Basic definition and types of toxicology

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Unit-I 12 Hrs

- Basic definition and types of toxicology (general, mechanistic, regulatory and descriptive)
- Regulatory guidelines for conducting toxicity studies OECD, ICH, EPA and Schedule Y
- OECD principles of Good laboratory practice (GLP)
- History, concept and its importance in drug development

Slides to share

- Definition
- Dose relationship
- Types of toxicity
- Routes of exposure
- Time
- Types of effect
- Need???

Definition

Toxicology

- Study of poisons
- The branch of science concerned with the nature, effects, and detection of poisons.

- **Poison**
  - Agents that produce adverse responses in biological organisms
- **Toxicologists**
  - Experts on poisons and poisoning.

Toxicology Terminology

Toxicants	substances that produce adverse biological effects of any nature may be chemical or physical in nature effects may be of various types *(acute, chronic, etc.)*
Toxins	specific proteins produced by living organisms *(mushroom toxin or tetanus toxin)* most exhibit immediate effects
Poisons	toxicants that cause immediate death or illness when experienced in very small amounts

Toxic agent or substance

Toxic agent is anything that can produce an adverse biological effect. It may be chemical, physical, or biological in form.

Toxic agents may be:

chemical *(such as cyanide)*,

physical *(such as radiation)* and

biological *(such as snake venom)*.

Toxic substance is simply a material which has toxic properties.

Dose
THE KEY CONCEPT in Toxicology

Father of Modern Toxicology

Paracelsus—1564

Mathieu Orfila - Modern father of toxicology

"*All things are poisonous, only the dose makes it non-poisonous.*"

All chemicals—synthetic or natural—have the capacity to be toxic

Dose-Response Relationship

- Key concept in toxicology is the **quantitative relationship** between the **concentration** of a xenobiotic in the body and the **magnitude** of the biological effect it produces.
- The magnitude of the effect of a xenobiotic is usually a function of the amount of xenobiotic to which a person is exposed (i.e., "The Dose Makes the Poison").
- In any given population, there will be a **range of sensitivities** to a xenobiotic. Extremely useful to know what is the average sensitivity of a population to a xenobiotic, and what the average dose required to elicit a toxic response will be.

Dose

- The **magnitude** of the toxic response is **proportional** to the concentration (how much) of the chemical at the **target site**.
- The **concentration** of a chemical at the target site is **proportional to** the **dose**.
- **Four** important processes control the amount of a chemical that reaches the target site.
  - **Absorption**
  - **Tissue distribution**
  - **Metabolism**
  - **Excretion**

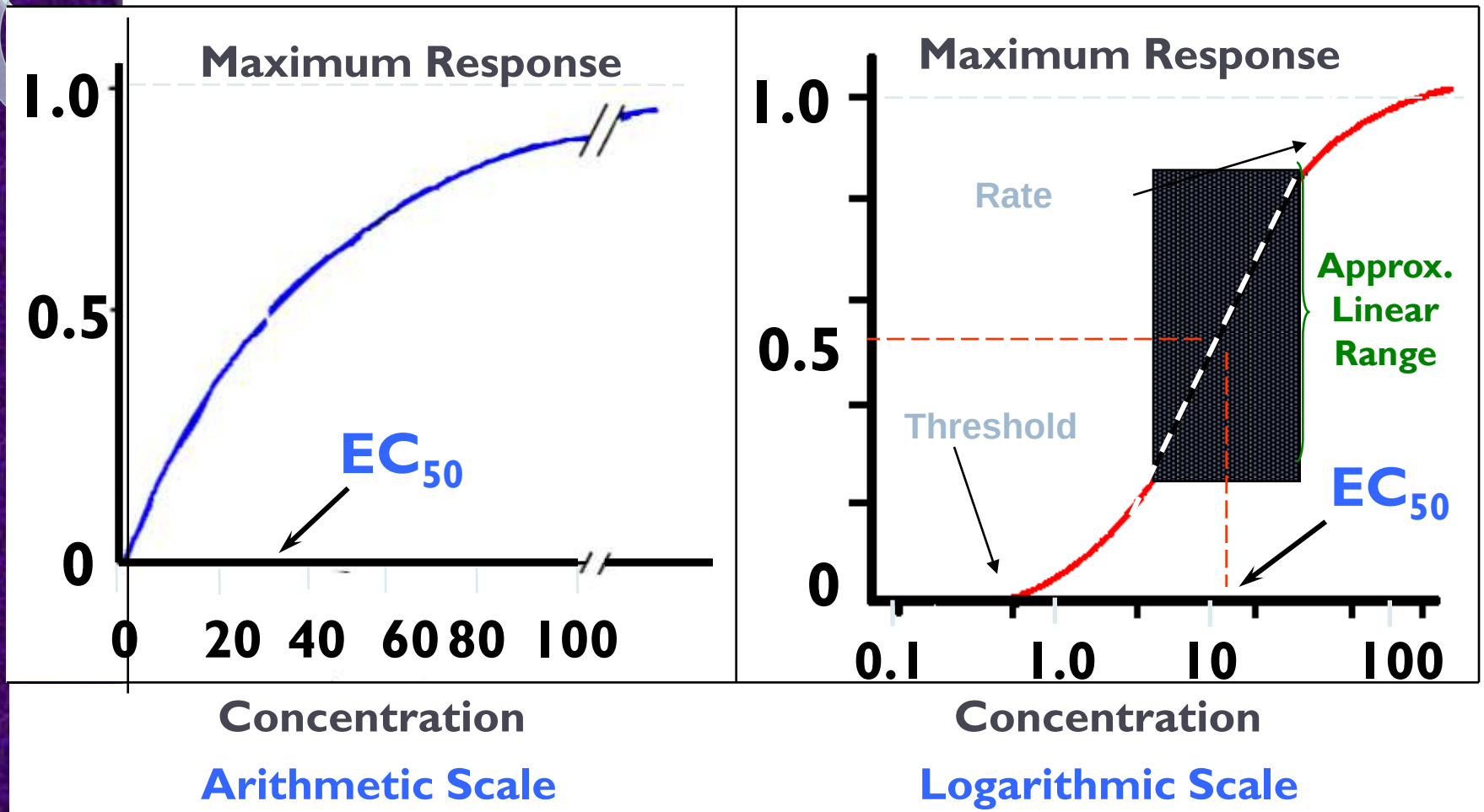
Dose

Determines whether a chemical will be beneficial or poisonous

	Beneficial Dose	Toxic Dose
Aspirin	300 – 1,000 mg	1,000 – 30,000 mg
Vitamin A	5000 units/day	50,000 units/day
Oxygen	20% (Air)	50 – 80% (Air)

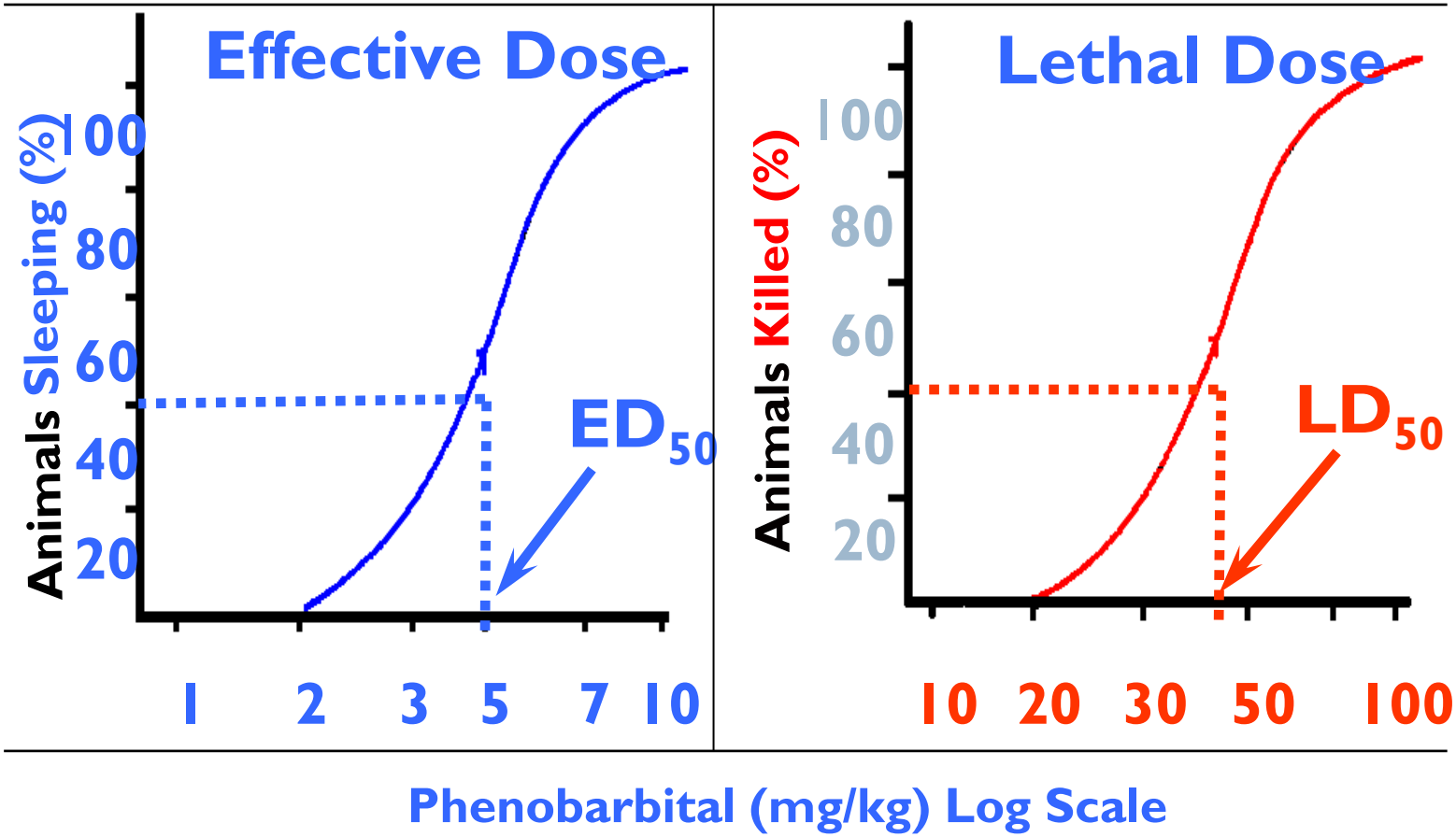
Dose-Response Curves

"The Dose Makes the Poison"

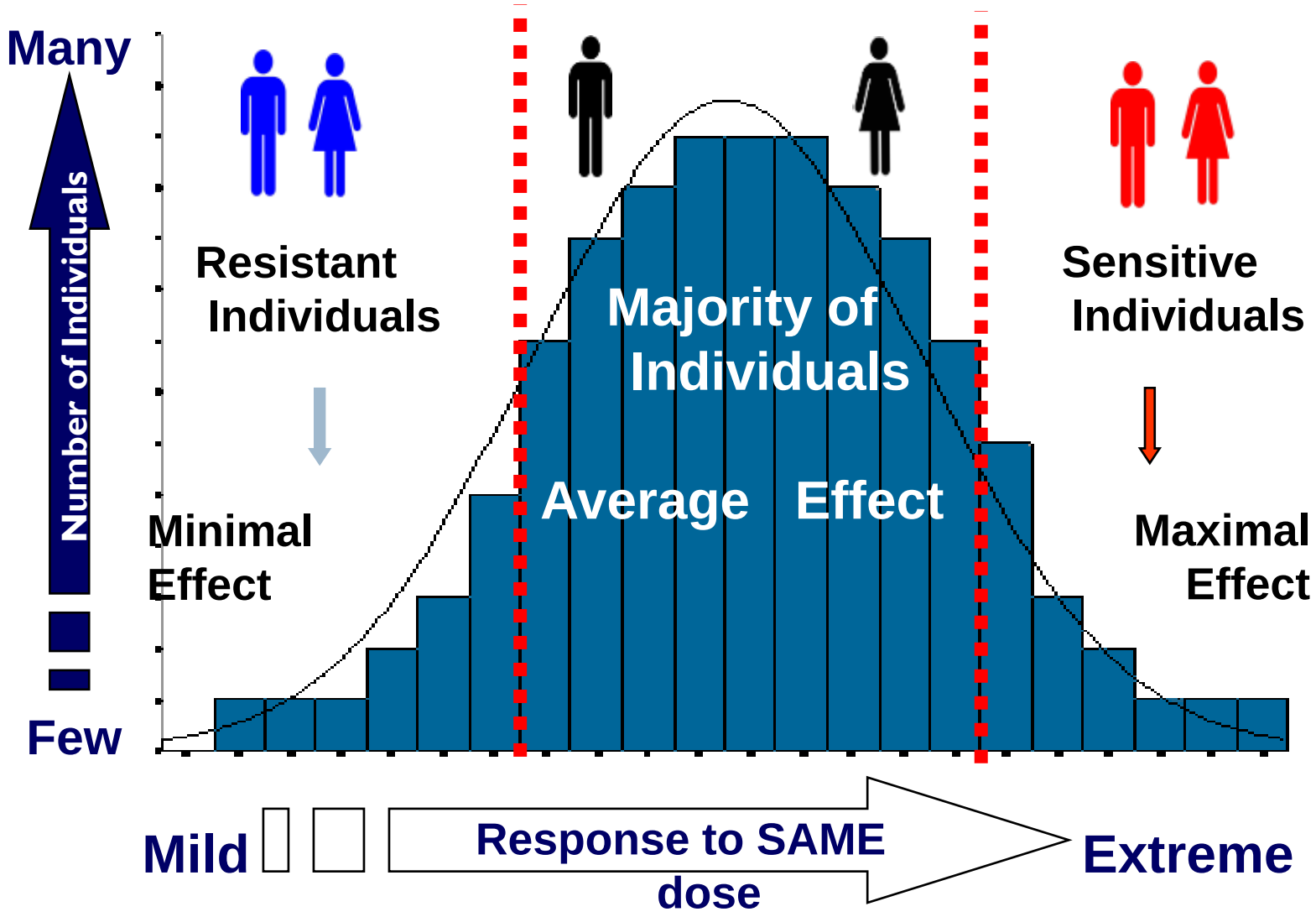


Dose-Response Relationship

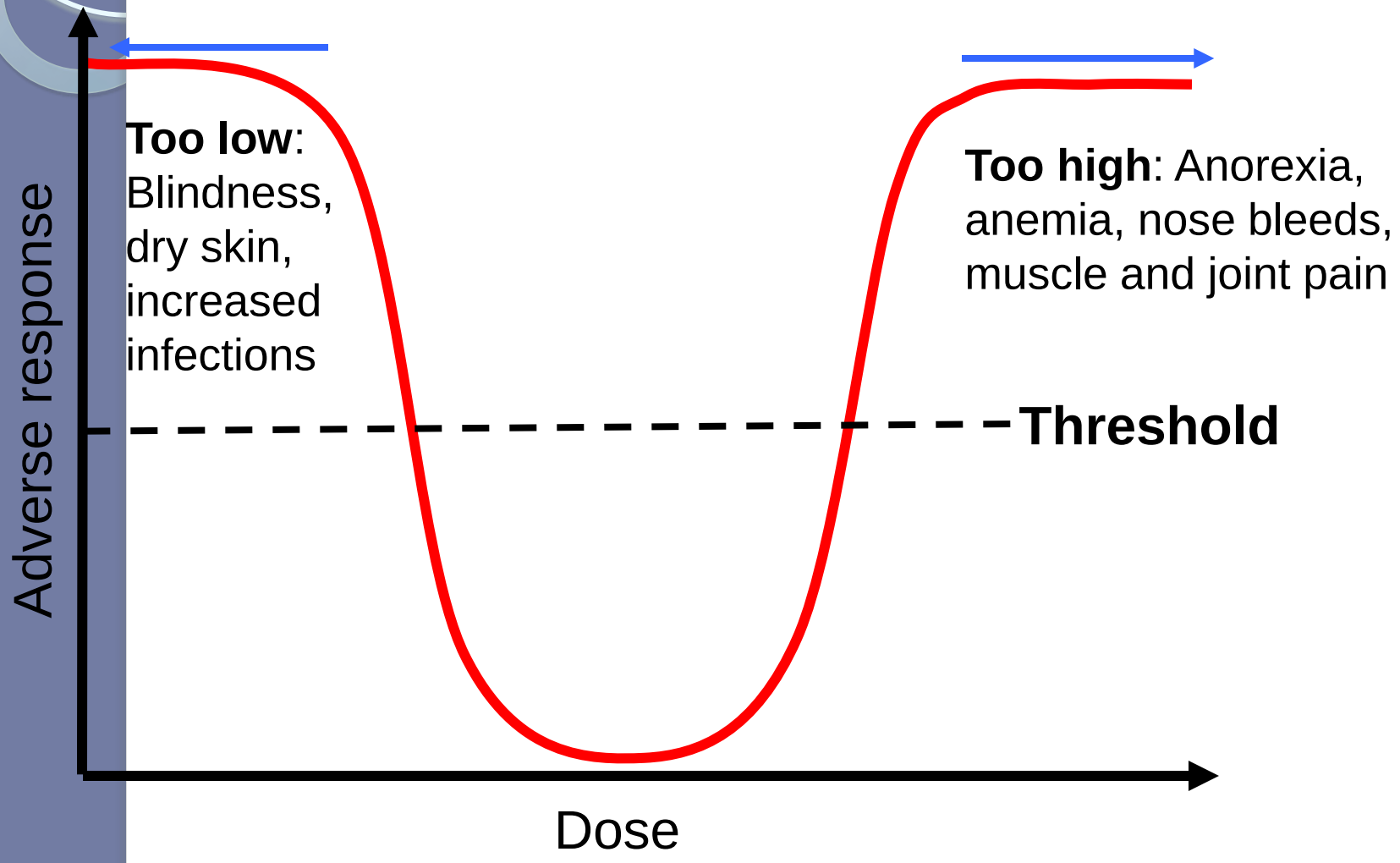
"The Dose Makes the Poison"



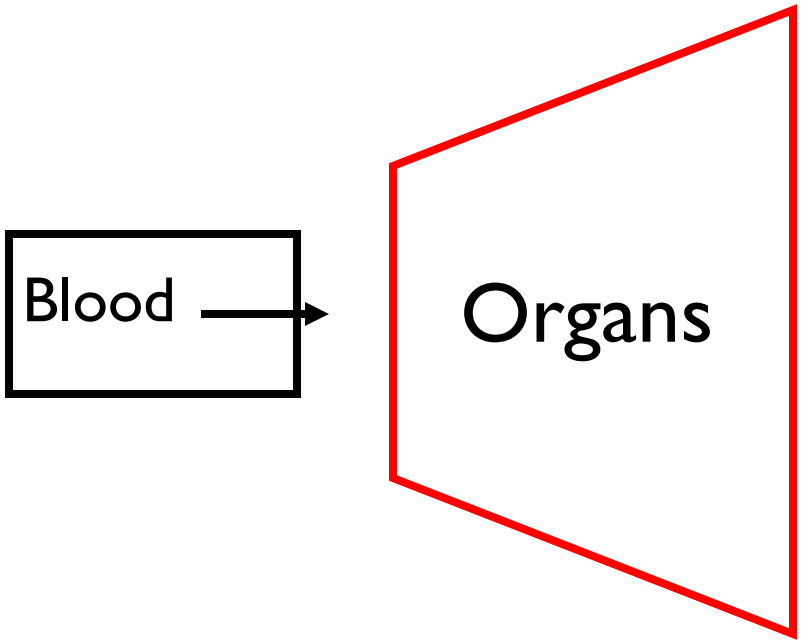
Population Dose-Response



Some chemicals have both therapeutic and toxic effects: Vitamin A



Organs Respond to Chemicals in Various Ways



Desired Effects

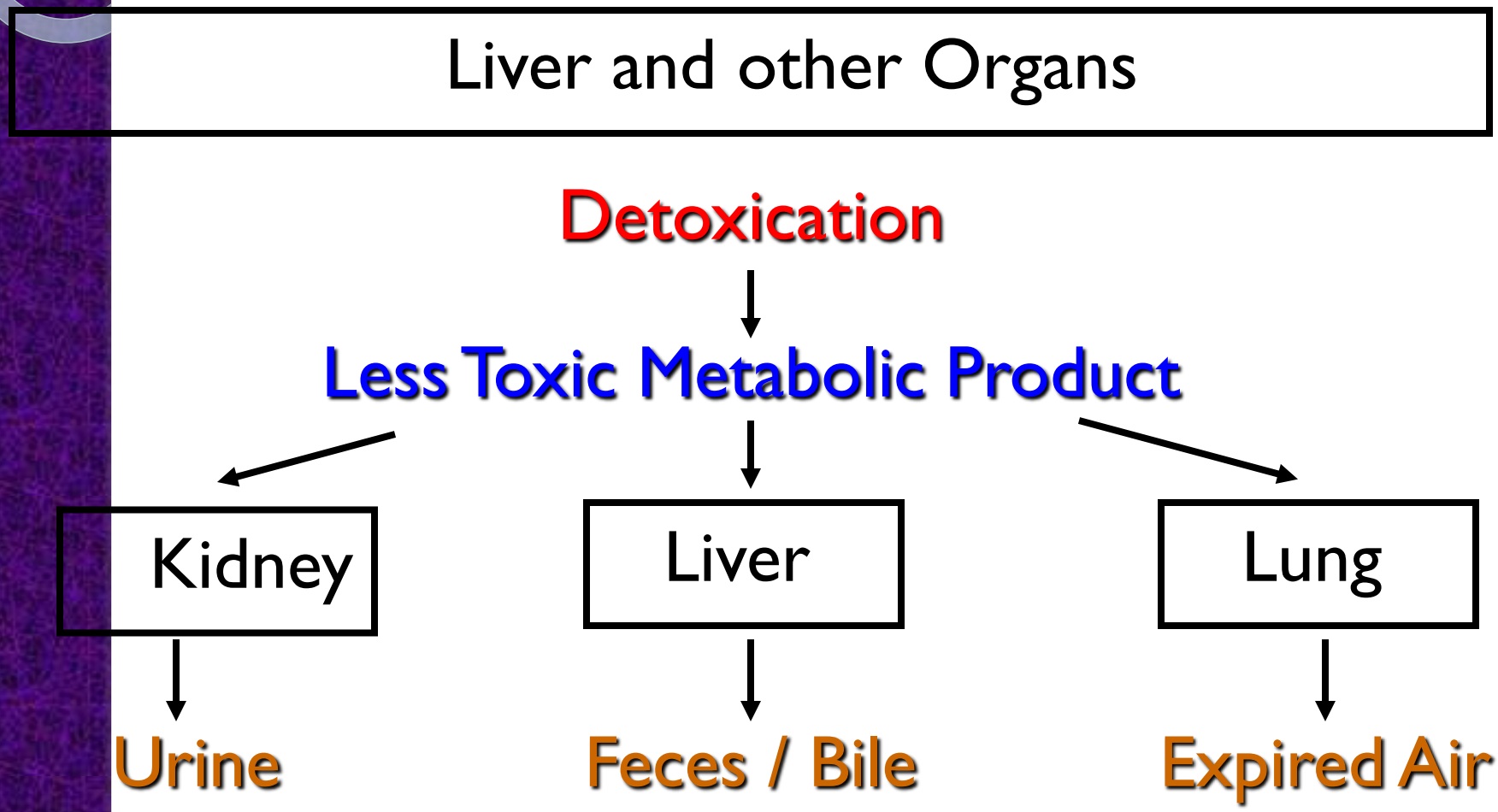
Nutritive

Therapeutic

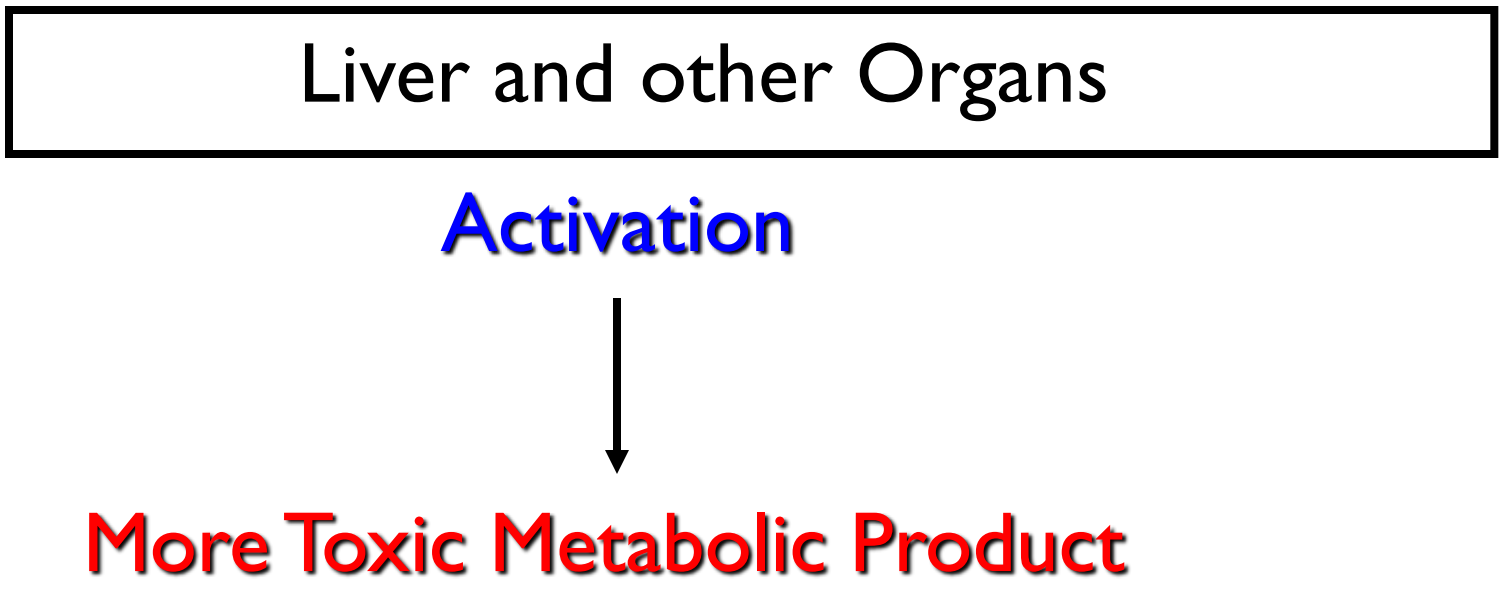
Undesired Effects

Toxic

Some Chemicals Are Transformed by the Body (Metabolized) to Aid Excretion



Some Chemicals are Partially Converted to Products that are More Toxic than the Parent Substance

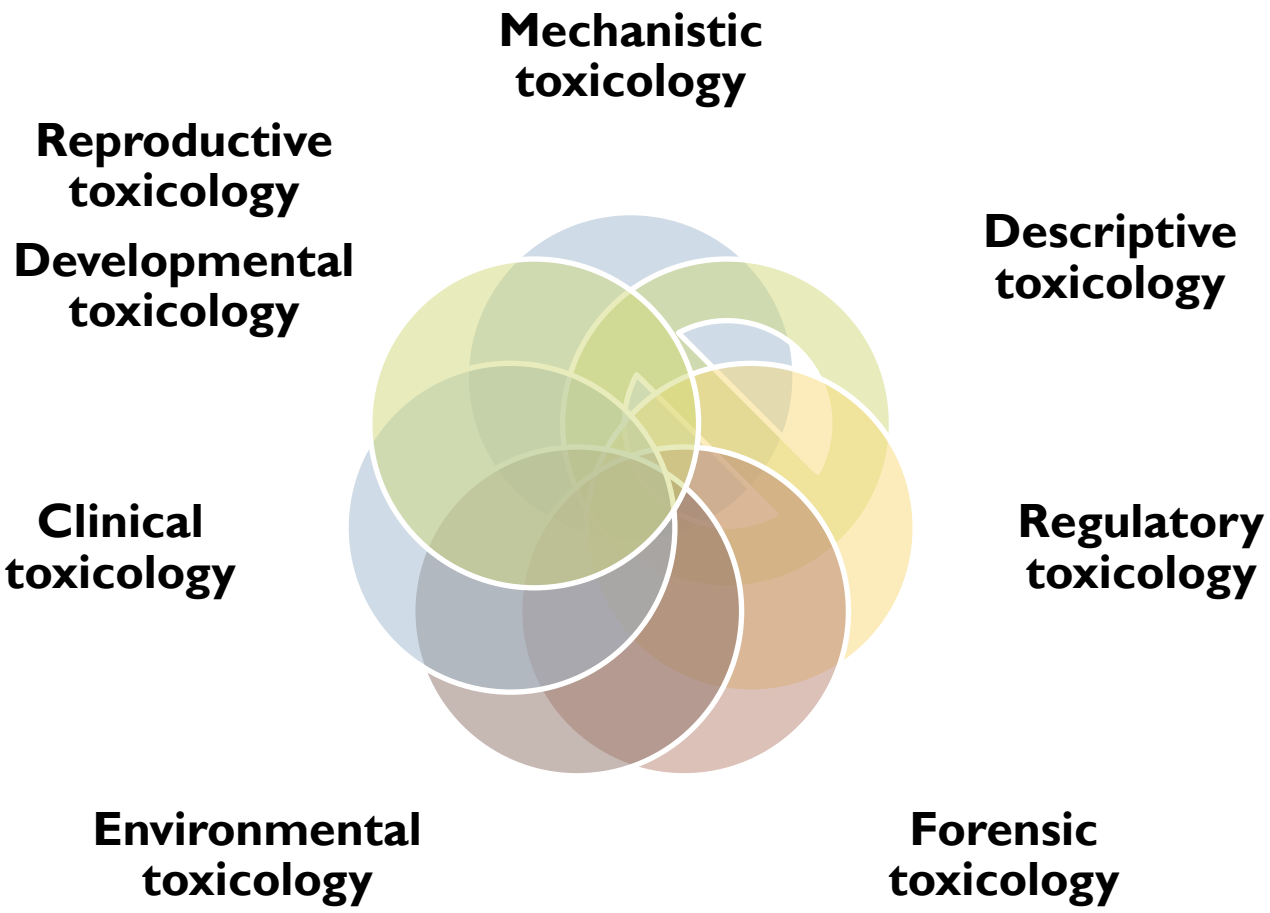


The science of Toxicology helps people make informed decisions and balance RISKS vs. BENEFITS

The study found the highest levels of pesticide residues in peaches, apples, pears…….

AND Spinach.

Types of toxicology



General Toxicology

- Toxicology is the science dealing with properties, actions, toxicity, fatal dose, detection of, interpretation of the result of toxicological analysis and treatment of poisons
- In other words- "It is the study of the adverse physicochemical effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects"

Mechanistic Toxicology

- Focuses on how chemicals produce adverse effects
- Biological systems protect themselves against adverse effects
- Involves cellular and molecular biology
- Chemistry, often xenobiotic metabolism.
- Xenobiotic: a chemical that is foreign to the organism
- Chemical research in toxicology usually investigates metabolic transformations of drugs or potentially hazardous chemicals
- How persistent is a chemical in the body?
- Are metabolic products toxic?
- Do test animals exhibit the same results as humans or other species of concern?

Descriptive toxicology

- Typically involves toxicity testing
- Broad spectrum of responses reflects toxicity
- Functional effects, such as immunological responses
- Growth inhibition
- Reproductive impairment
- Increase in cancer incidence
- Mortality

Descriptive toxicology

- Types of toxicity testing
- *In vitro* (test tube)—useful in detecting potential biochemical and genetic effects
- Use model systems (bacteria, cultured animal cells, DNA interactions)
- *In vivo* (animal)—are essential for detecting health effects
- Acute, chronic, multi-generation
- Experimental animals may be treated with high doses over a lifetime to evaluate potential to cause cancer
- *In silico* (computer-based)—biological experiments conducted by computer models; these depend on data previously collected in other experiments
- Completion of all toxicity tests may take five or six years and is very costly

Regulatory toxicology

- Setting rules and assuring compliance
- Product registration
- Allowable concentrations in food or environmental media
- Technical and legal issues may require negotiation and gathering of new information
- Risk and safety are estimated by total weight of evidence
- Toxicity evidence is the basis, but often rules are modified by political, legal considerations, as well a technical feasibility

Forensic toxicology

- **Forensic toxicology** is the use of **toxicology** and other disciplines such as analytical chemistry, pharmacology and clinical chemistry to aid medical or legal investigation of death, poisoning, and drug use.

Clinical toxicology

- Scientific study involving research, education, prevention and treatment of diseases caused by substances such as drugs and toxins

Environmental toxicology

- Environmental toxicology, also known as ecotox, is a multidisciplinary field of science concerned with the study of the harmful effects of various chemical, biological and physical agents on living organisms.
- Impacts of chemicals on environment
- Non human organisms

Developmental toxicology

- Adverse effects on the developing organism that occur any time during the life span of an organism.
- Exposure to chemical or physical agents.

Reproductive toxicology

- Due to the adverse effects on male or female reproductive system

Need of toxicity study

- A chemical compound will become useful drug only if it is having ***relevant pharmacological and therapeutic activity***.
- If it is ***free from short and long term toxicity***
- If it is ***superior*** in any way to existing drugs.
- To be certain that ***a new drug is safe*** and detail studies are made to know the effects of varying doses and their prolonged administration.

Types of exposure

Acute – (Short term) – A single exposure lasting less than 24 hours

Repeated exposure

- *Subacute*- exposure for 1 month or less.
- *Subchronic* – Repeated exposures of less than a lifetime (e.g.1- 3 months)
- *Chronic* – (Long term) – Exposures are essentially for the lifetime of the species (more than 3 months)

Types of effect

- Local
- Systemic
- Cumulative
- Poisoning

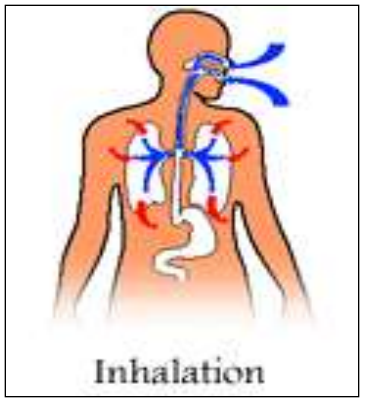
- **Local**
  - The site of action takes places at the **point of contact**
  - The site:
    - skin
    - mucous membrane of the eyes, nose, mouth, throat
    - or anywhere the along the respiratory or gastrointestinal system

- **Systematic**
  - The toxic substance has been absorbed and distributed throughout the body.
  - Elicit the major toxicity in 1 or 2 organs (target organs)
  - Includes
    - CNS, circulatory system,
    - visceral organs like liver, kidney, lung

- **Cumulative Effects**
  - Over a period of time, the material is only partially excreted and the remaining quantities are gradually collected
  - The retained toxic compound accumulates and becomes great enough to cause pathological response.
- **Poisoning**
  - A toxic substance is absorbed and distributed by the blood stream throughout the body
  - Absorption reaches a point where it causes impairment of physiological function

Route of Exposure

- The **route** (site) of exposure is an important determinant of the ultimate **dose**—different routes may result in different rates of absorption.
  - **Dermal (skin)**
  - **Inhalation (lung)**
  - **Oral ingestion (Gastrointestinal)**
  - **Injection**
- The route of exposure may be important if there are tissue-specific toxic responses.
- Toxic effects may be local or systemic



Time of Exposure

- **How long** an organism is exposed to a chemical is important

Duration and **frequency** contribute to **dose**. Both may alter toxic effects.

  - **Acute** Exposure = usually entails a single exposure
  - **Chronic** Exposures = multiple exposures over time (frequency)

Toxicological Paradigm