General Principles of Toxicology

Wrood Salim, MS.
Laboratory of toxicology -1

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Science of Toxicology

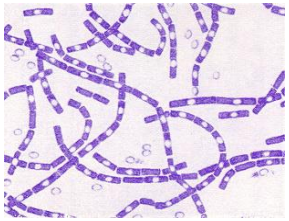
- **Toxicology** is the study of the adverse effects of chemicals on living organisms.
- A chemical that interacts with an organism that is not found in the normal metabolic pathway of that organism is called a **xenobiotic.**
- **A toxicologist** is trained person to examine the nature of those effects (including their cellular, biochemical, and molecular mechanisms of action) and assess the probability of their occurrence
- **Toxicology testing** (safety testing, toxicity testing)
  - Conducted to determine the degree to which a substance can damage a living or non-living organisms
  - It is often conducted by researchers to comply with governing regulations

Xenobiotic - man-made substance and/or produced by plants, animals, or bacteria but not normally found in the body.

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

*** Poisonous substances** are produced by plants, animals, or bacteria.

Phytotoxins
Zootoxins
Bacteriotoxins



Measures of Toxicity

- The normal procedure is to expose test animals
  - By ingestion, application to the skin, by inhalation, gavage, or some other method which introduces the material into the body, or
  - By placing the test material in the water or air of the test animals' environment

Testing Lab animals

- Commonly used:

– Rats, mice, dogs, monkeys etc

- Safety in experimental animals does not necessarily indicate the same in humans.

– Example: Thalidomide a human teratogen shows toxicity(caused shortening or complete absence of limbs) at doses as low as 0.5-1 mg/kg and has little or no effect in mice or rats at doses as high as 4000 mg/kg.

Measures of Toxicity

- Toxicity tests are routinely performed by pharmaceutical manufacturers in the investigation of a new drug.
- Toxicity is measured as clinical "endpoints" which include
  - Mortality (death)
  - Teratogenicity (ability to cause birth defects)
  - Carcinogenicity (ability to cause cancer), and,
  - Mutagenicity (ability to cause heritable change in the DNA)
- At this time we will discuss 2 measures of mortality – the LD_{50} and the LC_{50}

Measures of Toxicity: The Median Lethal Dose

LD_{50}

The amount (dose) of a chemical which produces death in 50% of a population of test animals to which it is administered by any of a variety of methods

mg/kg

Normally expressed as milligrams of substance per kilogram of animal body weight

Measures of Toxicity: The Median Lethal Concentration

LC_{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)

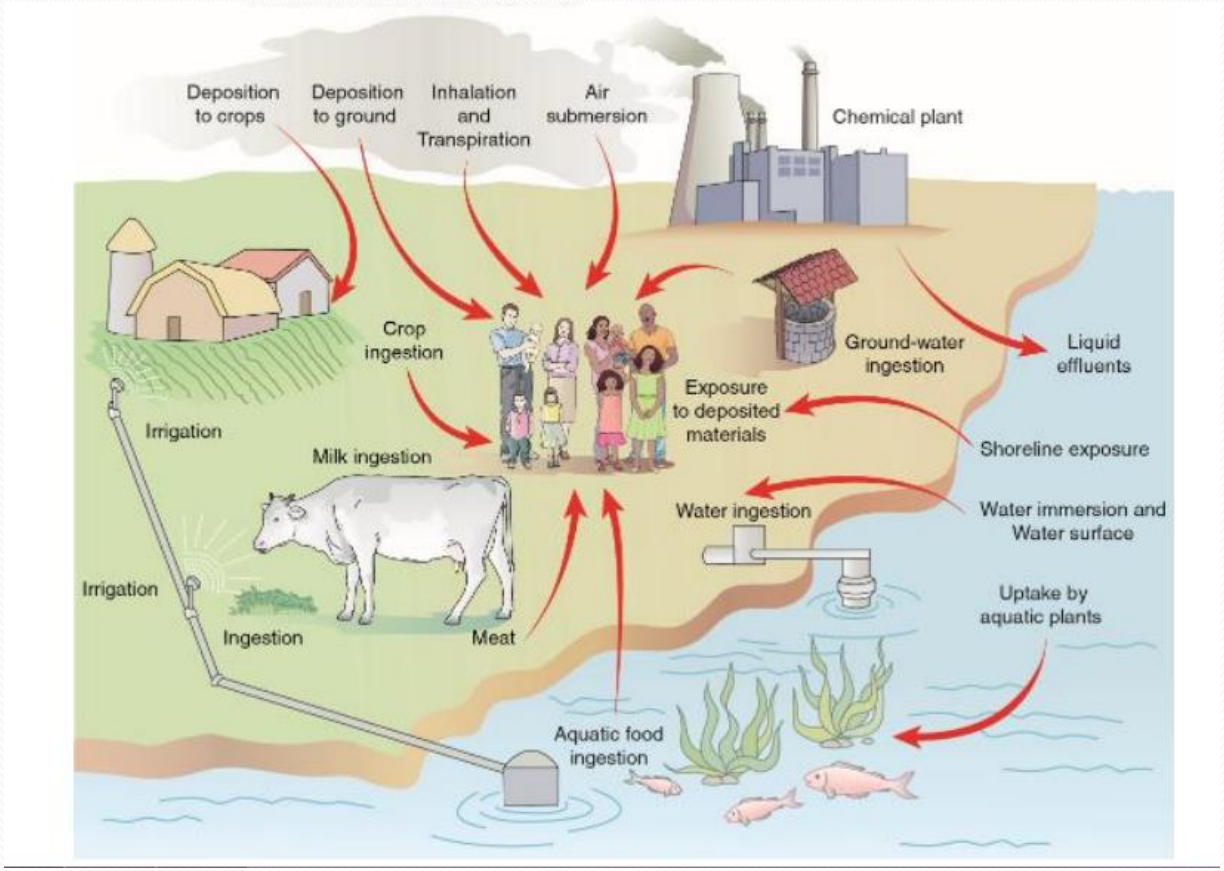
The exposure

Exposure, like many of the terms in toxicology, has several different aspects, the most important of which are

1) route of exposure,

2) frequency of exposure

3) duration of exposure



Routes and site of Exposure

An agent exerts its effects when it enters or comes into contact with the body, or in other words, when an individual has been exposed to it.

1) Oral ⇒ GI tract

2) Inhalation ⇒ Lungs

3) Topical, percutaneous, or dermal ⇒ Skin

4) Ocular, conjunctiva, cornea ⇒ Eyes

5) Other routes ⇒ IP, SC, IM, ID, IV.....

Duration and Frequency of Exposure

- Toxicologists usually divide the exposure of experimental animals to chemicals into four categories:
  - ***Acute* exposure** is defined as exposure to a chemical for less than 24 h
  - ***Subacute*** *exposure* refers to repeated exposure to a chemical for 1 month or less
  - ***Subchronic*** for 1 to 3 months
  - **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 the lapse of some 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

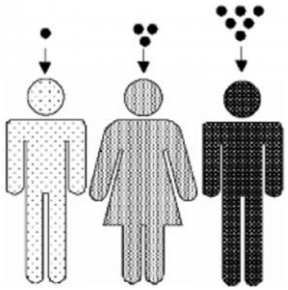
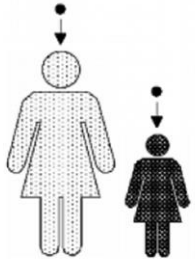
- If a chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible

Local versus Systemic Toxicity

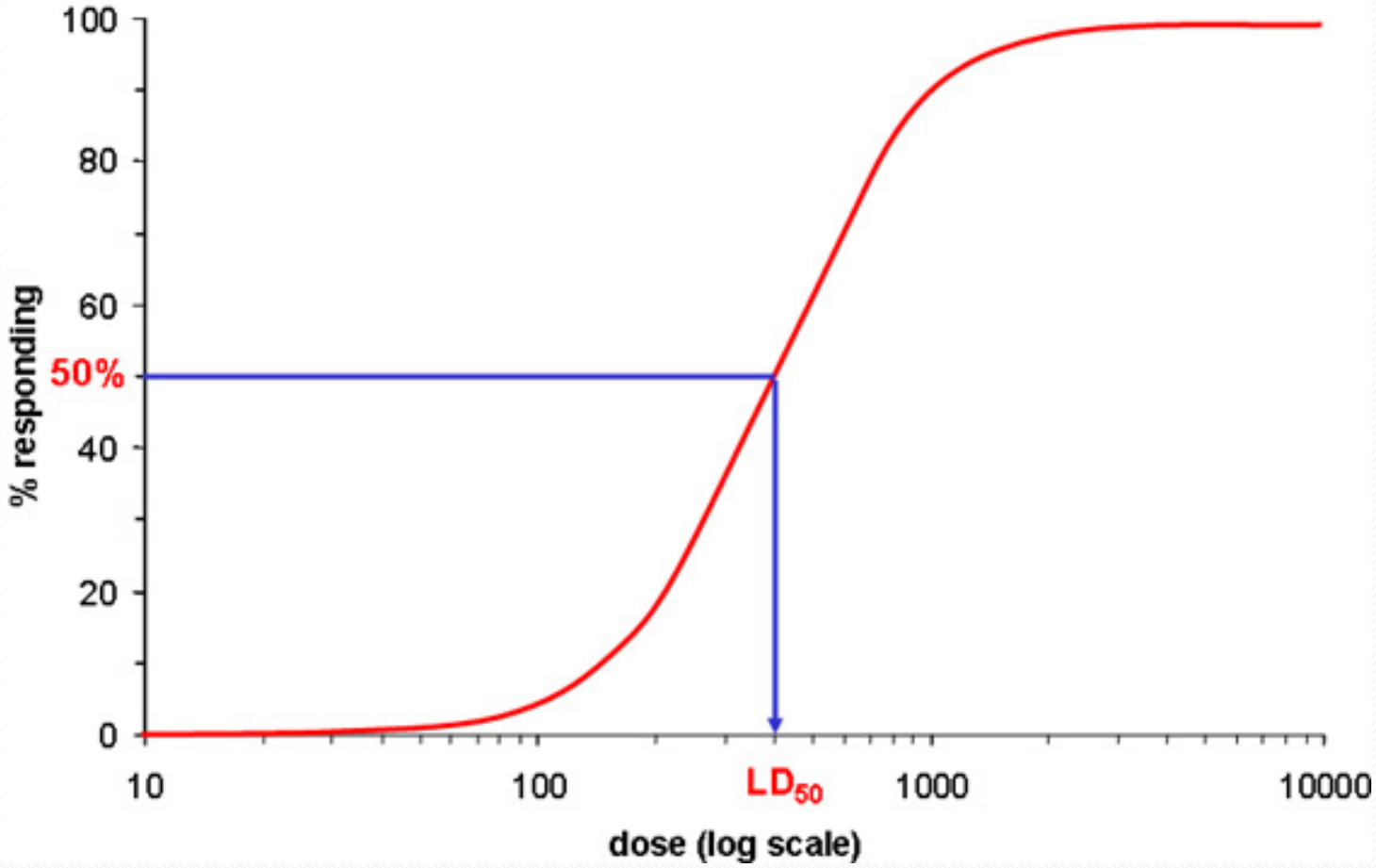
- Local effects
  - Occur at the site of first contact between the biological system and the toxicant
  - Target organs: hepatotoxicity
- Systemic effects
  - Require absorption and distribution of a toxicant from its entry point to a distant site at which deleterious effects are produced
  - CNS depression; multiple organic toxicities

Dose response

- The characteristics of exposure and the spectrum of effects come together in a correlative relationship customarily referred to as the dose-response relationship
- Two types
  - Individual to varying doses of a chemical, Response of an individual organism to varying doses of a chemical
  - Population of individuals

The Importance of Dose	The Importance of Size
	
The larger the dose, the greater the effect	The smaller the size, the greater the effect

dose-response relationship



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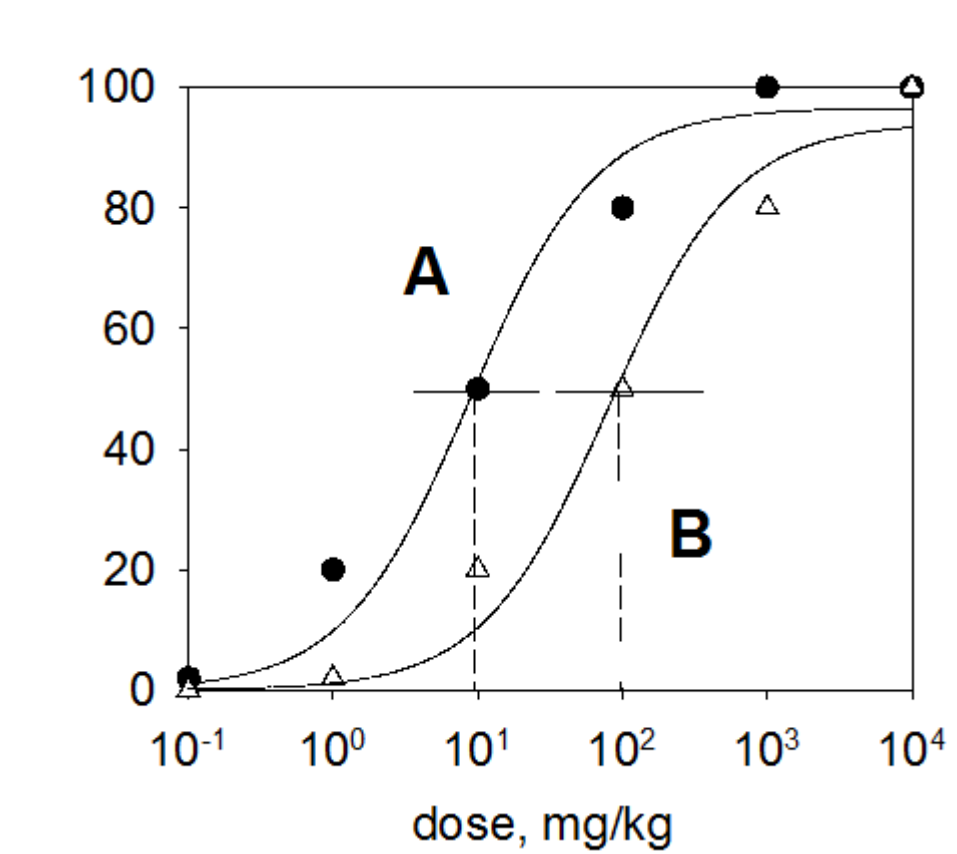
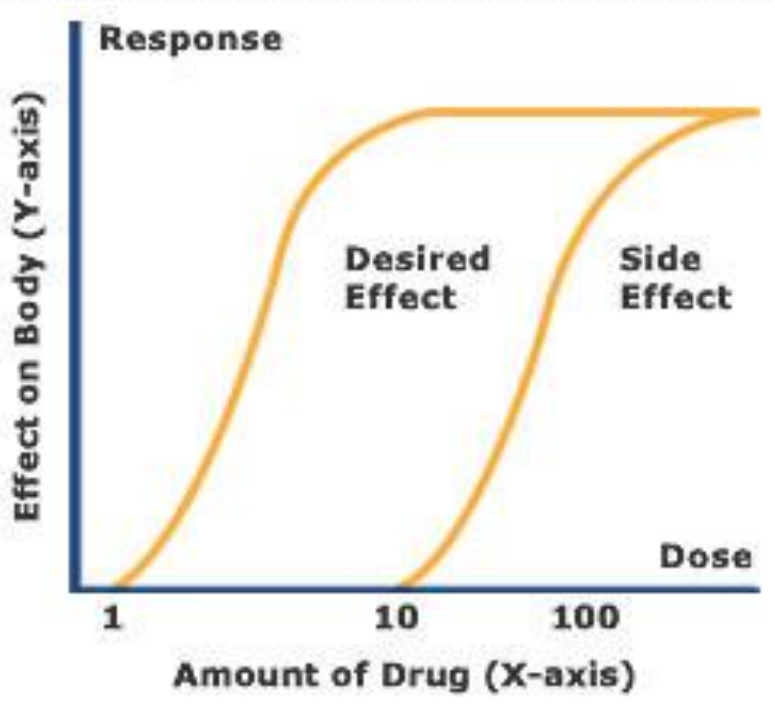
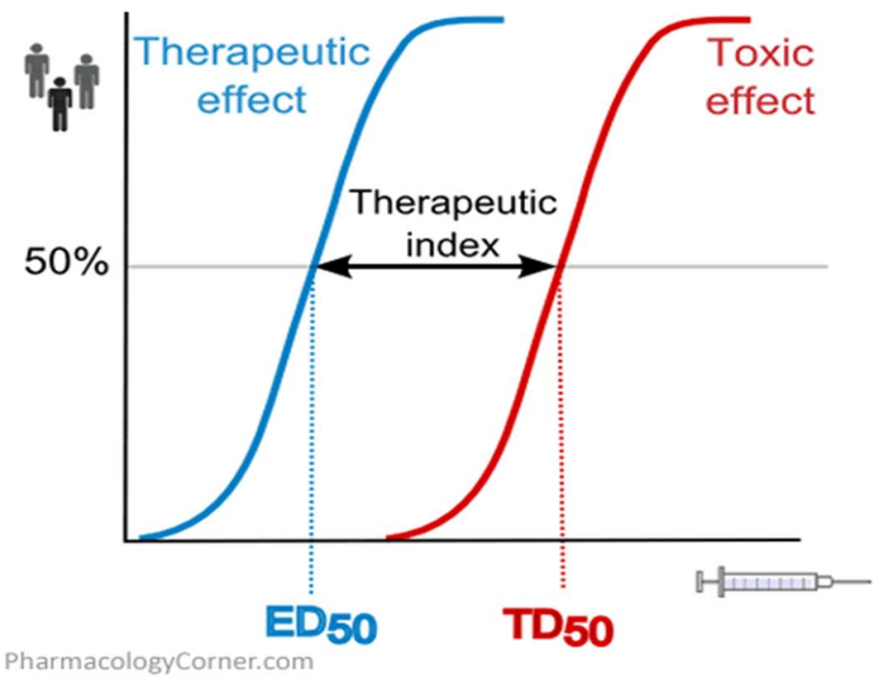




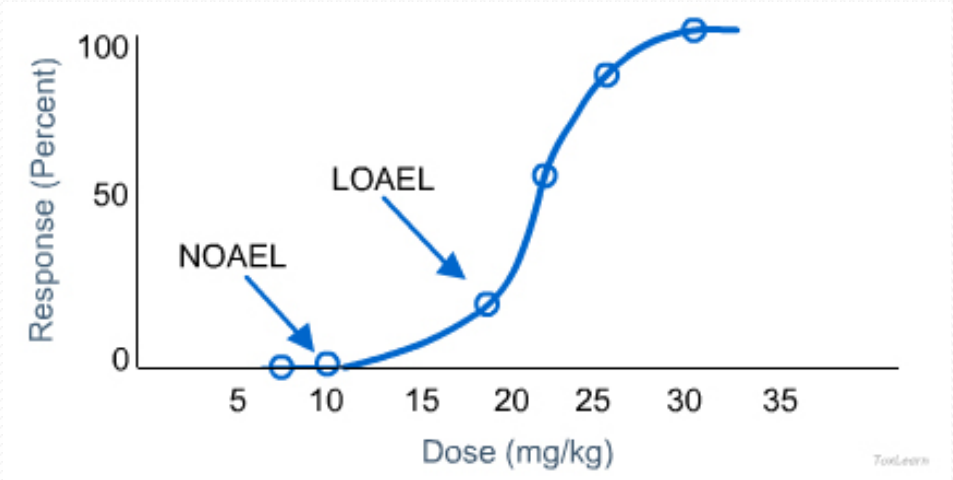
What Can Be Learned From A Dose-Response Curve?

- **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



What Can Be Learned From A Dose-Response Curve?

- NOAEL Value – No Observed Adverse Effect Level, The highest dose of a chemical that, in a given toxicity test, causes no observable effect in test animals
  - The NOAEL for the most sensitive test species and the most sensitive indicator of toxicity is usually employed for regulatory purposes
- LOAEL Value – Lowest Observed Adverse Effect Level, The lowest dose of a chemical that, in a given toxicity test, does cause an observable effect in test animals



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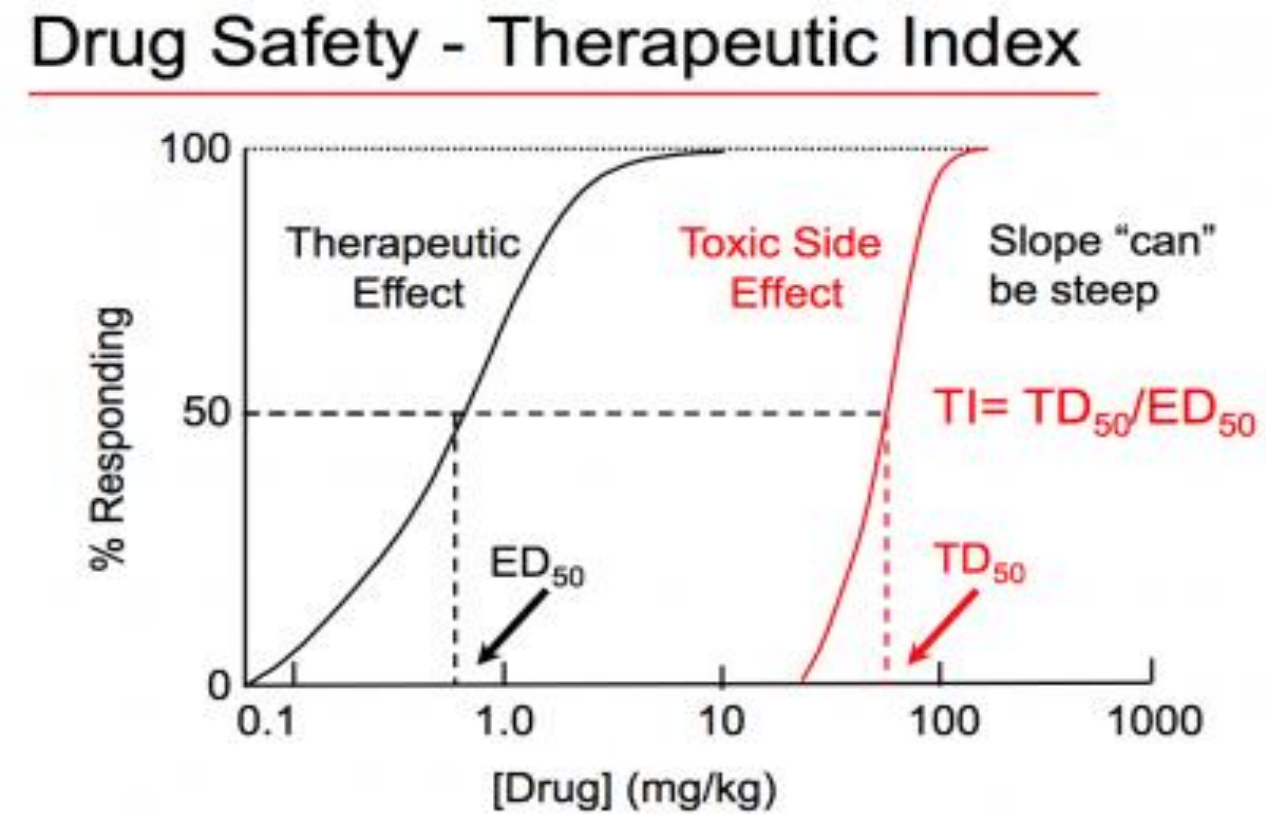

$$\text{Therapeutic Index} = \frac{\text{LD}_{50}}{\text{ED}_{50}}$$ in animal studies, or for humans, $$\text{Therapeutic Index} = \frac{\text{TD}_{50}}{\text{ED}_{50}}$$

TOXICITY RATING FOR HUMANS (70 KG BODY WEIGHT)

Toxicity Rating	Animal LD50	Lethal Dose 150pound Human
Extremely Toxic	Less than 5mg/Kg	A taste (less than 7 drops)
Highly Toxic	5 to 50 mg/Kg	7 drops to 1 teaspoon
Moderately Toxic	50 to 500mg/Kg	1 teaspoon to an ounce
Slightly Toxic	500 mg to 5g/Kg	One ounce to a pint
Practically Non-toxic	Above 5g/Kg	Above a pint