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

Copyright © 2025 by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

Acute toxicity studies are performed to:

1. Determine the short-term toxic potential of a substance.
2. Establish the **LD_{50} (Median Lethal Dose)**:
    - LD_{50} = 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)**:

$$\text{Therapeutic Index} = \frac{LD_{50}}{ED_{50}}$$

- 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

Copyright © 2025 by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

- 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 LD_{50}).

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

Copyright © 2025 by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

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

LD_{50} — Median Lethal Dose

- LD_{50} is the most important endpoint in acute toxicity.
  - LD_{50} provides a numerical measure of **how toxic** a substance is.
  - Expressed as:

    mg of substance per kg of body weight (mg/kg)

  - **Lower LD_{50}** = More toxic substance.
  - Used to compare toxicity across substances.

Example (Approximate) LD_{50} 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., CCl_4 → 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

Copyright © 2025 by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

- 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:**

Copyright © 2025 by Engacy Learning Private Limited. All rights reserved. Reproduction or distribution without written consent is strictly prohibited.

First Hope

FREE PREVIEW

Click here to visit our website

PHARMACY PREMIUM NOTES

Complete subject and semesters are available on FirstHope app only.

Scan or click here

Click here to get the app >

Available on Google Play

JOIN THE FIRSTHOPE COMMUNITY

Join our Telegram channel

Click here to join Telegram >

Scan or click here

@FirstHopeNotes

Instagram

@firsthope.official

Click here to follow >

YouTube channel

FirstHope-Pharmacy / Live streams

Click here to watch >

WhatsApp channel

Follow FirstHope on WhatsApp

Click here to join >

FirstHope website

firsthope.co.in

Click here to visit >

B.Pharm / D.Pharm / M.Pharm / Pharm.D

Preview notes. Complete subjects and semesters in the FirstHope app.