

Principles of Animal toxicology

Introduction to Animal Toxicology

- Animal toxicology is a core component of preclinical pharmacology and toxicology, where drugs and chemicals are tested on animal models to assess their safety profile before proceeding to human use.
- **It evaluates:**
 - The nature and severity of toxic effects
 - Target organs affected by the compound
 - Dose-response relationships
 - Reversibility or irreversibility of toxic effects
 - The relationship between exposure duration and toxicity
- **Understanding toxicological outcomes is critical for:**
 - Drug development and approval
 - Formulating dosing guidelines
 - Identifying risks in special populations (e.g., children, pregnant women)
 - Preventing adverse drug reactions in humans
- **Toxicity is categorized based on duration and frequency of exposure into:**
 1. **Acute toxicity**
 2. **Subacute (or subchronic) toxicity**
 3. **Chronic toxicity**
- Each has different study designs, objectives, endpoints, and significance.

Acute Toxicity

Definition

- Acute toxicity refers to the adverse effects (harmful physiological or biochemical changes) that occur in an organism after a single dose or multiple doses given within 24 hours of a substance (e.g., drug, chemical, poison).
- The toxic response develops rapidly, usually within minutes to hours, and can continue up to 14 days after exposure.
- It is one of the first and most important toxicity evaluations performed during preclinical testing of drugs and chemicals.

Purpose / Objectives of Acute Toxicity Studies

Acute toxicity studies are performed to:

1. Determine the short-term toxic potential of a substance.
2. Establish the **LD₅₀ (Median Lethal Dose)**:
 - LD₅₀ = Dose that **kills 50%** of the test animals.
3. Identify **toxic symptoms** associated with overdose.
4. Determine:
 - Target organ toxicity
 - Possible mechanisms of toxicity
5. Help decide **safe starting doses** for:
 - Subsequent animal studies (subacute/chronic studies)
 - Initial clinical trials in humans
6. Classify the chemical into **hazard classes** for regulatory labeling.

Importance in Pharmacy and Medical Science

- Helps predict toxicity during drug overdose in humans.
- Forms basis for calculating **Therapeutic Index (TI)**:

$$\text{Therapeutic Index} = \frac{\text{LD}_{50}}{\text{ED}_{50}}$$

- Higher TI = Safer Drug.
 - Supports **poison management, emergency drug treatment**, and **pharmacovigilance**.
 - Essential for drug **scheduling and labeling** (e.g., "Poison", "High-risk drug").

Study Design (How Acute Toxicity is Conducted)

Animals Used

- Rodents are commonly used (mice or rats).
- Both male and female animals are included.
- Healthy, adult animals with controlled environment.

Routes of Administration

- The substance is given:
 - **Orally (most common)**
 - Intraperitoneal (IP)
 - Intravenous (IV)
 - Intramuscular (IM)
 - Dermal

- Inhalation (via gas chambers or aerosol exposure)

Dosing Strategy

- A single dose is given at one time.
- Or multiple small doses within 24 hours.
- Dose levels may be fixed, or variable (to determine LD₅₀).

Observation Period

- Animals are observed for 14 days after dosing for:
 - Behavioral changes
 - Clinical signs
 - Delayed toxicity effects
 - Mortality

Parameters Monitored During the Study

A. Behavioral Signs

- Excitation, agitation
- Sedation, drowsiness
- Tremors, convulsions
- Altered locomotor activity
- Ataxia (loss of coordination)
- Coma

B. Autonomic Signs

- Salivation
- Sweating (in some animals)
- Pupil dilation or constriction
- Respiratory rate changes
- Abnormal heart rate

C. Systemic Effects

- Vomiting, diarrhea
- Cyanosis (bluish discoloration)
- Jaundice (liver involvement)
- Hematuria (blood in urine)

D. Mortality Recording

- Death timing pattern also reveals mechanism:
 - Within minutes → neurotoxicity / cardiotoxicity
 - Within hours → hepatic or metabolic toxicity
 - Delayed → renal or bone marrow toxicity

LD₅₀ — Median Lethal Dose

- LD₅₀ is the most important endpoint in acute toxicity.
 - LD₅₀ provides a numerical measure of **how toxic** a substance is.
 - Expressed as:

mg of substance per kg of body weight (mg/kg)
 - **Lower LD₅₀** = More toxic substance.
 - Used to compare toxicity across substances.

Example (Approximate) LD₅₀ Values

Substance	LD ₅₀ (mg/kg, oral in rats)	Toxicity Level
Botulinum toxin	0.000001	Extremely toxic
Nicotine	50	Highly toxic
Paracetamol	1944	Low acute toxicity
Water	90,000	Practically non-toxic

Mechanisms of Acute Toxicity

- The toxic outcome may result from:
 - **Receptor overstimulation** (e.g., nicotine, atropine poisoning)
 - **Enzyme inhibition** (e.g., organophosphate pesticides → acetylcholinesterase inhibition)
 - **Membrane disruption** (e.g., snake venom phospholipases)
 - **Oxidative stress** (e.g., CCl₄ → free radical formation → liver necrosis)
 - **Cellular energy depletion** (e.g., cyanide → blocks oxidative phosphorylation)

Post-Mortem and Histopathology

- Dead or euthanized animals undergo necropsy to examine:
 - **Organ discoloration**
 - **Hemorrhage**
 - **Edema**
 - **Degeneration or necrosis of tissues**

- Common target organs:
 - Liver
 - Kidney
 - Heart
 - Brain
 - Lungs

Advantages of Acute Toxicity Studies

- Quick and useful for screening potential drug hazards.
- Helps in dose selection for longer toxicity tests.
- Provides crucial emergency toxicology knowledge.

Limitations

- Does not predict chronic (long-term) toxic effects.
- Animal response may not always match human response.
- Ethical concerns due to pain, suffering, and death.

Sub-Acute Toxicity (Also Called Subchronic Toxicity)

Definition

- Sub-acute toxicity refers to the toxic effects that result from repeated exposure to a drug or chemical for a short but continuous duration, usually 14 days to 90 days (2 weeks to 3 months).
- Unlike acute toxicity (single dose) which evaluates immediate toxicity, sub-acute toxicity evaluates cumulative effects resulting from daily dosing over a period of time.

Purpose / Objectives of Sub-Acute Toxicity Studies

- **Sub-acute studies are conducted to:**
 1. Evaluate cumulative and progressive toxicity of a substance.
 2. Identify target organs damaged after repeated exposure (e.g., liver, kidney, heart, nerves).
 3. Establish dose–response relationship.
 4. **Determine:**
 - NOAEL (No Observed Adverse Effect Level)
 - LOAEL (Lowest Observed Adverse Effect Level)
 5. **Provide dosing information for:**

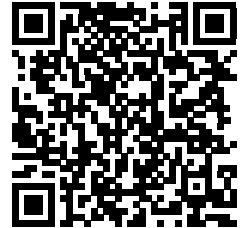


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