General Toxicology

General Principles of Toxicology

Lab. 1
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"What is there that is not poison?
All things are poison and nothing (is) without poison. Solely the dose determines that a thing is not a poison."

Paracelsus (1493–1541)





Introduction:

- **Toxicology** is the study of the adverse effects of chemicals on living organisms.
- **Xenobiotic** is a chemical that interacts with an organism and not found in the normal metabolic pathway of that organism.
- **Toxicologist** is a trained person to examine the nature of those adverse effects (including their cellular, biochemical, and molecular mechanisms of action) and assess the probability of their occurrence

- **Toxicant** A substance capable of producing harmful biological effects.

- **Toxin** A poisonous substance produced naturally by a living organism, such as bacteria, fungi, plants, or animals.

- **Poisons** A substance capable of causing harmful effects, including severe illness or death, depending on the dose and exposure.

Phytotoxin



Bacteriotoxin



Zootoxin



Measurement of toxicity:

The normal procedure is to expose test animals by:

- ingestion,
- application to the skin,
- inhalation or
- by placing the test material in the water or air of the test animals' environment

- Safety in experimental animals does not necessarily indicate the same in humans. For example thalidomide, a human teratogen, shows toxicity (caused shortening or complete absence of limbs) at doses as low as 0.5-1 mg/kg & has little or no effect in mice or rats at doses as high as 4000 mg/kg.



Toxicity tests are routinely performed by pharmaceutical manufacturers in the investigation of a new drug. These test measure:

- mortality (death),
- teratogenicity (ability to cause birth defects)
- carcinogenicity (ability to cause cancer), &
- mutagenicity (ability to cause heritable change in the DNA).

Median lethal dose (LD50):

The amount (dose) of a chemical which produces death in 50% of a population of test animals.

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

The Median Lethal Concentration (LC50):

- 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 .

- Normally expressed as milligrams of substance per liter (mg/l) of air or water (or as ppm).

The Exposure:

- Route & site of exposure
- Frequency of exposure
- Duration of exposure

Rout & site of exposure:

- Oral ⇒ GI tract
- Inhalation ⇒ Lungs
- Topical, percutaneous, or dermal ⇒ Skin
- Ocular, conjunctiva, cornea ⇒ Eyes
- Other routes ⇒ IP, SC, IM, ID, IV…

Duration & frequency of exposure:

Toxicologists usually divide the exposure of experimental animals to chemicals into four categories:

1. **Acute** exposure is defined as exposure to a chemical for less than 24 h
2. **Subacute** exposure refers to repeated exposure to a chemical for 1 month or less
3. **Subchronic** for 1 to 3 months
4. **Chronic** for more than 3 months

Immediate versus delayed toxicity:

- Immediate toxic effects occur or develop rapidly after a single administration of a substance, whereas delayed toxic effects occur after a period of time.

- Carcinogenic effects of chemicals usually have long latency periods, 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.

Local versus systemic toxicity:

- **Local effects**

Occur at the site of first contact between the biological system & the toxicant.

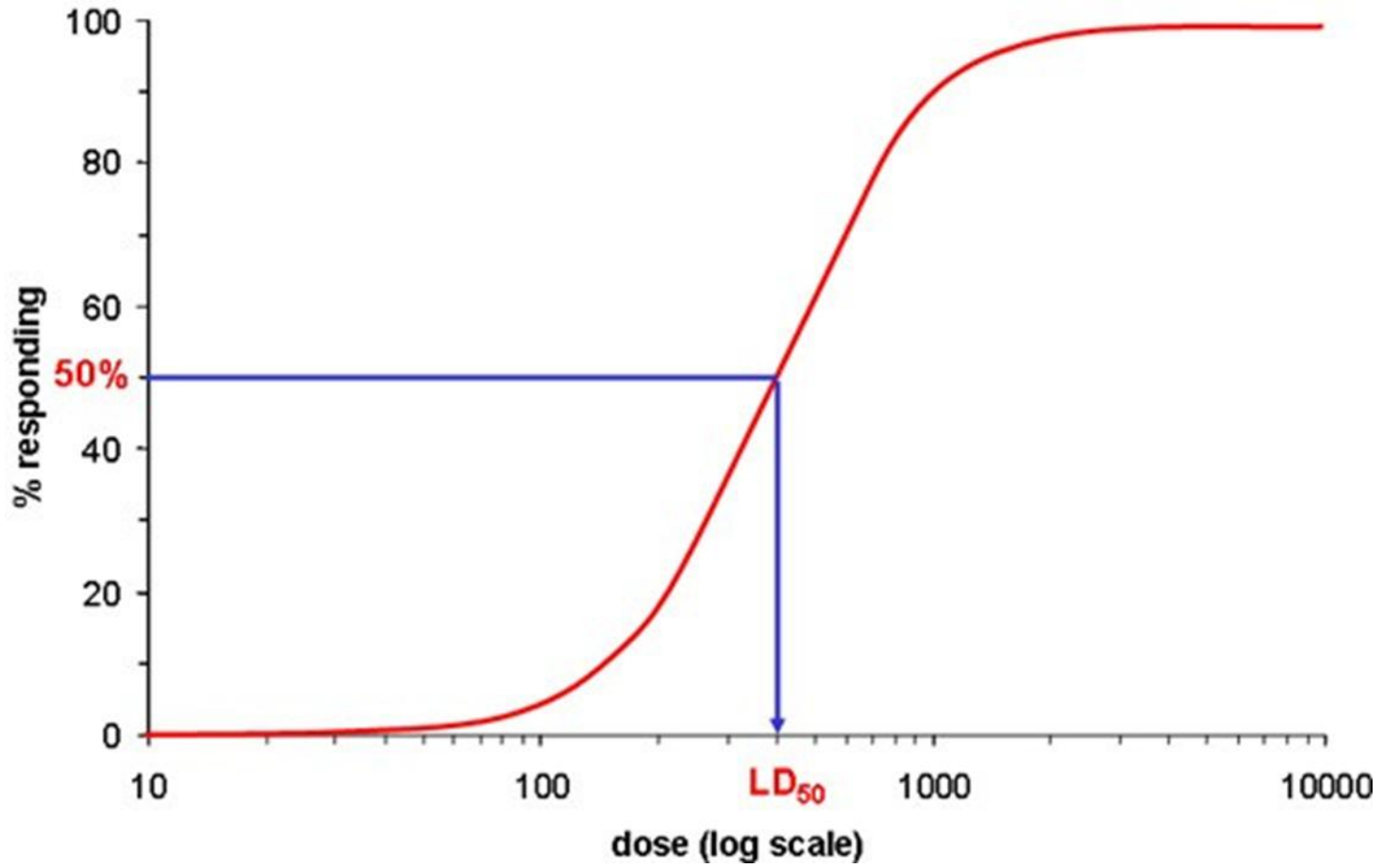
- **Systemic effects**

Require absorption & distribution of a toxicant from its entry point to a distant site at which deleterious effects are produced.

Dose-response relationship:

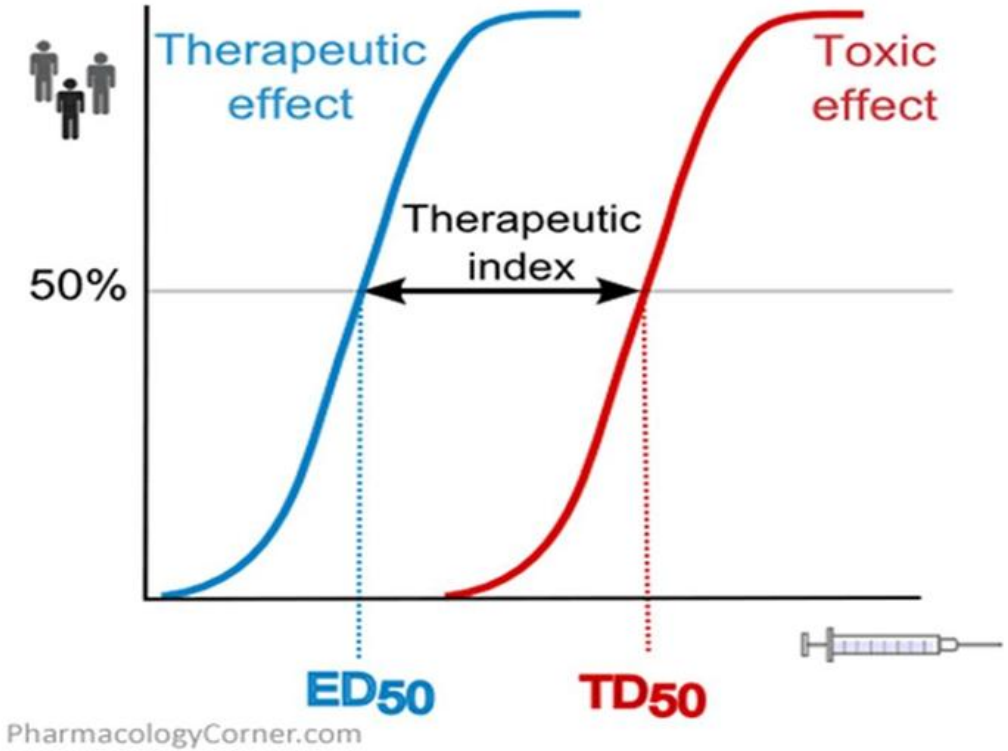
The characteristics of exposure and the spectrum of effects come together in a correlative relationship referred to dose-response relationship.

Dose - response relationship

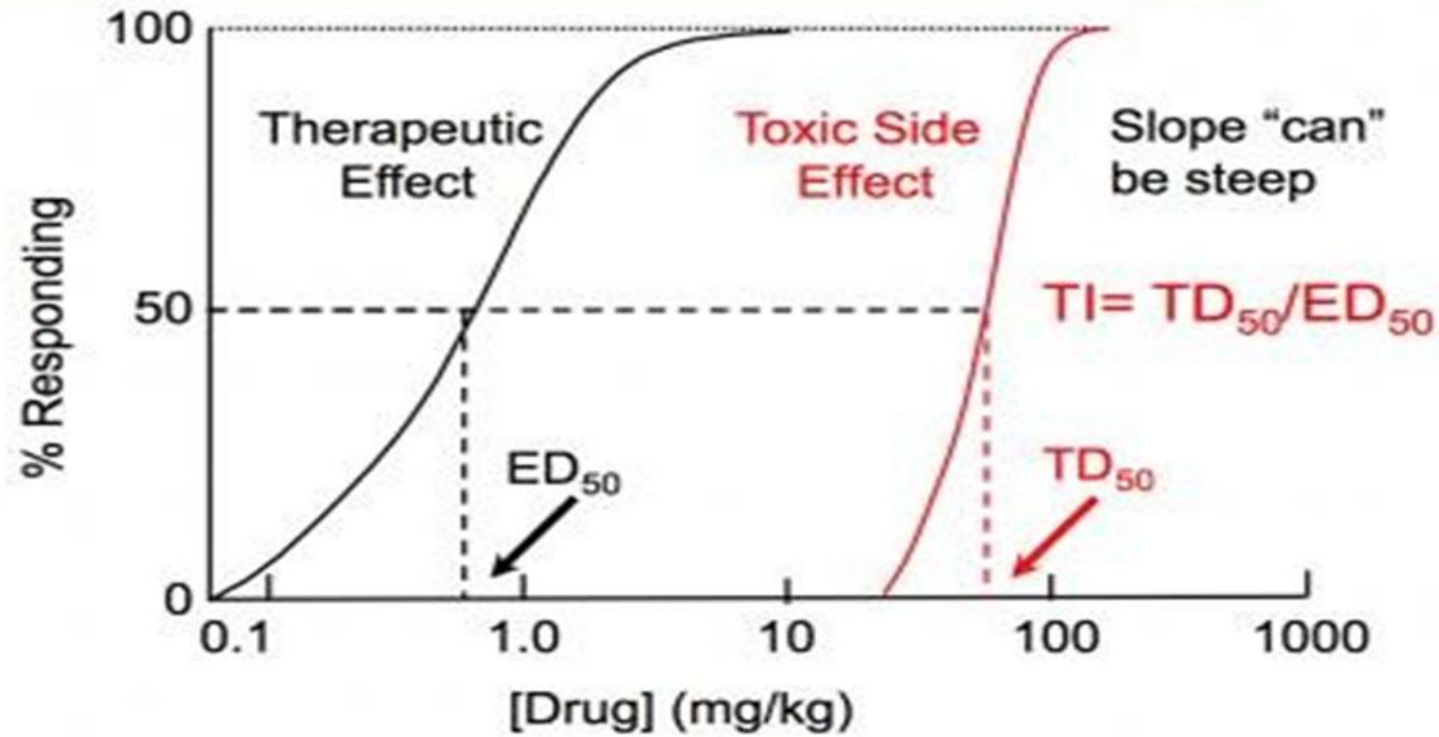


What can be learned from a dose-response curve?

- **LD50** – Median Lethal Dose, quantity of the chemical that is estimated to be fatal to 50% of the organisms.
- LD50 values are the standard for comparison of acute toxicity between chemical compounds and between species.
- **TD50** – Median Toxic Dose
- **ED50** – Median Effective Dose
- **LC50** – Median Lethal Concentration



Drug Safety - Therapeutic Index



$$\text{Therapeutic Index} = \frac{\text{LD}_{50}}{\text{ED}_{50}}$$ in animal studies, or for humans, $$\text{Therapeutic Index} = \frac{\text{TD}_{50}}{\text{ED}_{50}}$$

Toxicity rating for humans (70-74 kg) body weight

Toxicity Rating	LD50 (milligrams per kg of body weight)*	Average Lethal Dose†	Examples
Supertoxic	Less than 0.01	Less than 1 drop	Nerve gases, botulism toxin, mushroom toxins, dioxin (TCDD)
Extremely toxic	Less than 5	Less than 7 drops	
Very toxic	5–50	7 drops to 1 teaspoon	Potassium cyanide, heroin, atropine, parathion, nicotine
Toxic	50–500	1 teaspoon to 1 ounce	Mercury salts, morphine, codeine
Moderately toxic	500–5,000	1 ounce to 1 pint	Lead salts, DDT, sodium hydroxide, sodium fluoride, sulfuric acid, caffeine, carbon tetrachloride
Slightly toxic	5,000–15,000	1 pint to 1 quart	Methyl (wood) alcohol, ether, Phenobarbital, amphetamines (speed), kerosene, aspirin
Essentially nontoxic	15,000 or greater	More than 1 quart	Ethyl alcohol, Lysol, soaps
			Water, glycerin, table sugar

*Dosage that kills 50% of individuals exposed
†Amounts of substances in liquid form at room temperature that are lethal when given to a 70.4-kg (155-pound) human

Clinical Thinking Question

Two chemicals have the following LD_{50} values

- Chemical A = 50 mg/kg
- Chemical B = 500 mg/kg

Which chemical has higher acute toxicity? Why


Thank
you