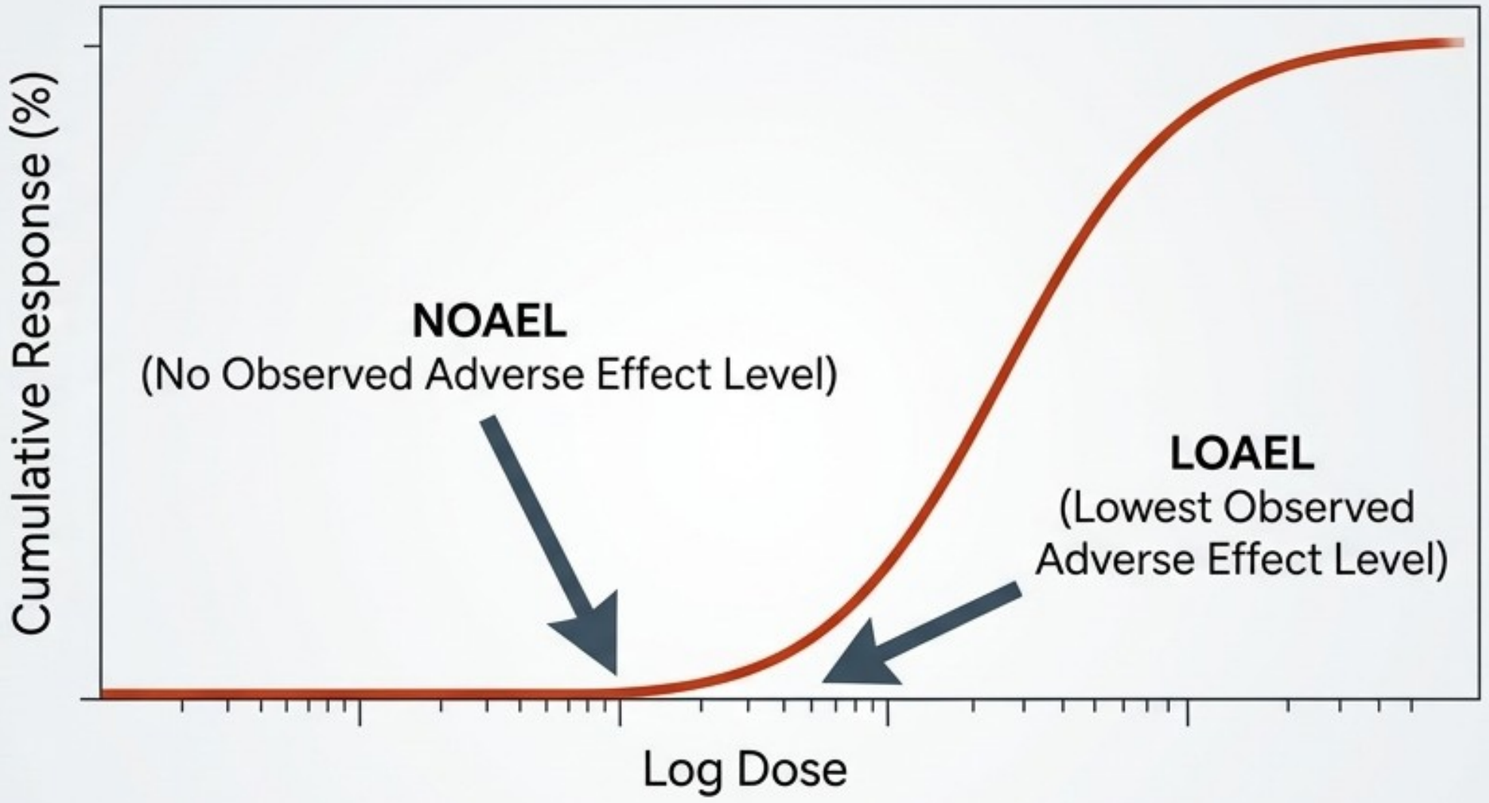
The Biological Reality of LOAEL

LOAEL (Lowest-Observed-Adverse-Effect Level): The lowest experimentally tested dose causing a statistically significant adverse effect. Because scientists only test discrete doses, the true biological threshold remains hidden between NOAEL and LOAEL.



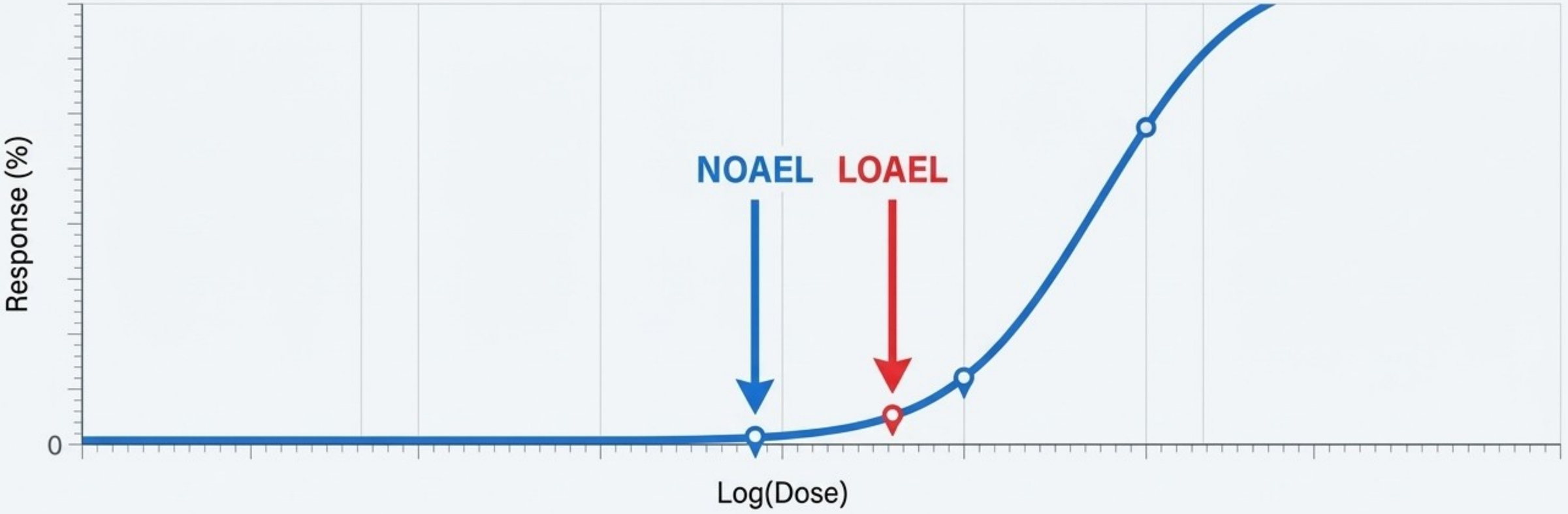
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Sub-lethal Adverse Effect Thresholds: NOAEL & LOAEL



Modern toxicological risk assessment for non-carcinogens relies entirely on finding the NOAEL to establish Acceptable Daily Intakes (ADI), moving beyond mere survival to ensure quality of life.

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Defining Toxicological Endpoints

NOEL / NOAEL (No Observed Adverse Effect Level)

The highest tested dose (in mg/kg) revealed by long-term animal studies that induces zero adverse toxic effects. This is the baseline metric for all regulatory safety.

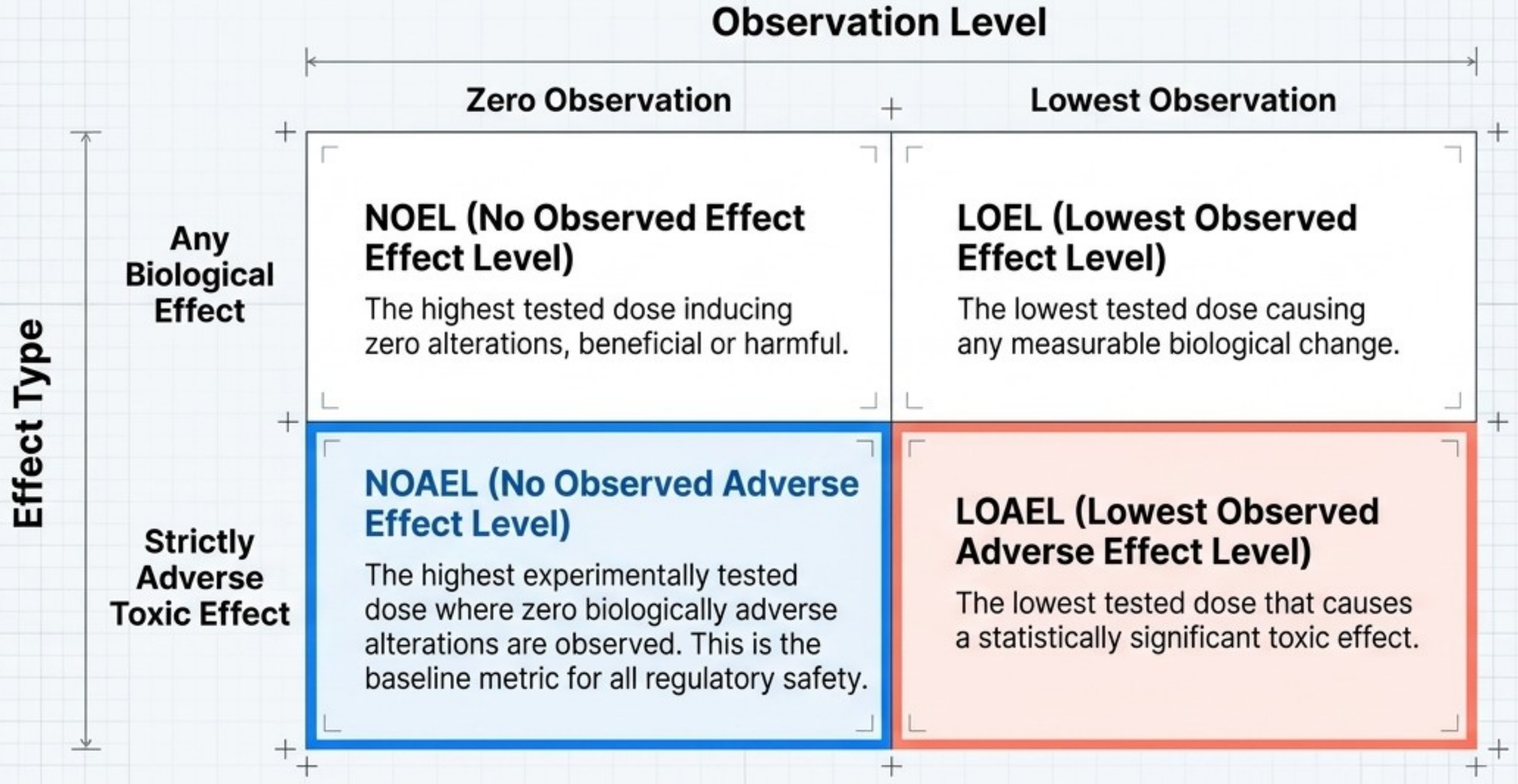
LOEL / LOAEL (Lowest Observed Adverse Effect Level)

The lowest tested dose that causes a statistically significant toxic effect.

Note: These thresholds are highly sensitive to experimental design, particularly the spacing of doses and the species selected.

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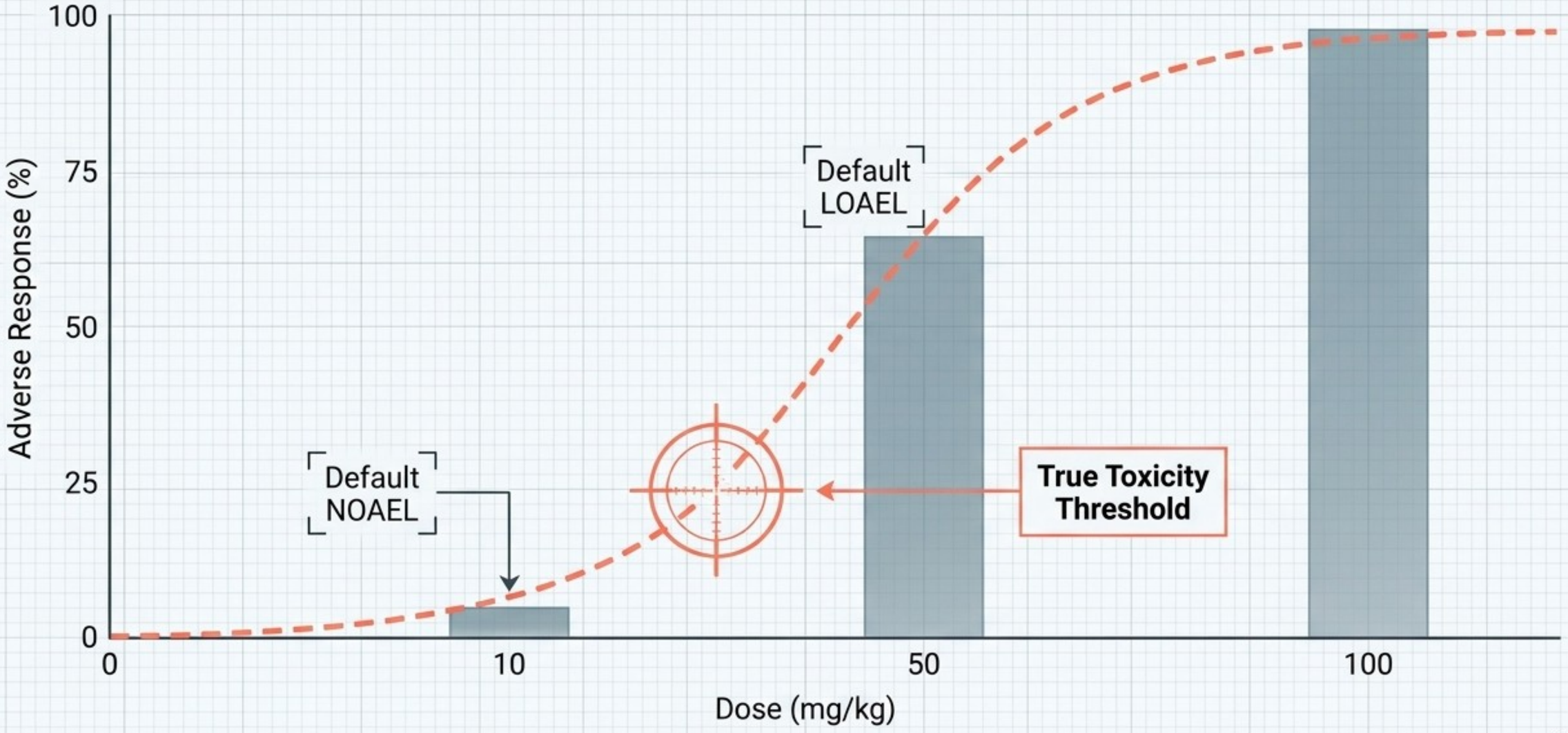
Defining Toxicological Endpoints



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Overcoming Protocol Dependency with Benchmark Doses

NOAEL and LOAEL are constrained entirely by the arbitrary doses a researcher chooses to test. Modern Benchmark Dose (BMD) modeling fits mathematical curves to all available data points to calculate the true, hidden threshold, eliminating protocol dependency.



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The Non-Carcinogen Principle

For non-carcinogens and non-genotoxic carcinogens, toxicology assumes a strict biological threshold exists below which zero toxicity occurs.

The Dilemma



We have found the exact safe dose in a highly controlled, genetically identical animal population.

The Reality

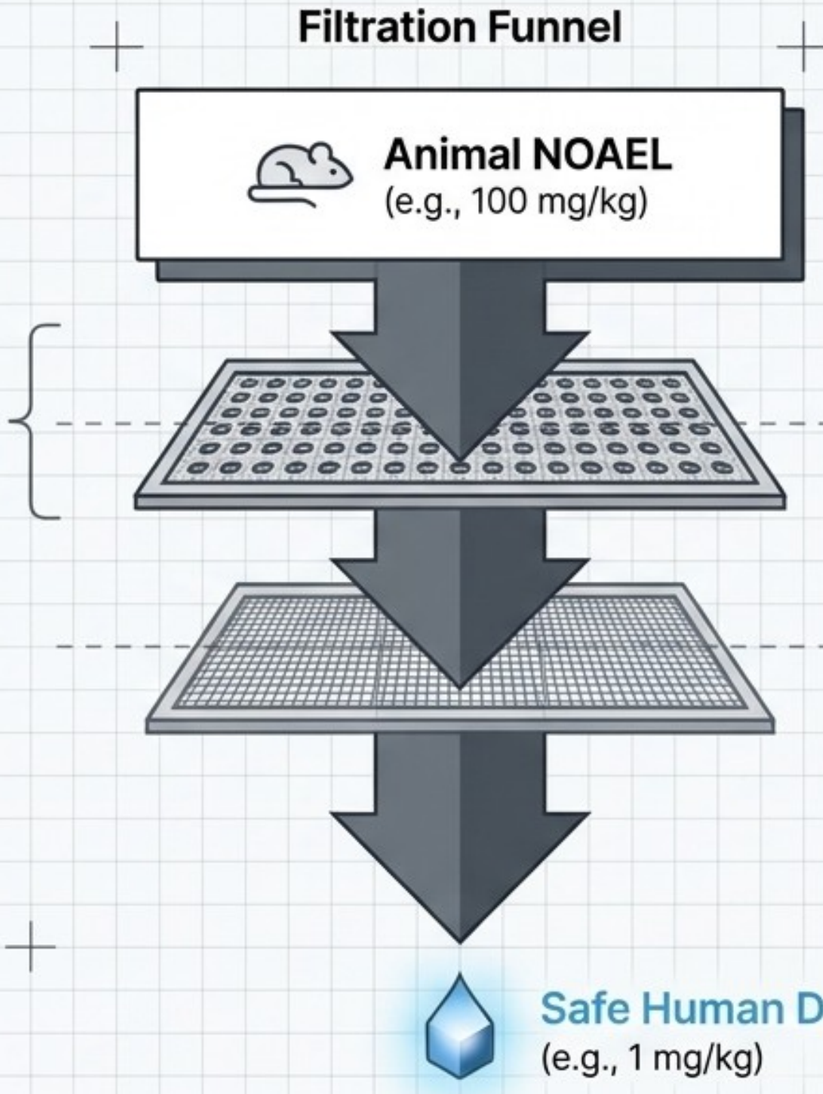


We must protect the most vulnerable sub-populations in a highly diverse, metabolically unpredictable human society.

The Mandate: To guarantee protection, regulatory agencies apply conservative default scaling, deliberately shrinking the animal safety threshold to determine the safe human baseline.

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Extrapolating Animal Data to Human Populations



÷ 10

10x for Interspecies Differences

Accounts for biological variations between animals and humans.

÷ 10

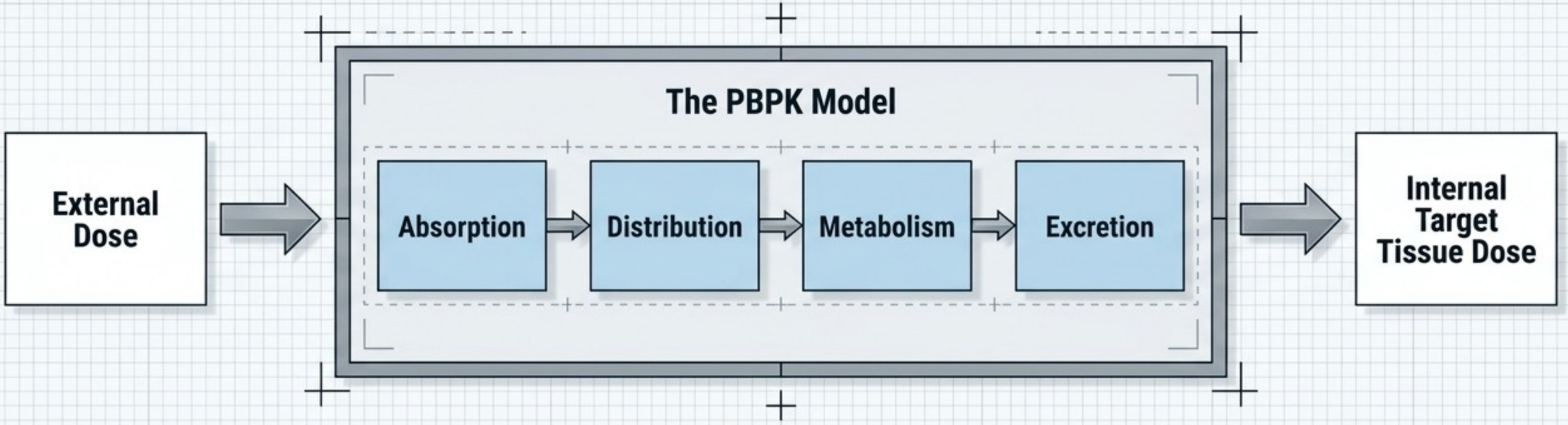
10x for Intraspecies Differences

Accounts for genetic, age, and health variability within the human population.

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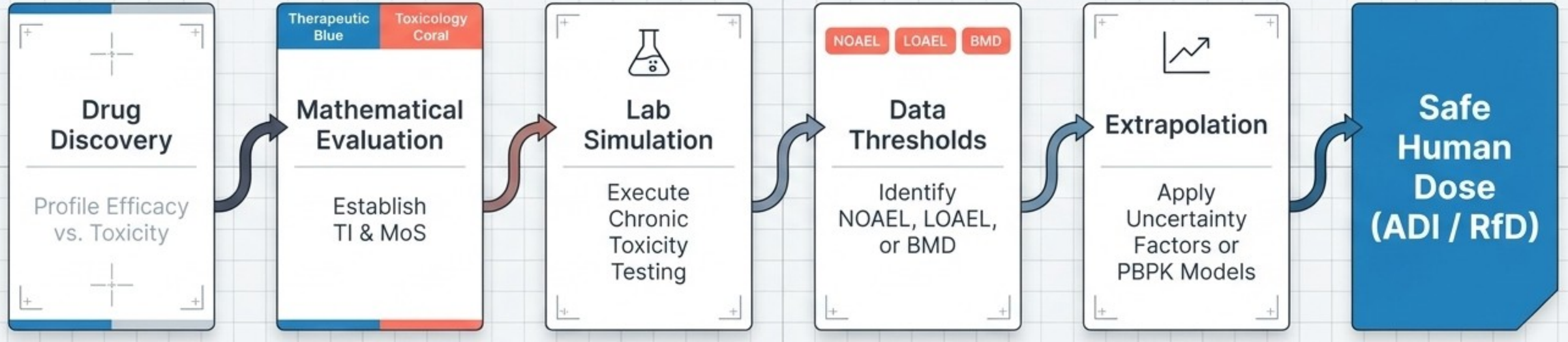
Replacing Default Assumptions with Kinetic Data

Physiologically Based Pharmacokinetic (PBPK) models eliminate the need for blunt 100x uncertainty factors. By analyzing chemical-specific ADME properties, toxicologists can calculate exact internal tissue dosimetry for highly precise human extrapolation.



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The Continuous Blueprint of Drug Safety



Quantifying safety is a continuous mathematical and empirical bridge connecting abstract pharmacological potential to precise, highly calibrated human protection.

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Applied Risk Assessment: Calculating the ADI

The Non-Carcinogen Principle: **For non-carcinogens and non-genotoxic carcinogens, toxicology assumes a strict threshold exists below which no toxicity occurs.**



Step 1: Animal Data

Identify the **NOAEL** in the most sensitive animal species tested.



Step 2: Safety/ Uncertainty Factors

Divide the **NOAEL** by uncertainty factors (typically 100x) to account for animal-to-human translation and individual human genetic variability.



Step 3: Acceptable Daily Intake (ADI)

The final regulatory threshold representing the safe daily exposure limit for humans over a lifetime.

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