Toxicology

Part 1:

- **Principles of Toxicology**
- **Pharmacokinetics and dynamics**

"What is there that is not poison? All things are poison and nothing[is] without poison" The right dose differentiates a poison and a remedy."

Paracelsus (1493–1541)

Definitions

- (A poison): any agent capable of producing a harmfull response in a biological system, seriously injuring function or producing death.
- The term toxin generally refers to toxic substances that are produced by biological systems such as plants, animals, fungi, or bacteria.
- The term toxicant is used in speaking of toxic substances that are produced by anthropogenic (human-made) activities or by both natural and anthropogenic activities.

- Toxicology is the study of the adverse effects of chemical or physical agents on living organisms.

- A toxicologist is trained person who examine the nature of those effects on human, animal, and environmental health.

- Toxicological research examines the cellular, biochemical, and molecular mechanisms of action as well as functional effects of toxins such as neurobehavioral and immunological, and assesses the probability of their occurrence.

- Dose: The amount of chemical entering the body. This is usually given as milligrams of chemical per kilogram of body weight (mg/kg). How often (duration and frequency), and how the dose is administered are all important parameters.

- Adverse Effect (Response): Any change from an organism's normal state that is irreversible at least for a period of time.
- Producing an adverse effect depends on the concentration of the active compound at the target site, and the conditions of exposure.

- Risk assessment is the quantitative estimate of the potential effects on human health and environmental significance of various types of chemical exposures (e.g., pesticide residues on food, contaminants in drinking water).

Chemical	Beneficial Dose	Toxic Dose
Aspirin	300-1000 mg	1000-30,000mg
Vitamin A	500 units/d	50,000 units/d
Oxygen	20% in air	50-100% in air

Different Areas of Toxicology

- A mechanistic toxicologist : is concerned with identifying and understanding the cellular, biochemical, and molecular mechanisms by which chemicals produce a toxic effects on living organisms.

- Mechanistic data may be very useful in demonstrating that an adverse outcome (e.g., cancer, birth defects) observed in laboratory animals is directly relevant to humans.

- For example, the relative toxic potential of organophosphate insecticides in humans, rodents, and insects can be accurately predicted on the basis of an understanding of common mechanisms (inhibition of acetylcholinesterase) and differences in biotransformation for these insecticides among the different species.

- Mechanistic data are also useful in the design and production of safer alternative chemicals and in rational therapy for chemical poisoning and treatment of disease.

- **New areas of "pharmacogenomics" and "toxicogenomics"** provides an exciting opportunity in the future for mechanistic toxicologists to:

✓identify and protect genetically susceptible individuals from harmful environmental exposures

✓customize drug therapies that enhance efficacy and minimize toxicity, based on an individual's genetic makeup.

- **A descriptive toxicologist** is concerned directly with **toxicity testing**, which provides information for safety evaluation and appropriate requirements.

- The appropriate toxicity tests in **cell culture systems** or **experimental animals** are designed to yield information to evaluate risks posed to humans and the environment from exposure to specific chemicals.
- **Drugs and food additives, insecticides, herbicides, solvents.**

- The recent advent (rising) of so-called “omics” technologies (genomics, proteomics, metabonomics, etc.) form a part of toxicogenomics.

- **(Organizing) regulatory toxicologist** has the responsibility for deciding, on the basis of data provided by descriptive and mechanistic toxicologists, whether a drug or other chemical poses a sufficiently low risk to be marketed for a stated purpose or subsequent human or environmental exposure resulting from its use.

Examples:

- The Food and Drug Administration (FDA) is responsible for allowing drugs, cosmetics, and food additives to be sold in the market according to the Federal Food, Drug and Cosmetic Act (FFDCA).

- The U.S. Environmental Protection Agency (EPA) is responsible for regulating most other chemicals according to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), the Resource Conservation and Recovery Act (RCRA), the Safe Drinking Water Act, and the Clean Air Act.

- **Forensic toxicology** It is concerned primarily with the medico-legal aspects of the harmful effects of chemicals on humans and animals.

- Forensic toxicologists are primarily responsible for establishing the cause of death and determining its circumstances in a **post-mortem** investigation.

- **Clinical toxicology** designates an area of professional confirmation in the field of medical science.
- It is concerned with disease caused by or associated with toxic substances .

- Generally, clinical toxicologists are physicians who receive specialized training in emergency medicine and poison management.
- Efforts are directed at treating patients poisoned with drugs or other chemicals and the development of new techniques to treat certain intoxication

- Public contact about treatment and prevention is often through the national network of poison control centers.

- **Environmental toxicology** focuses on the impacts of chemical pollutants in the environment on biological organisms.

- Although toxicologists are concerned with the effects of environmental pollutants on human health.
- It is most commonly associated with studies on the impacts of chemicals on nonhuman organisms such as fish, birds, terrestrial animals, and plants.

General Characteristics of the Toxic Response

- Among chemicals there is a wide spectrum of doses needed to produce harmful effects, serious injury, or death.

- **Lethal dose (LD 50)** : the dosage of chemicals needed to produce death in 50% of treated animals.

- Normally expressed as milligrams of substance per kilogram of animal body weight, **mg/kg.**

- **LC_{50} (lethal concentration 50) :**The concentration of a chemical in an environment (generally air or water) which produces death in 50% of an exposed population of test animals in a specified time frame

mg/L

Normally expressed as milligrams of substance per liter of air or water (or as ppm)

1 liter of water = 1 kg

1 mg / kg = 1 ppm

1mm3 / liter = 1 ppm

1 mg / liter = 1 ppm

ppm: particle per million

Unit	Gram Equivalents	Exp. Form
Kilogram (kg)	1000.0 g	10^3 g
Gram (g)	1.0 g	1 g
Milligram (mg)	0.001 g	10^{-3} g
Microgram (µg)	0.000,001 g	10^{-6} g
Nanogram (ng)	0.000,000,001 g	10^{-9} g
Picogram (pg)	0.000,000,000,001 g	10^{-12} g
Femtogram (fg)	0.000,000,000,000,001g	10^{-15} g

- Some chemicals produce death in microgram doses and are commonly thought of as being extremely toxic.
- Other chemicals may be relatively harmless after doses in excess of several grams.

- It should be noted, however, that measures of acute lethality such as LD50 may not accurately reflect the full spectrum of toxicity associated with exposure to a chemical.

  - Carcinogenic, teratogenic, or neurobehavioral effects at doses that produce no evidence of acute toxicity.
  - Genetic factors can account for individual susceptibility to a range of responses.

Table 2.1
Approximate Acute LD_{50}s of Some Representative Chemical Agents

AGENT	LD_{50}, MG/KG*
Ethyl alcohol	10000
Sodium chloride	4000
Ferrous sulfate	1500
Morphine sulfate	900
Phenobarbital sodium	150
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
d—Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

*LD_{50} is the dosage (mg/kg body weight) causing death in 50% of exposed animals.

CLASSIFICATION OF TOXIC AGENTS

1. Target organs (liver, kidney, blood, CNS etc.)
2. The use (pesticide, solvent, food additive, etc.)
3. Source (animal and plant toxins)
4. Effects (cancer, mutation, liver injury, etc.)
5. Physical state (gas, dust, liquid)
6. Chemical stability or reactivity (explosive, flammable, oxidizer)
7. Chemical structure (halogenated hydrocarbon, etc.)
8. Poisoning potential (extremely toxic, very toxic, slightly toxic, etc.)
9. Biochemical mechanisms of action (e.g.cholinesterase inhibitor)

Toxicity Rating	Dose for a 70 kg Person
Super Toxic	< 5 mg/kg
Extremely Toxic	5–50 mg/kg
Very Toxic	50–500 mg/kg
Moderately Toxic	0.5–5 g/kg
Slightly Toxic	5–15 g/kg
Practically Nontoxic	> 15 g/kg

SPECTRUM OF UNDESIRED EFFECTS

Allergic Reactions:

- Chemical allergy is an immunologically mediated adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one... **hypersensitivity, allergic reaction, sensitization reaction.**

- ❖ Once sensitization has occurred, allergic reactions may result from exposure to relatively very low doses of chemicals
- ❖ Sensitization reactions are sometimes very severe and may be fatal.
- ❖ allergic reactions are dose-related
- ❖ The manifestations of allergy may involve various organ systems and range in severity from minor skin disturbance to fatal anaphylactic shock.

TABLE 6.6 Examples of Type I Hypersensitivity Syndromes: Causes, Effects, and Signs and Symptoms

Syndrome	Causes	Effects	Signs and symptoms
Allergic rhinitis (hay fever)	Pollen, mold spores	↑ Capillary permeability in nasal and frontal sinuses and mucosal membranes, ↑ vasodilation	Congestion, sneezing, headache, watery eyes
Food allergies	Lectins and proteins present in nuts, eggs, shellfish, dairy products	↑ Capillary permeability, ↑ vasodilation, ↑ smooth muscle contraction	Congestion, sneezing, headache, watery eyes, nausea, vomiting
Atopic dermatitis (allergic dermatitis)	Localized exposure to drugs and chemicals	Initial local mast cell release of cytokines, followed by activation of neutrophils and eosinophils	Local erythematous reaction
Asthma	Chemicals, environmental, behavioral	Chronic obstructive reaction of LRT involving airway hyperactivity and cytokine release	Dyspnea, edema resulting from mucous hypersecretion, bronchoconstriction, airway inflammation

Abbreviation: LRT, lower respiratory tract.

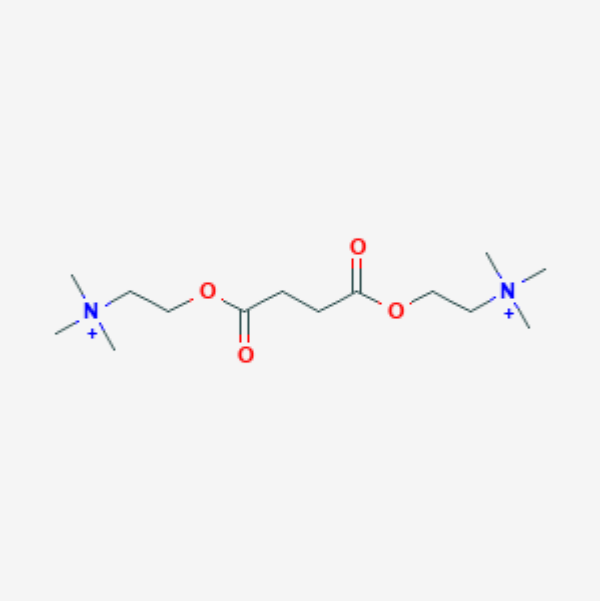
IDIOSYNCRATIC REACTIONS:

- **Abnormal** reactivity to a chemical.
- A classic example of an idiosyncratic reaction is provided by patients who exhibit prolonged muscular relaxation and apnea

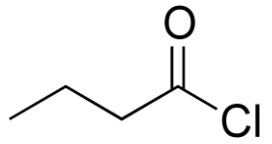
  (inability to breathe) lasting several hours

  after a standard dose of succinylcholine.

Succinylcholine is a skeletal muscle relaxant for intravenous (IV) administration indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.



- Succinylcholine usually produces skeletal muscle relaxation of only short duration because of its very rapid metabolic degradation by an enzyme that is present normally in the bloodstream called plasma **butyrylcholinesterase**.



Immediate versus delayed Toxicity

- **Immediate toxic effects** can be defined as those that occur or develop **rapidly** after a single administration of a substance.

- **Delayed toxic effects** are those that occur after the a period of time. Carcinogenic effects of chemicals usually have a long latency period, often 20 to 30 years after the initial exposure, before tumors are observed in humans.

Reversible versus Irreversible Toxic Effects

- If a chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible.
- Ex: for a tissue such as liver, which has a high ability to regenerate, most injuries are reversible, whereas injury to the CNS is largely irreversible because differentiated cells of the CNS cannot divide and be replaced.
- Carcinogenic and teratogenic effects of chemicals, once they occur, are usually considered irreversible toxic effects.

LOCAL VERSUS SYSTEMIC TOXICITY

- **Local effects** are those that occur at the site of first contact between the biological system and the toxicant
- Such effects are produced by the ingestion of caustic substances or the inhalation of irritant materials.
- For example, chlorine gas reacts with lung tissue at the site of contact, causing damage and swelling of the tissue, with possibly fatal consequences, even though very little of the chemical is absorbed into the bloodstream.

- **Systemic effects** require absorption and distribution of a toxicant from its site of exposure to a distant site, at which harmful effects are produced.

- Most substances except highly reactive materials produce systemic effects. For some materials, both effects can be demonstrated.

Example:

- **Tetraethyl lead produces effects on skin at the site of absorption and then is transported systemically to produce its typical effects on the CNS and other organs**

- Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs; instead, they usually produce their major toxicity in only one or two organs....**target organs of toxicity** of a particular chemical.

- The target organ of toxicity is often not the site of the highest concentration of the chemical.
- For example, lead is concentrated in bone, but its toxicity is due to its effects in soft tissues, particularly the brain.

- The target organ of toxicity most frequently involved in systemic toxicity is the CNS (brain and spinal cord).

- **Muscle and bone are least often the target tissues for systemic effects.**

- **With substances that have a predominantly local effect, the frequency with which tissues react depends largely on the site of exposure (skin, gastrointestinal tract, or respiratory tract).**

Interaction of Chemicals

- Chemical interactions are known to occur by a number of mechanisms, such as alterations in absorption, protein binding, and the biotransformation and excretion of one or both of the interacting toxicants.

1. **An additive effect:** occurs when the combined effect of two chemicals is equal to the sum of the effects of each agent given alone (example: 2 + 3 = 5).

2. A **synergistic** effect occurs when the combined effects of two chemicals are much greater than the sum of the effects of each agent given alone (example: 2 + 2 = 20)

3. **Potentiation** occurs when one substance does **not** have a toxic effect on a certain organ or system but when added to another chemical makes that chemical much more toxic (example: 0 + 2 = 10).

- Isopropanol, for example, is not hepatotoxic, but when it is administered in addition to carbon tetrachloride, the hepatotoxicity of carbon tetrachloride is much greater than when it is given alone

4. **Antagonism** occurs when two chemicals administered together interfere with each other's actions or one interferes with the action of the other (example: 4 + 6 = 8; 4 + (−4) = 0; 4 + 0 = 1).....basis of many **ANTIDOTES**

- **Functional**: producing opposite effects on the same physiologic function
  - Many chemicals, when given at toxic dose levels, produce convulsions, and the convulsions often can be controlled by giving anticonvulsants such as the benzodiazepines.

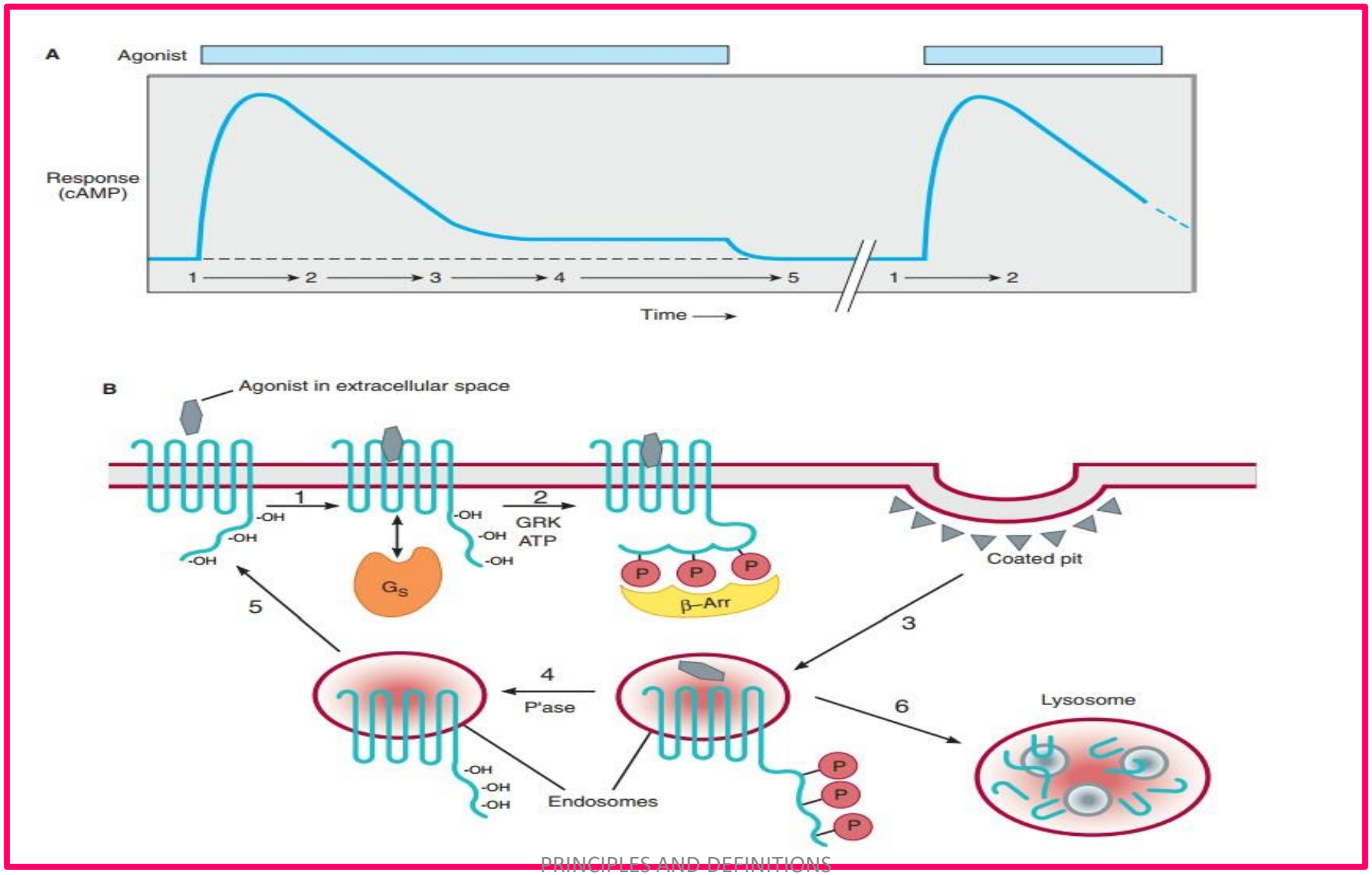
- **Chemical**: a chemical reaction between two compounds that produces a less toxic product.... antidotes
  - Low-molecular-weight protein protamine sulfate to form a stable complex with heparin

- **Dispositional:** the prevention of absorption of a toxicant by ipecac or charcoal and the increased excretion of a chemical by administration of an osmotic diuretic or alteration of the pH of the urine

- **Receptor:** two chemicals that bind to the same receptor produce less of an effect when given together than the addition of their separate effect or when one chemical antagonizes the effect of the second chemical .... ***blockers***.

- The receptor antagonist naloxone is used to treat the respiratory depressive effects of morphine and other morphine-like narcotics by competitive binding to the same receptor.

Desensitization



Route and Site of Exposure

1. The gastrointestinal tract (ingestion)
2. Lungs (inhalation)
3. Skin (topical, percutaneous, or dermal)
4. Intravenous route: Toxic agents generally produce the greatest effect and the most rapid response
5. Other parenteral (other than intestinal canal) routes.

- An approximate descending order of effectiveness: intravenous> inhalation> intraperitoneal>subcutaneous>intramuscular> intradermal>oral>dermal.

- Occupational exposure to toxic agents most frequently results from breathing contaminated air (inhalation) and/or direct and prolonged contact of the skin with the substance (dermal exposure)

- Accidental and suicidal poisoning occurs most frequently by oral ingestion

Factors affect the toxic effect of a substance:

1. Body barriers
2. Concentration of the agent
3. Total volume of the vehicle
4. Properties of the vehicle to which the biological system is exposed
5. Rate of exposure

Duration and Frequency of Exposure

- **Acute exposure**: exposure to a chemical for less than 24 hours, a single administration, or repeated exposures may be given within a 24-hours period for some slightly toxic or practically nontoxic chemicals.
- **Subacute exposure:** repeated exposure to a chemical for 1 month or less.
- **Subchronic**: for 1 to 3 months
- **Chronic:** for more than 3 months

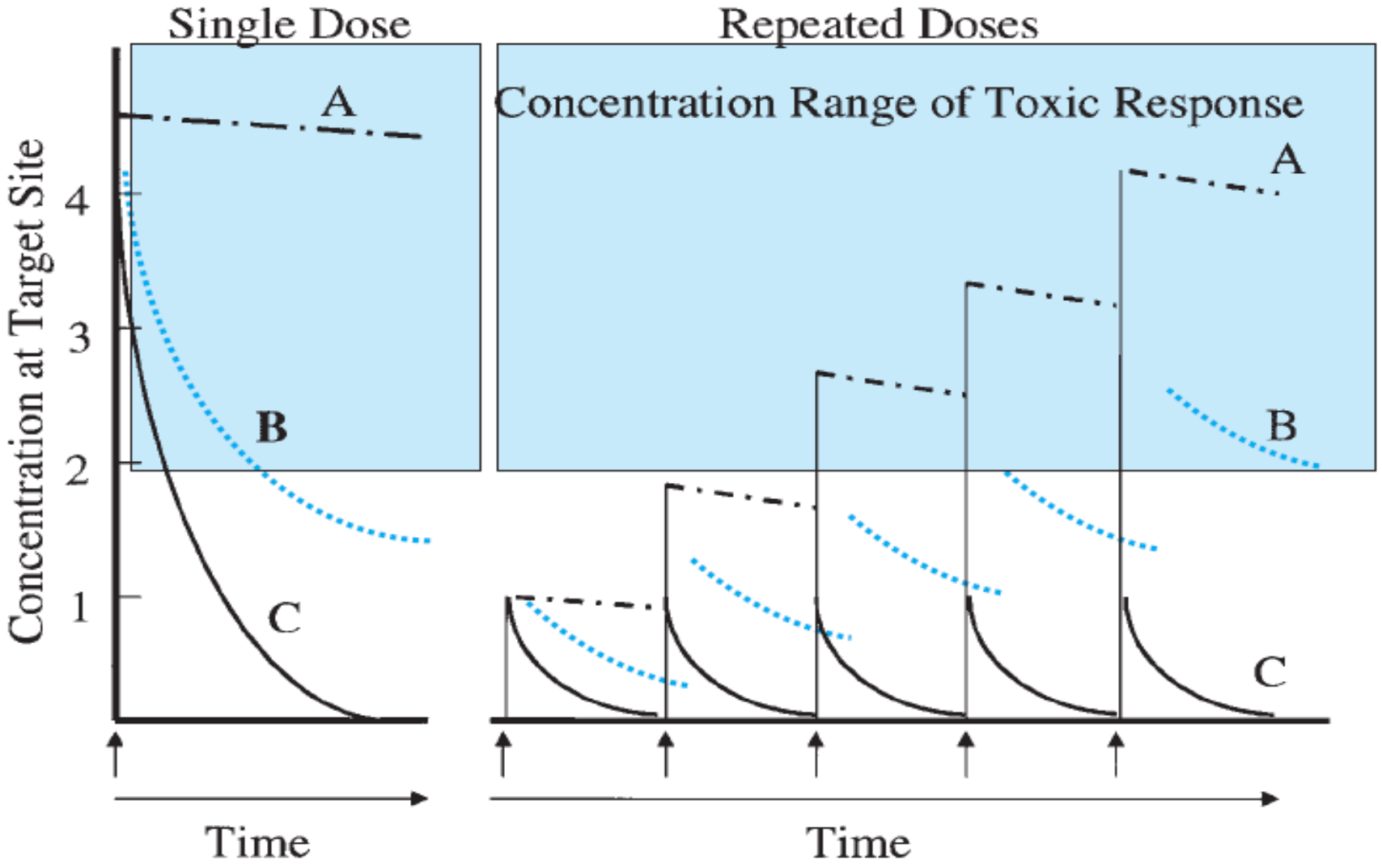


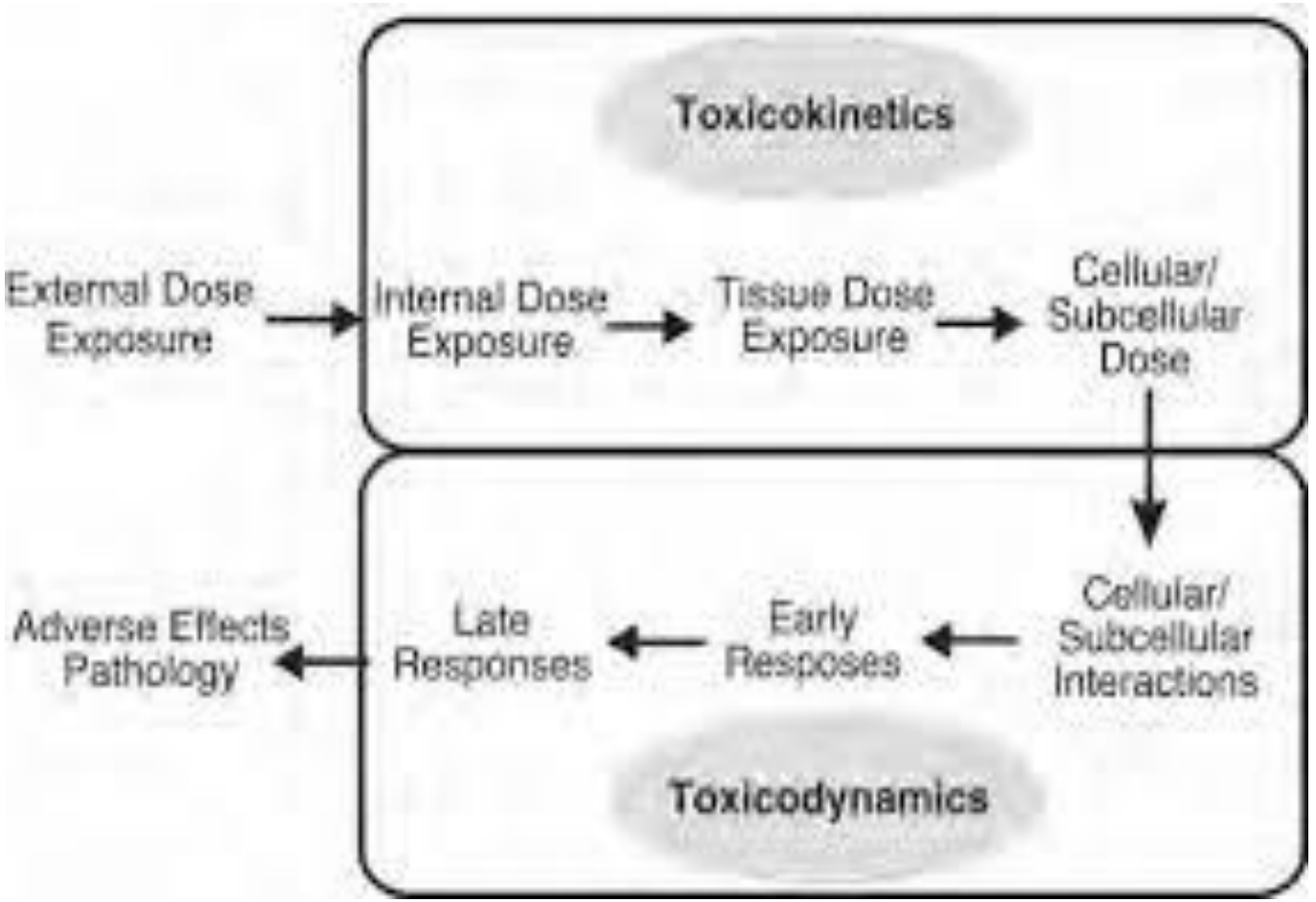
Figure 2-2. Diagrammatic view of the relationship between dose and concentration at the target site under different conditions of dose frequency and elimination rate.

Line A. A chemical with very slow elimination (e.g., half-life of 1 year). *Line B.* A chemical with a rate of elimination equal to frequency of dosing (e.g., 1 day). *Line C.* Rate of elimination faster than the dosing frequency (e.g., 5 h). Blue-shaded area is representative of the concentration of chemical at the target site necessary to elicit a toxic

The effect depend on:
•the frequency of exposure.
•duration of exposure.
•interval between doses is sufficient to allow for complete repair of tissue damage

PHARMACODYNAMICS OF TOXINS

DOSE-RESPONSE RELATIONSHIP


Toxicokinetics
External Dose Exposure
Internal Dose Exposure
Tissue Dose Exposure
Cellular/ Subcellular Dose
Cellular/ Subcellular Interactions
Early Responses
Late Responses
Adverse Effects Pathology
Toxicodynamics

Dose–response relationship:

- The relationship between the dose of a chemical (independent variable) and the response produced (dependent variable) follows a predictable pattern.

- The response depends on:

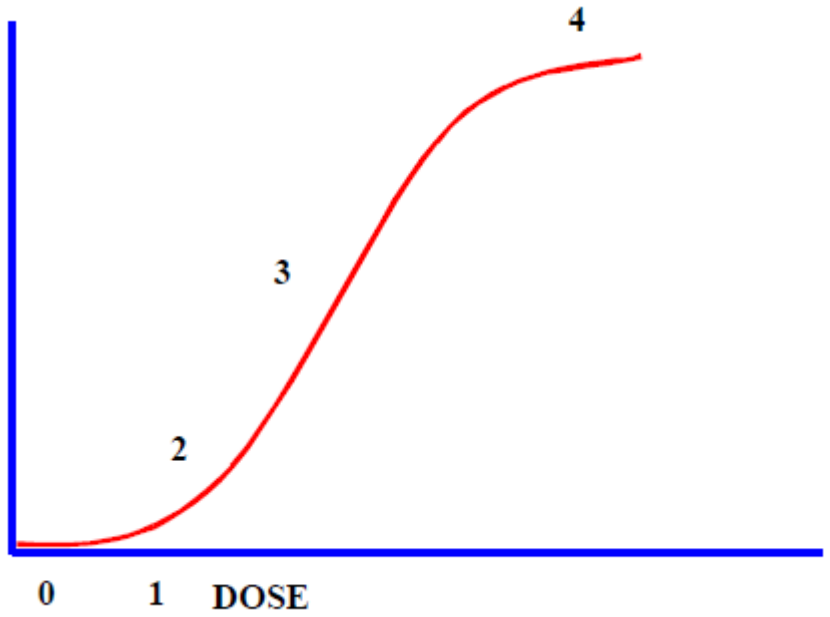
❖ the quantity of chemical exposure or administration within a given time period.

Two types of dose– response relationships:

1. **The individual dose–response relationship:** describes the relationship of an individual subject or system to increasing and/or continuous doses of a chemical

As the dose of a toxicant increases, so does the response, either in terms of the proportion of the population responding or in terms of the severity of the graded
responses.

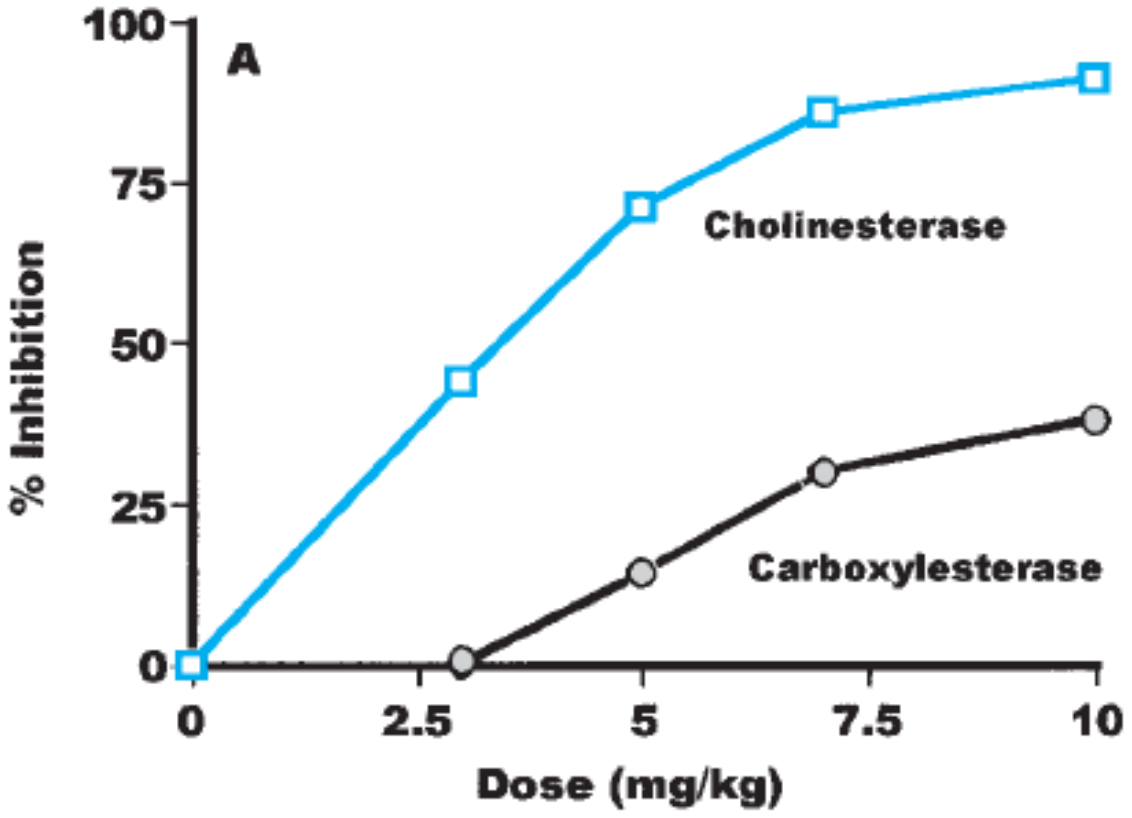
0-1: no effect
1-2: slight effect
2-3: increasing effect as the dose increases (moderate)
4: maximum effect (death)



Individual, or Graded, Dose–Response Relationships

Ex: doses of the organophosphate insecticide (chlorpyrifos) inhibition effect on two enzymes

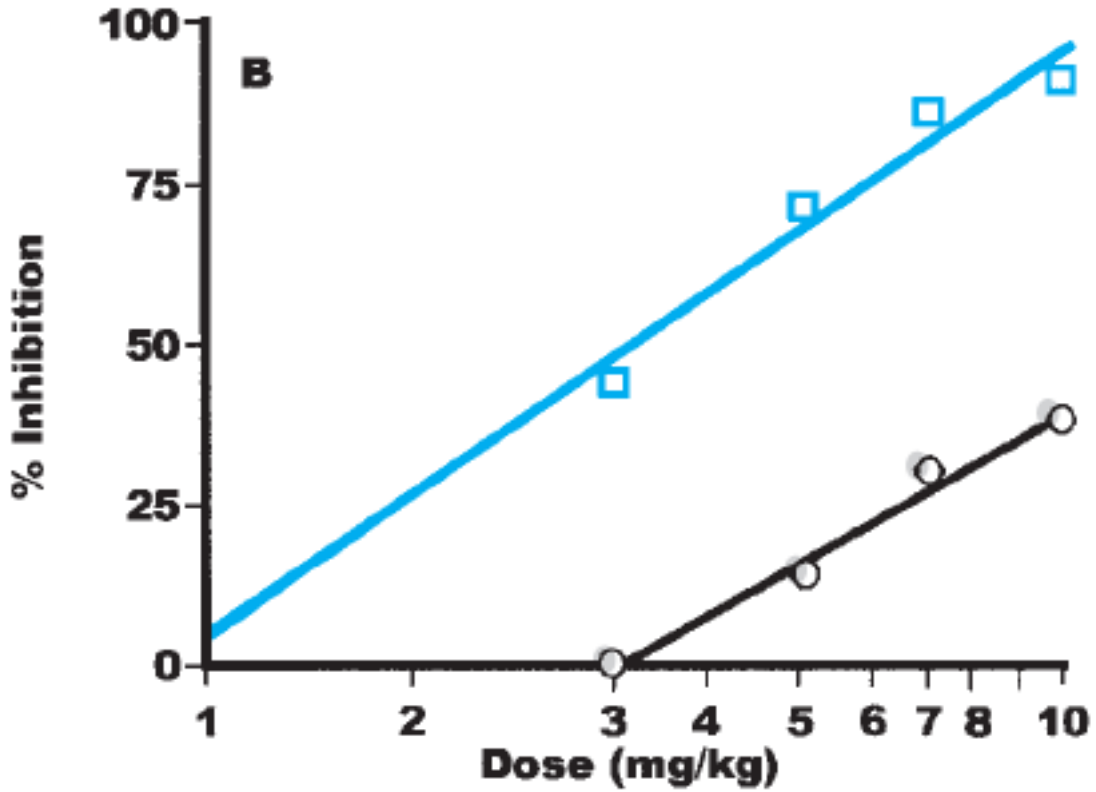
Open circles and blue lines represent acetylcholinesterase activity and closed circles represent carboxylesterase activity in the brains of pregnant female Long-Evans rats given 5 daily doses of chlorpyrifos.



A. Dose–response curve plotted on an arithmetic scale.

B. Same data plotted on a semi-log scale.
exposure to chloryprifos: Dose response profiles for cholinesterase and carboxylesterase activity

In the brain, the degree of inhibition of both enzymes is clearly dose-related and spans a wide range, although the amount of inhibition per unit dose is different for the two enzymes.



In the brain, cholinesterase is more easily inhibited than carboxylesterase

clinical signs and symptoms for chlorpyrifos would follow a dose–response relationship similar to that for brain cholinesterase.

- **A quantal dose–response relationship:** characterizes the distribution of individual responses to different doses

- Generally classified as an "all-or-none effect," where the test system or organisms are quantified as either "responders" or "non-responders."

- A typical quantal dose-response curve is illustrated by the lethal dose 50% (LD50) distribution.

LD50 is a statistically calculated dose of a chemical that causes death in 50% of the animals tested.

Chemical	LD_{50} (mg/kg)
Ethyl Alcohol	10,000
Sodium Chloride	4,000
Ferrous Sulfate	1,500
Morphine Sulfate	900
Strychnine Sulfate	150
Nicotine	1
Black Widow	0.55
Curare	0.50
Rattle Snake	0.24
Dioxin (TCDD)	0.001
Botulinum toxin	0.0001

- **LD50:**

1. Provides a screening method for toxic evaluation, particularly useful for new unclassified substances.
2. Requires large numbers of animals
3. Does not provide information regarding mechanistic effects or target organ
4. Does not suggest complementary or selective pathways of toxicity.
5. limited by the route and duration of exposure.

Factors That Influence the LD50

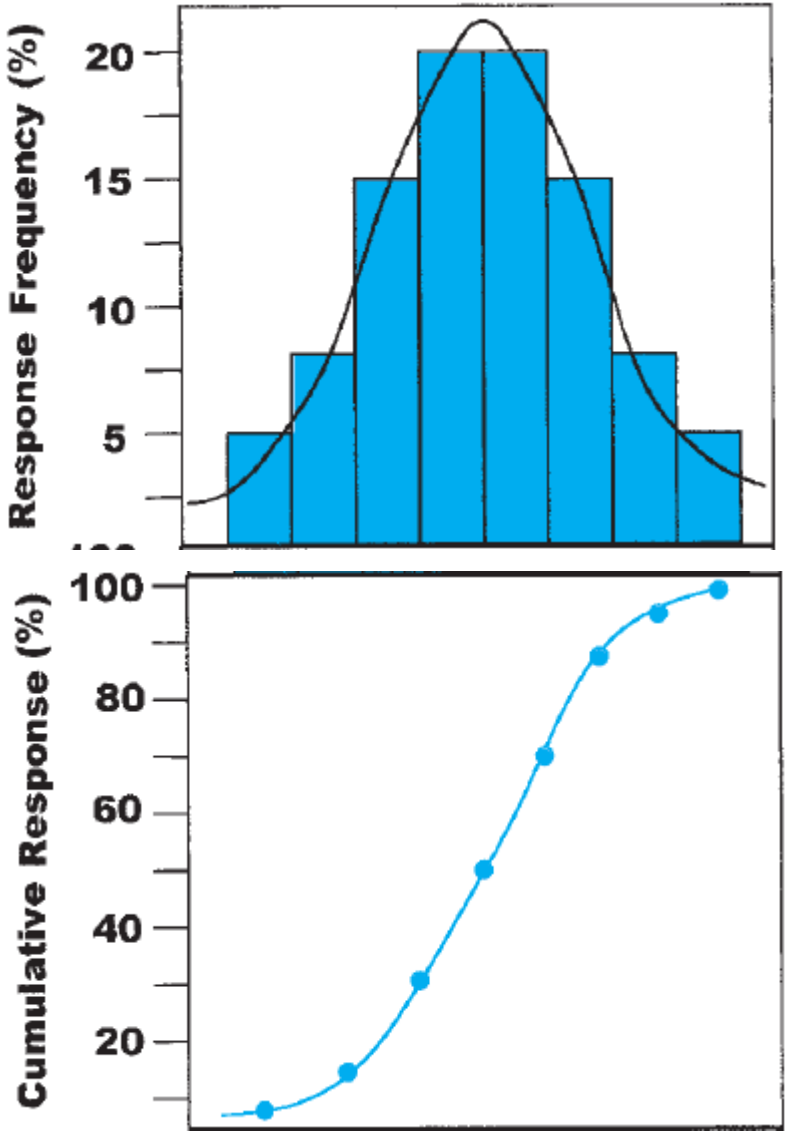
1. The selection of the species
2. The route of administration, and the time of day of exposure and observation.
3. Adherence to the same criteria in each trial experiment.

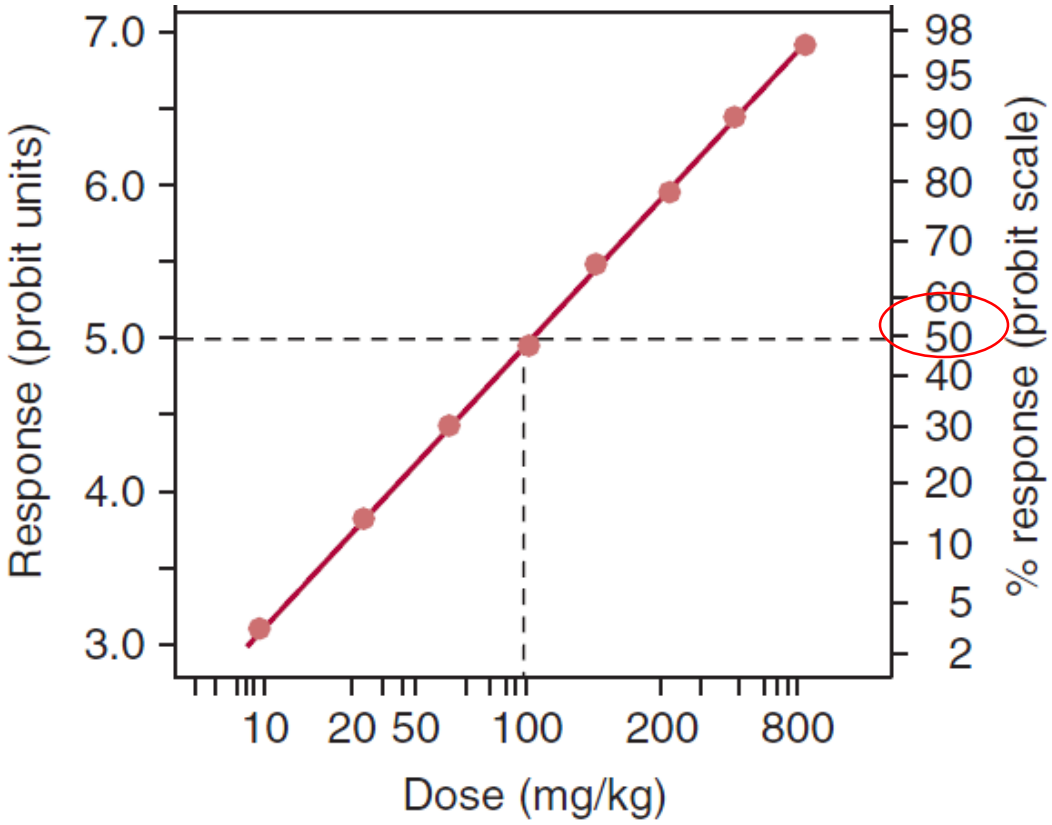
- The same species must be of the same age, sex, strain, weight….. Also, the animal care maintenance should be similar in each run, with attention to light and dark cycles, feeding, and waste disposal schedules.

- The doses administered are also continuous, or at different levels
- The response is generally mortality, gross injury, tumor formation, or some other criteria by which a standard deviation or “cut-off” value can be determined.

- Factors such as therapeutic dose or toxic dose, can be determined using quantal dose response curves, from which are derived the effective dose 50% (ED50) and the toxic dose 50% (TD50), respectively.

- As the concentration of a chemical in the affected compartment increases, the degree of response must increase proportionately if this assumption is valid.





Quantal Dose–Response Relationships

Therapeutic index (TI)

- The calculated relationship between the lethal (or toxic) and the effective dose.

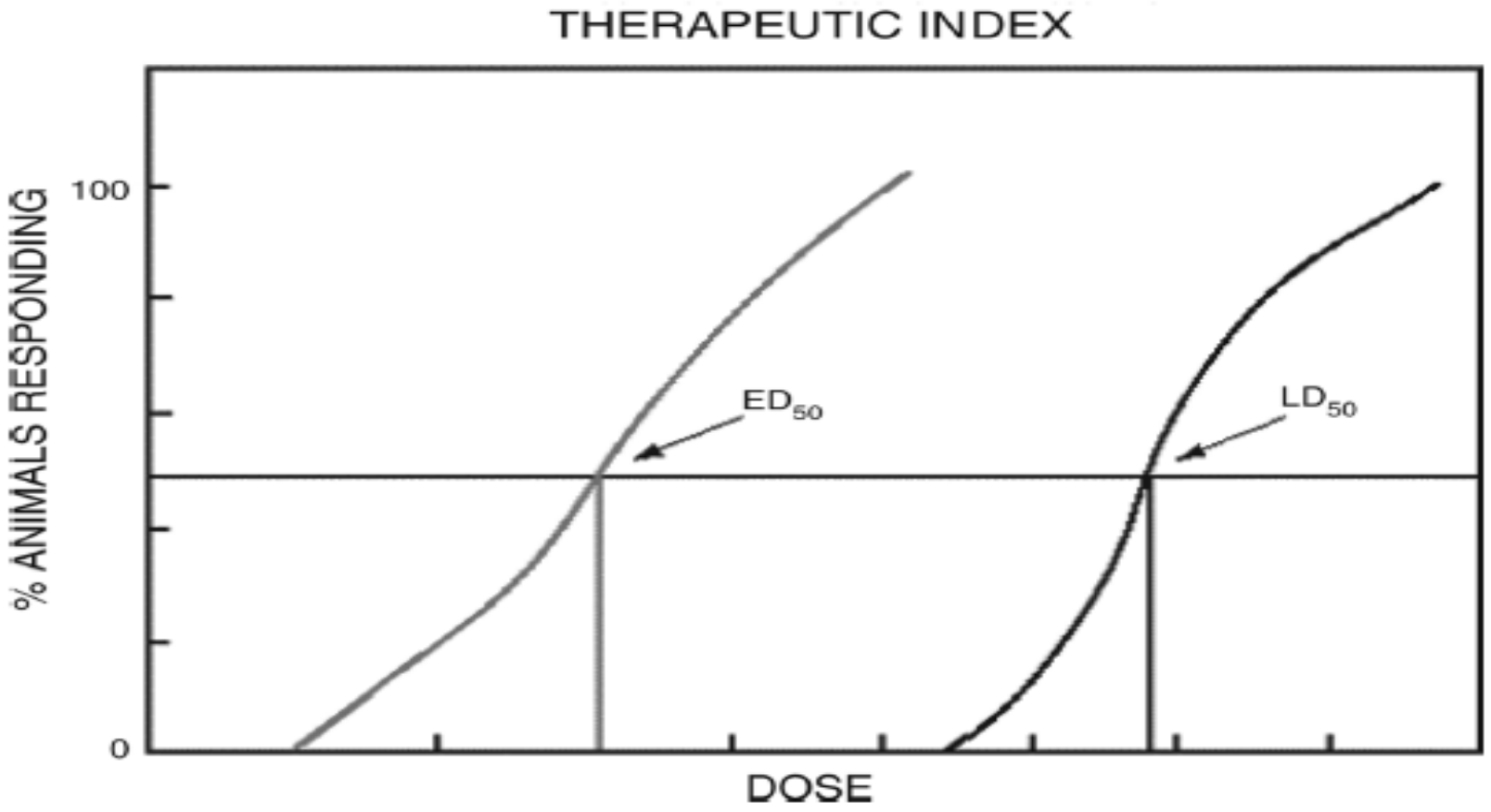


FIGURE 7.4 Graph of TI. The TI is used to determine the difference between an effective dose and a toxic (or lethal) dose. The TI increases as the difference between the effective (therapeutic) dose and the toxic dose is amplified. The calculation allows for an estimation of the potential usefulness of the agent as a therapeutic tool. *Abbreviation:* TI, therapeutic index.

$$TI = \frac{LD_{50} \text{ or } TD_{50}}{ED_{50}}$$

TD: toxic dose
LD: lethal dose
ED: effective dose

Shape of the Dose–Response Curve

ESSENTIAL NUTRIENTS:

- e.g., vitamins and essential trace elements
- The shape of the "**GRADED**" dose– response relationship in an individual over the entire dose range is actually **U-SHAPED.**
- At very low doses, there is a high level of adverse effect, which decreases with an increasing dose.
- This region of the dose–response relationship for essential nutrients is commonly referred to as a *deficiency.*

- As the dose is increased to a point where the deficiency no longer exists, no adverse response is detected and the organism is in a state of homeostasis.

- As the dose is increased to abnormally high levels, an adverse response (usually qualitatively different from that observed at deficient doses) appears and increases in magnitude with increasing dose, just as with other toxic substances.

Ex: high doses of vitamin A can cause liver toxicity and birth defects.

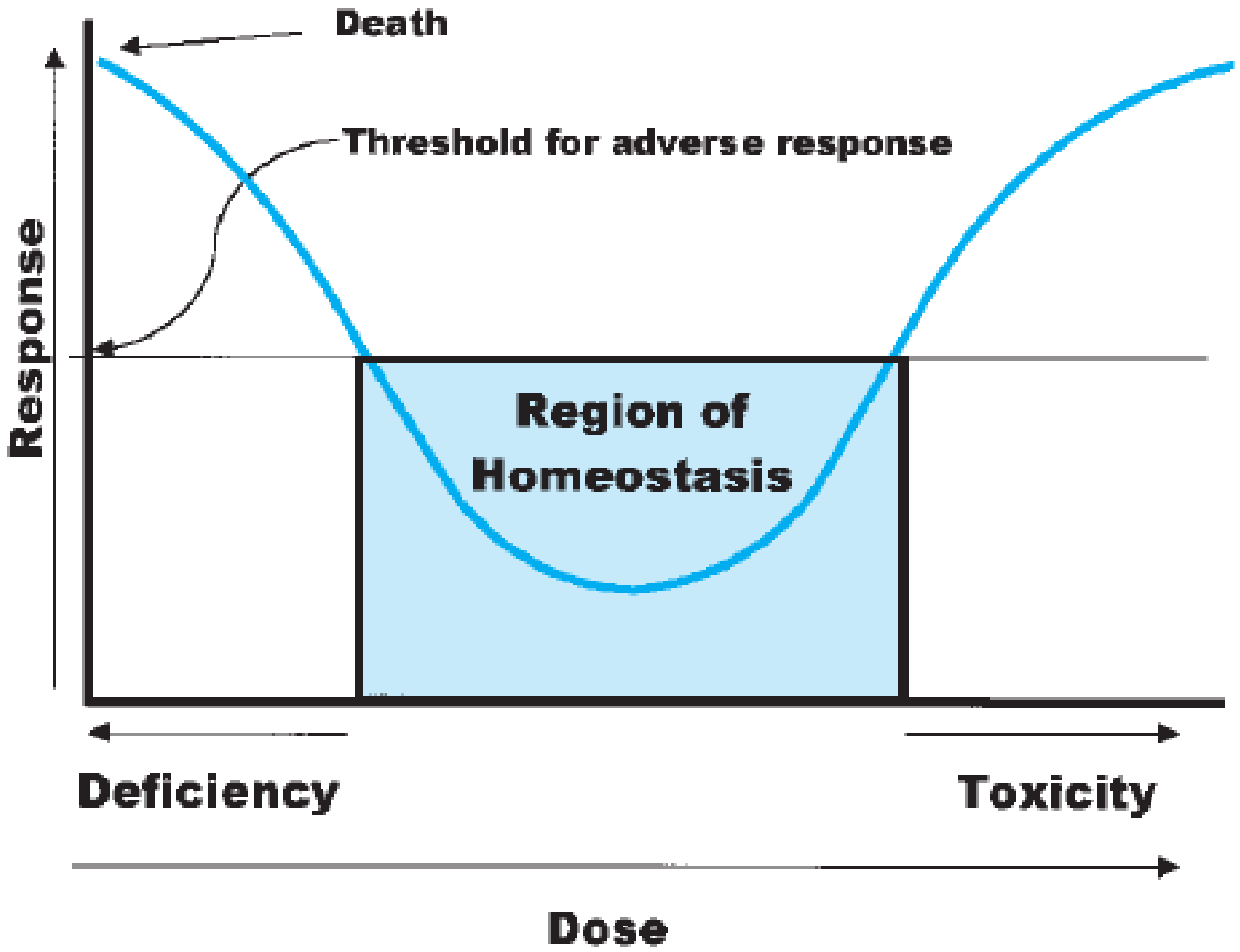


Figure 2-6. Individual dose–response relationship for an essential substance such as a vitamin or trace element.

Threshold: dose below which the probability of an individual responding is zero.

Pharmacokinetic of toxins:

Absorption, Distribution, Metabolism & Elimination.

- Overdose of a drug can alter the usual pharmacokinetic processes, and this must be considered when applying kinetics to poisened patients

- For example, dissolution of tablets or gastric emptying time may be slowed so that absorption and peak toxic effects are delayed.

- With a dramatic increase the concentration of drug in the blood, protein binding capacity may be exceeded, resulting in an increased fraction of free drug and greater toxic effect

- The toxicant may have to pass many barriers to get to its site of action.

- The intensity of a toxic effect depends primarily on the concentration and persistence of the toxicant at its site of action.

- The ultimate poison is the chemical species that reacts with the endogenous target molecule (e.g., receptor, enzyme, DNA, protein, lipid) or critically alters the biological (micro) environment, initiating structural and/or functional alterations that result in toxicity.

- The accumulation of the ultimate toxicant at its target is facilitated by its absorption, distribution to the site of action, reabsorption, and toxication (metabolic activation).

- Presystemic elimination, distribution away from the site of action, excretion, and detoxification oppose these processes and work against the accumulation of the ultimate toxicant at the target molecule.

The body has defenses:

- Membrane barriers
  - Passive and facilitated diffusion, active transport
- Biotransformation enzymes, antioxidants
- Elimination mechanisms.

Absorption

- Is the transfer of a chemical from the site of exposure, usually an external or internal body surface (e.g, skin, mucosa, and respiratory tracts), into the systemic circulation.

- The rate of absorption is related to:

1. The concentration of the chemical at the absorbing surface, which depends on the rate of exposure and the dissolution of the chemical.

2. The area of the exposed site.
3. The characteristics of the epithelial layer through which absorption takes place (eg, the thickness of the *stratum corneum* in the skin)
4. The intensity of the subepithelial microcirculation
5. The physicochemical properties of the toxicant.
6. Lipid solubility: lipid soluble are absorbed more readily than are water-soluble substances

Route	Absorption
Intravenous	No limiting factors in absorption (100% bioavailable)
Inhalation	Must penetrate alveolar sacs of lungs but then into capillary bed
Ingestion	Requires absorption through GI tract and is subject to 1st pass effect stomach (acids), small intestine (long contact time, large surface area--villi
Intraperitoneal	Like ingestion (still 1st pass effect) but does not require absorption through the GI tract
Dermal/Topical	Requires absorption through the skin absorption through epidermis, then dermis; site and condition of skin

Presystemic Elimination:

- Not unusual for chemicals absorbed from the GI tract because they must first pass through the GI mucosal cells, liver, and lung before being distributed to the rest of the body by the systemic circulation.
- For example, ethanol is oxidized by alcohol dehydrogenase in the gastric mucosa
- Such processes may prevent a considerable quantity of chemicals from reaching the systemic blood, but may contribute to injury of the digestive mucosa, liver, and lungs by chemicals

Distribution

- The process in which a chemical agent trans-locates throughout the body

- Blood carries the agent to and from its site of action, storage depots, organs of transformation, and organs of elimination

Ex: **Storage**

- DDT in Fatty tissues
- Lead and Fluoride in Bone

- Distribution may change over time

Rate of distribution (rapid) dependent upon:

- Blood flow.
- Characteristics of toxicant (affinity for the tissue, and the partition coefficient).
- Lipid-soluble compounds move readily into cells by diffusion.
- Highly ionized and hydrophilic xenobiotics (eg, aminoglycosides) are largely restricted to the extracellular space unless specialized membrane carrier systems are available to transport them.

Mechanisms Facilitating Distribution to a Target:

- Distribution of toxicants to specific target sites may be enhanced by:

(1) THE POROSITY OF THE CAPILLARY ENDOTHELIUM

(2) SPECIALIZED MEMBRANE TRANSPORT

(3) ACCUMULATION IN CELL ORGANELLES

(4) REVERSIBLE INTRACELLULAR BINDING.

Mechanisms Opposing Distribution to a Target:

The processes include:

- Binding to plasma proteins, ex: DDT
- Specialized barriers ex: Brain capillaries
- Distribution to storage sites such as adipose tissue or bone,
  ex: chlorinated hydrocarbon insecticides in AT
- Association with intracellular binding protein
- Export from cells, Ex: brain capillary.

Target organs

- Adverse effect is dependent upon the concentration of active compound at the target site for enough time.

- Not all organs are affected equally
  - ❖Greater susceptibility of the target organ
  - ❖Higher concentration of active compound
- Liver--high blood flow, oxidative reactions, functionality.
- Kidney--high blood flow, concentrates chemicals.

- **Lung-**--high blood flow, site of exposure
- **Neurons-**--oxygen dependent, irreversible damage
- **Myocardium-**--oxygen dependent
- **Bone marrow**, **intestinal mucosa-**--rapid divided

- Adverse effects can occur at the level of the molecule, cell, organ, or organism

1. **Molecularly**, chemical can interact with
   Proteins, Lipids and DNA

2. **Cellularly**, chemical can:

- Interfere with receptor-ligand binding
- Interfere with membrane function
- Interfere with cellular energy production
- Bind to biomolecules
- Perturb homeostasis (Ca).

Excretion

- It is the removal of chemicals from the blood and their return to the external environment. It is a physical mechanism, whereas biotransformation is a chemical mechanism for eliminating the toxicant.

- The major excretory structures in the body are the renal glomeruli, which hydrostatically filter small molecules (<60 kDa) through their pores.

- Renal transporters have a preferential affinity for smaller (<300 Da), and hepatic transporters for larger (>400 Da) amphiphilic molecules.

- The major excretory organs—kidney and liver—can efficiently remove only highly hydrophilic, usually ionized chemicals such as organic acids and bases.

- The route and speed of excretion depend largely on the physicochemical properties of the toxicant.

- The reasons for this are as follows:

(1) In the renal glomeruli, only compounds dissolved in plasma water can be filtered;

(2) Transporters in hepatocytes and renal proximal tubular cells are specialized for secretion of highly hydrophilic organic acids and bases

(3) Only hydrophilic chemicals are freely soluble in the aqueous urine and bile

(4) Lipid-soluble compounds are readily reabsorbed by transcellular diffusion.

Other routes of excretion

(1) Excretion by the mammary gland after the chemical is dissolved in milk lipids

(2) Excretion in bile: can be extracted by the liver and excreted into the bile. The bile drains into the small intestine and is eliminated in the feces.

(3) Volatile, nonreactive toxicants such as gases and volatile liquids diffuse from pulmonary capillaries into the alveoli and are exhaled.

(4) Sweat.

(5) Saliva.

Metabolism

- Metabolism (biotransformation)—the process by which administered chemicals (parent compounds) are modified by the organism, usually via enzymes.

- The primary objective of metabolism is to make chemical agents more water soluble and easier to excrete by:

- Decreasing lipid solubility ….. Decreased amount that reaches the target organ/s.

- Increasing ionization….Increased rate of excretion….Decrease toxicity

- In some situations, biotransformation results in the formation of reactive metabolites—bioactivation. Whether it is the parent compound or the metabolite, it is the active compound that does the damage.

Key organs of Biotransformation:

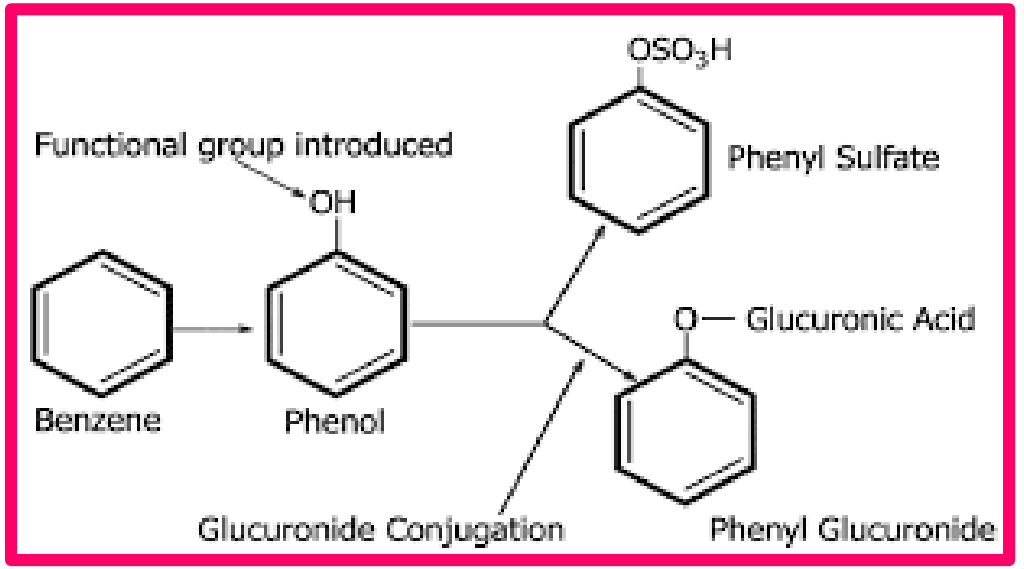
- LIVER (High)
- Lung, Kidney, Intestine (Medium)
- Others (Low)

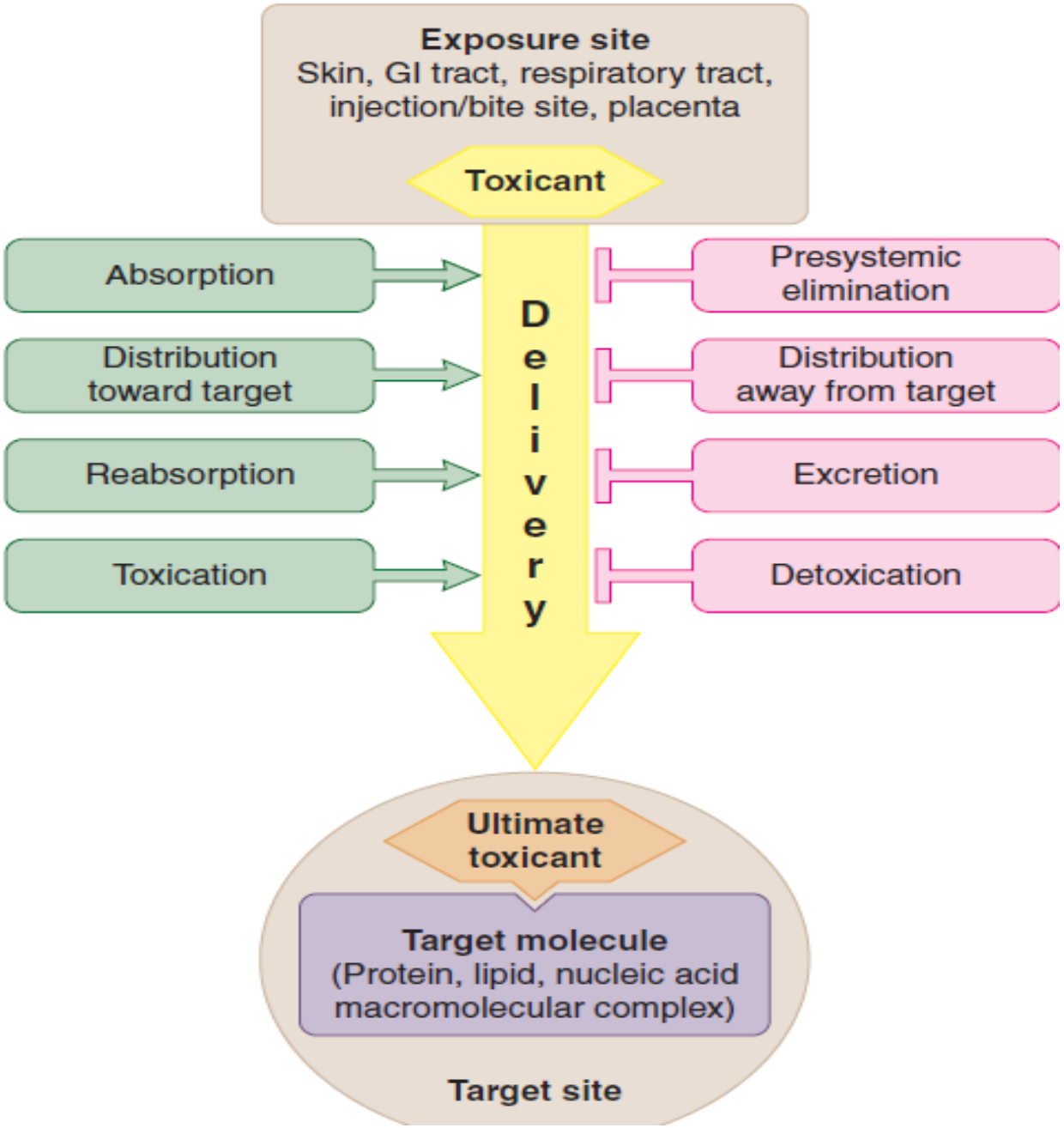
- Biotransformation can affect the rate of clearance of compounds

- Ex: Phenobarbital from 5 months w/o biotransformation to 8hr with Biotransformation.

Biotransformation Pathways:

- **Phase I enzymes:** the toxicant becomes more soluble.
- **Phase II Enzymes:** Linking with a soluble agent {e.g. functional group} (conjugation)




Exposure site
Skin, GI tract, respiratory tract, injection/bite site, placenta
Toxicant
Absorption
Distribution toward target
Reabsorption
Toxication
Delivery
Presystemic elimination
Distribution away from target
Excretion
Detoxication
Ultimate toxicant
Target molecule
(Protein, lipid, nucleic acid macromolecular complex)
Target site

References

- Toxicology : the basic science of poisons, casarett and doulls, 8 ed ,2013,unit 1, chapter2,3
- Clinical toxicology , principles and mechanisms, 2 ed , Frank A. Barile,2010,chapter7