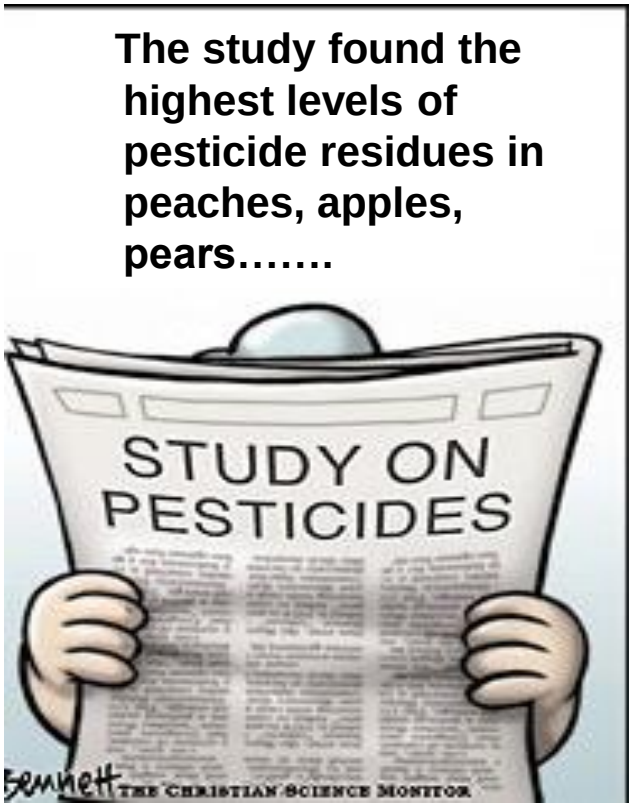
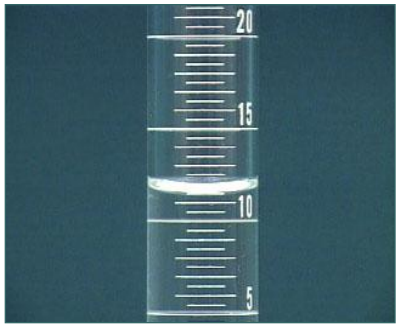
Dosage of the drug or chemical

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



Exposure

- In order for a chemical to produce a biological effect, it must first reach a target individual (**exposure pathway**).
- Then the chemical must reach a target site within the body **(toxicokinetics).**
- Toxicity is a function of the effective **dose (how much)** of a foreign chemical (xenobiotic) **at** its target site, integrated over **time (how long).**



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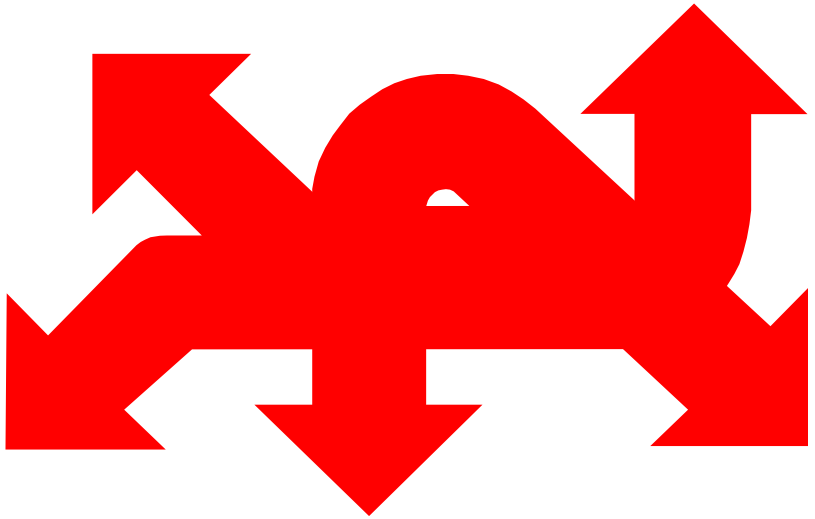
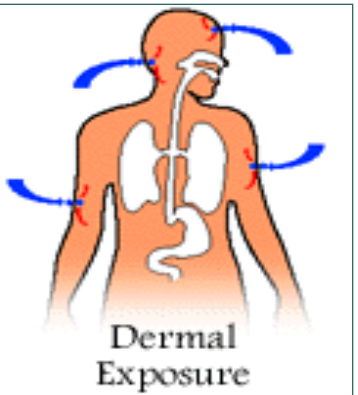
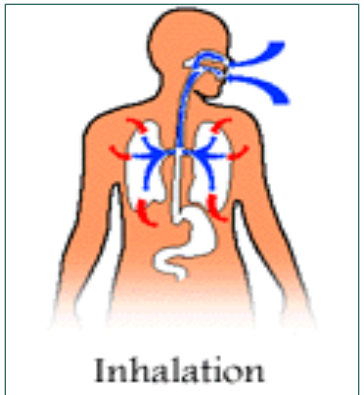
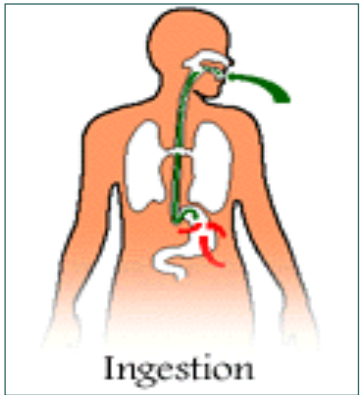
MAIN ROUTES OF EXPOSURE

- Inhalation
- Ingestion
- Skin contact
- Injection









•The route of exposure may be important if there are tissue-specific toxic responses.

•Toxic effects may be local or systemic

Exposure

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.

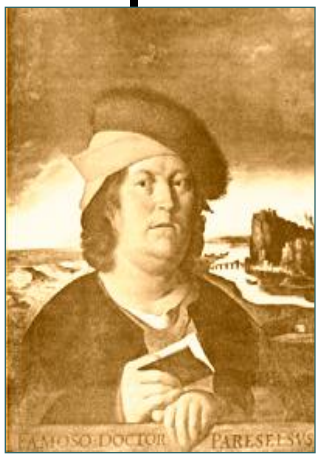
- **Acute** Exposure = usually entails a single exposure
- **Chronic** Exposures = multiple exposures over time (frequency)

EFFECTS OF EXPOSURE

- ACUTE - a “one-time” event
  - rapid absorption of material
  - exposure sudden & severe
  - critical period for death/survival
- CHRONIC - small doses over long time
  - rate of intake > rate of elimination
  - material remains in tissue; injures

Dose

THE KEY CONCEPT in Toxicology



Father of Modern Toxicology

Paracelsus—1564

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

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

Dose

Determines Whether a Chemical Will Be Beneficial or Poisonous

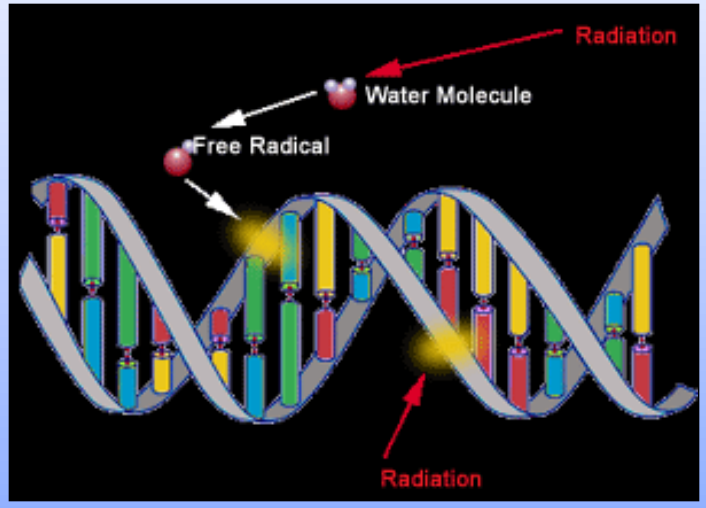
	Beneficial Dose	**Toxic Dose**
Aspirin	300 – 1,000 mg	1,000 – 30,000 mg
Vitamin A	5000 units/day	50,000 units/day
Oxygen	20% (Air)	50 – 80% (Air)

Dose

All Interactions between
chemicals and biological systems follow a
Dose-Response Relationship

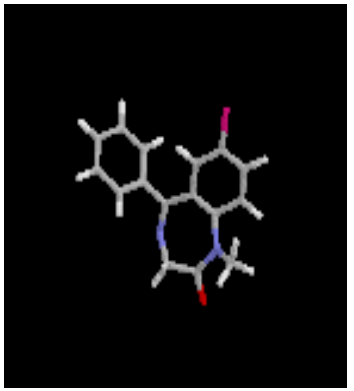
Dose-Response Relationship

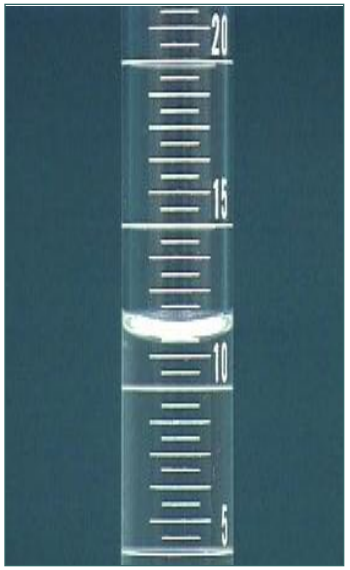
- A key concept in Toxicology is the **quantitative relationship** between the **concentration** of a xenobiotic in the body and the **magnitude** of the biological effect it produces.
- The magnitude of the effect of a xenobiotic is usually a function of the amount of xenobiotic to which a person is exposed (i.e., “The Dose Makes the Poison”).
- In any given population, there will be a **range of sensitivities** to a xenobiotic. It is 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.

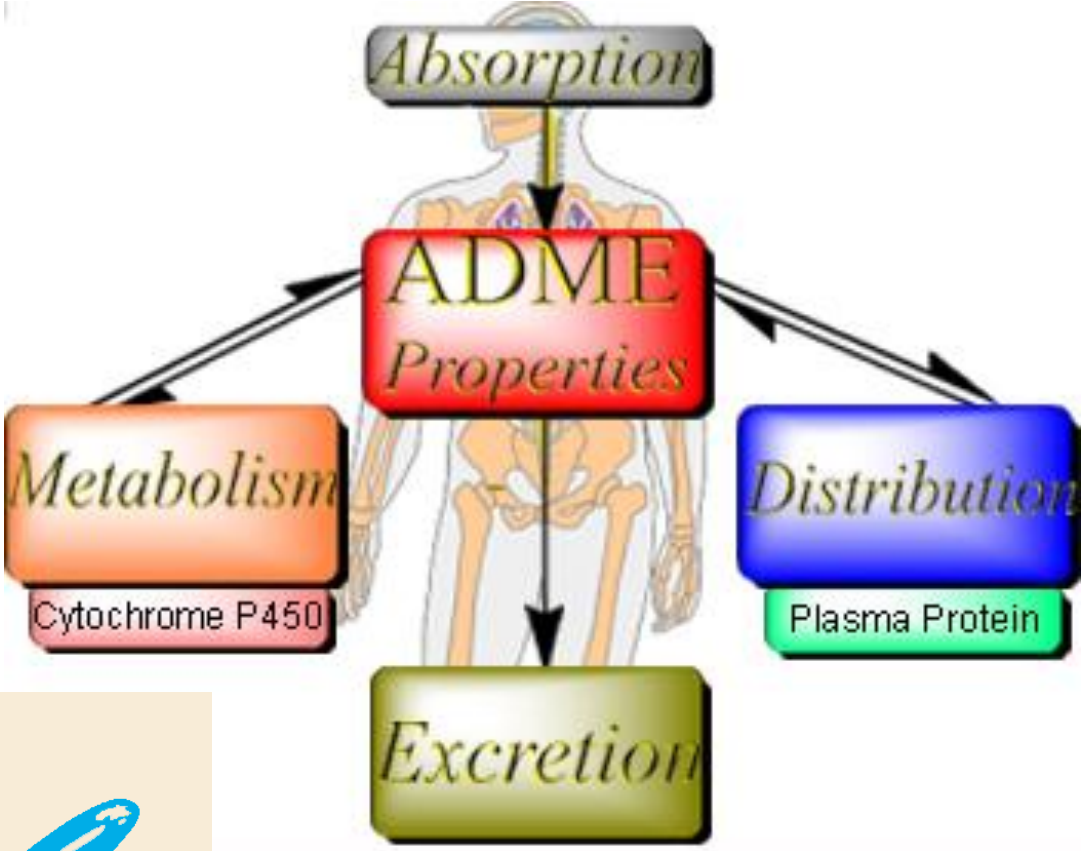


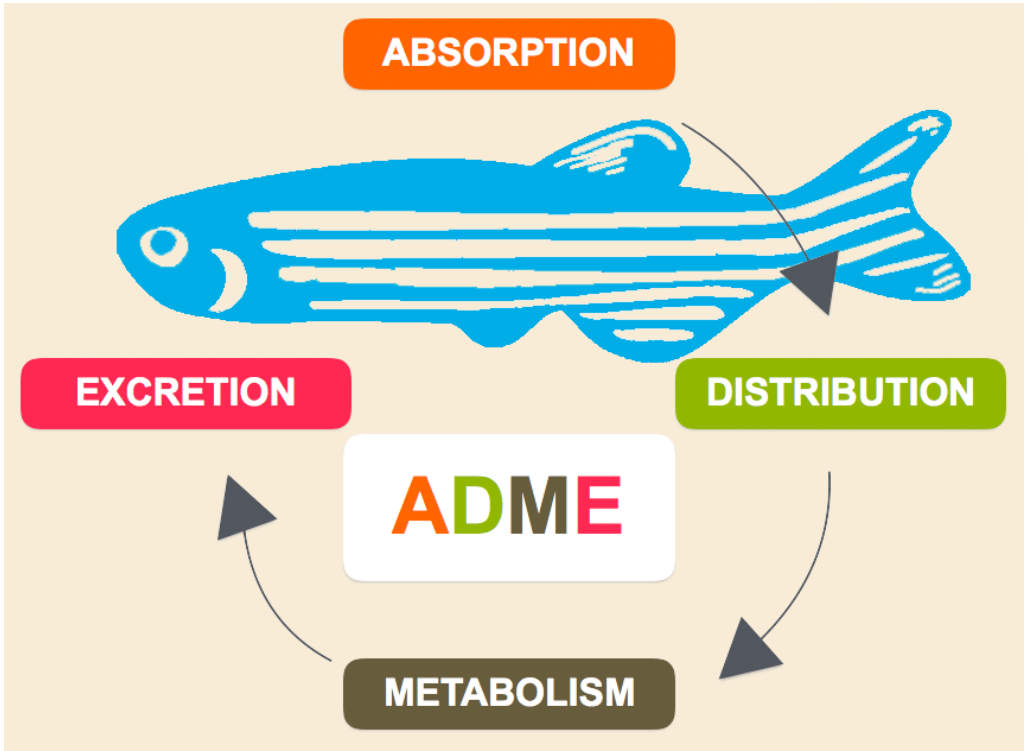
Dose

- 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**

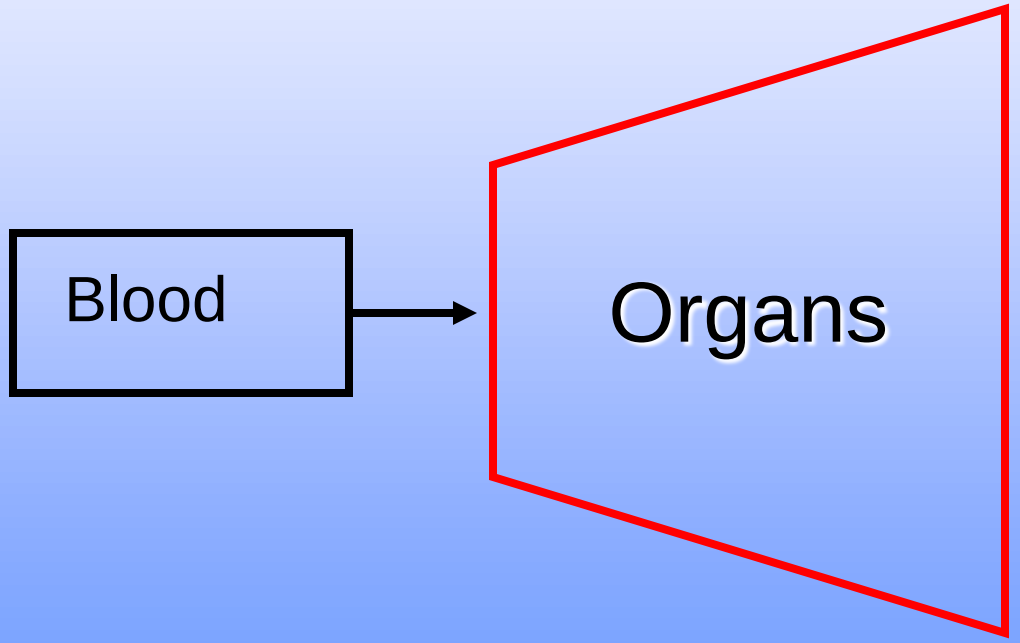





Absorption
ADME
Properties
Metabolism
Cytochrome P450
Distribution
Plasma Protein
Excretion


ABSORPTION
EXCRETION
DISTRIBUTION
ADME
METABOLISM

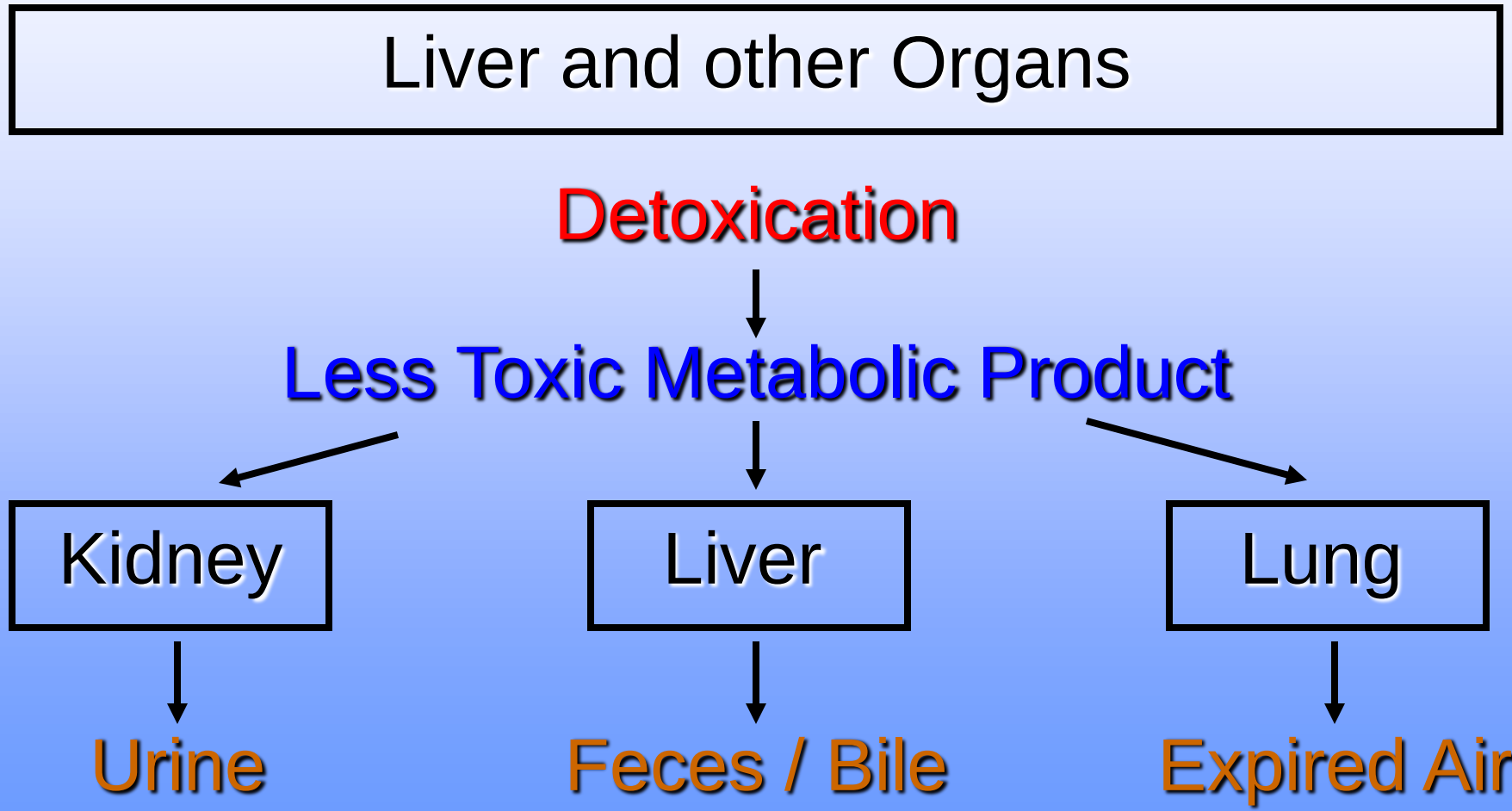
Distribution: organs Respond to Chemicals in Various Ways



Desired Effects
Nutritive
Therapeutic

Undesired Effects
Toxic

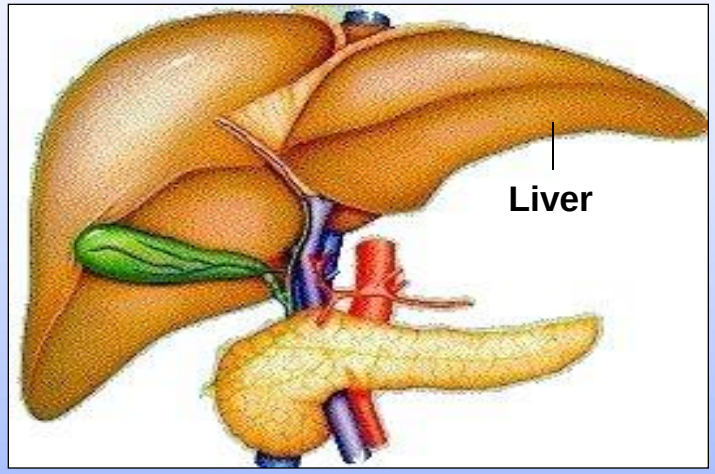
Some Chemicals Are Transformed by the Body (Metabolized) to Aid Excretion



Biotransformation

Metabolism

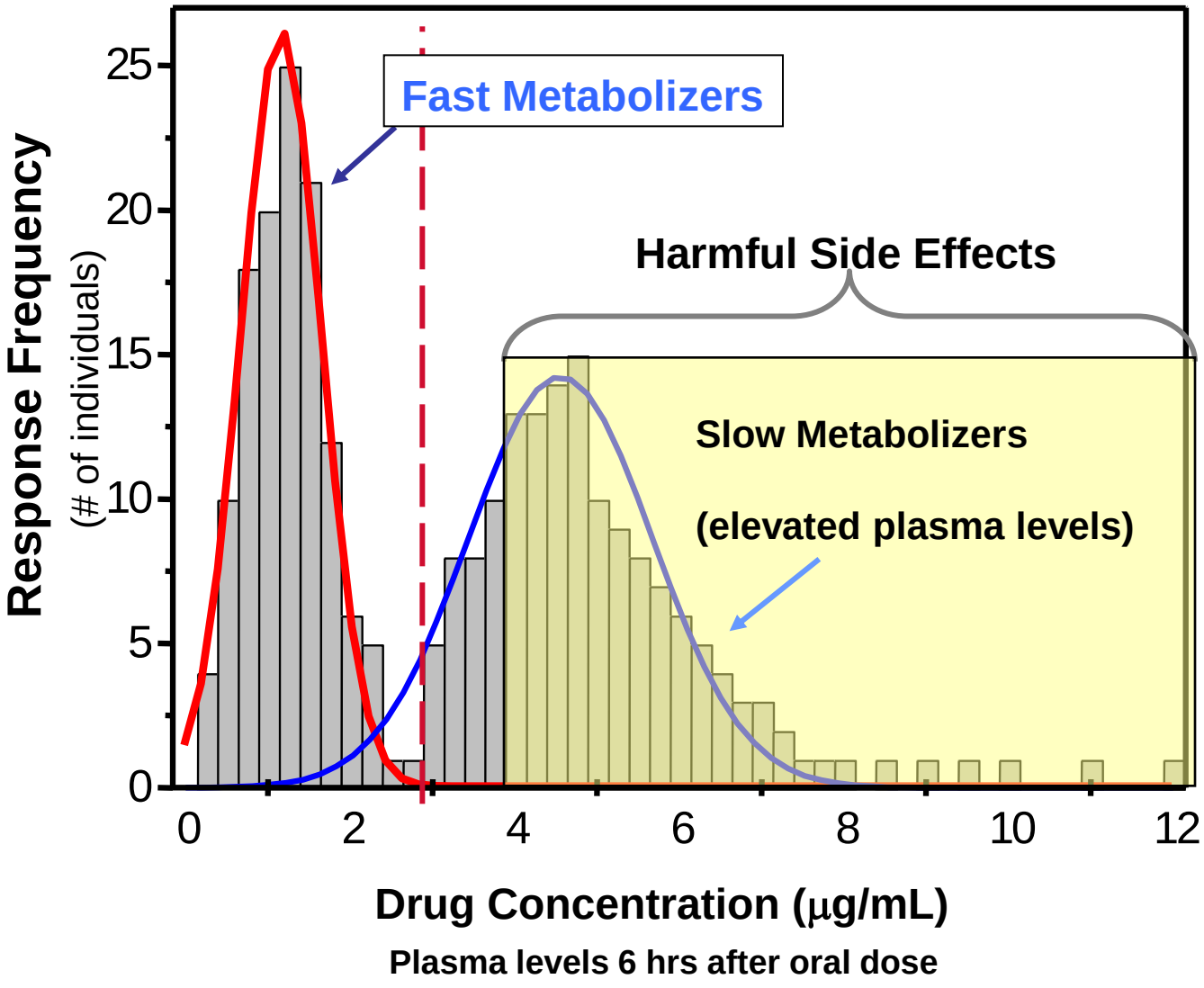
- major mechanism for terminating the biological activity of chemicals
- frequently the single most important determinant of the **duration and intensity** of the pharmacological response to a chemical



The LIVER is the primary site of metabolism

Biotransformation occurs in the Liver, kidney, lung, gastrointestinal track, and other organs

Pharmacogenetics of Metabolism



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

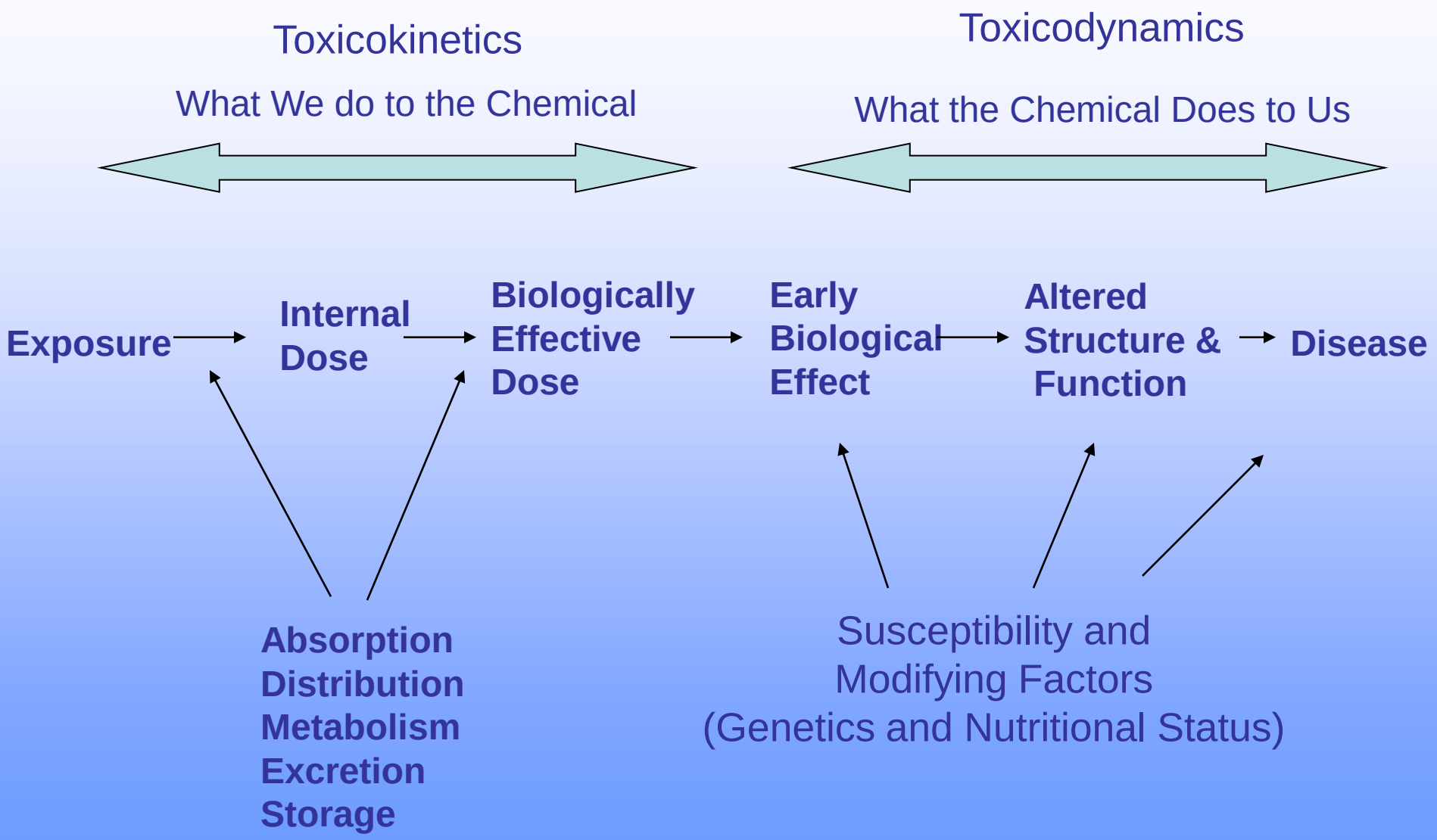
Liver and other Organs

Activation

More Toxic Metabolic Product

(Parathion to Paraoxon)

Toxicological Paradigm



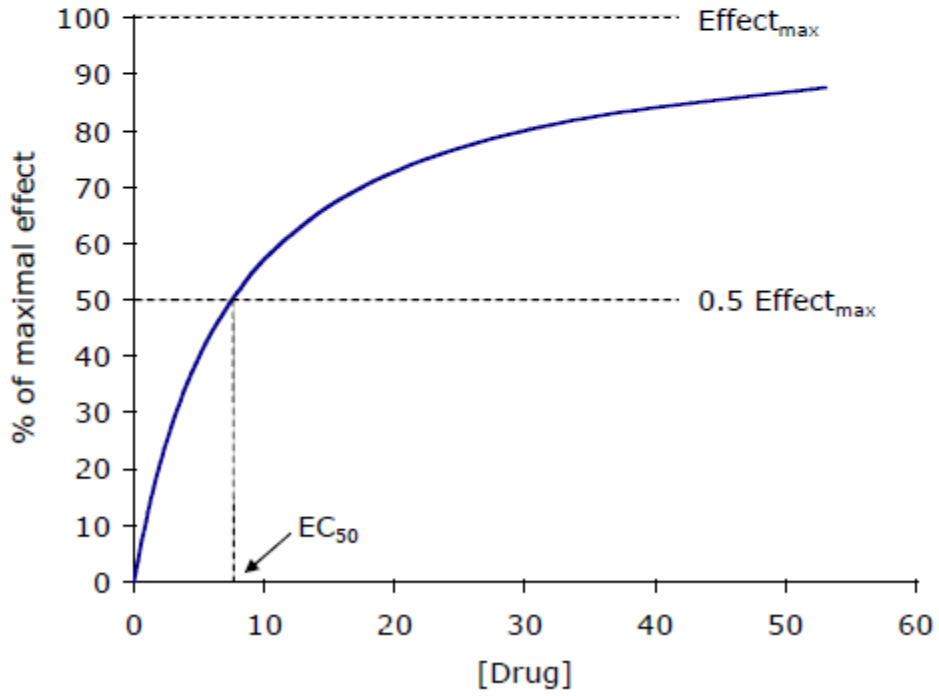
Dose-response analysis

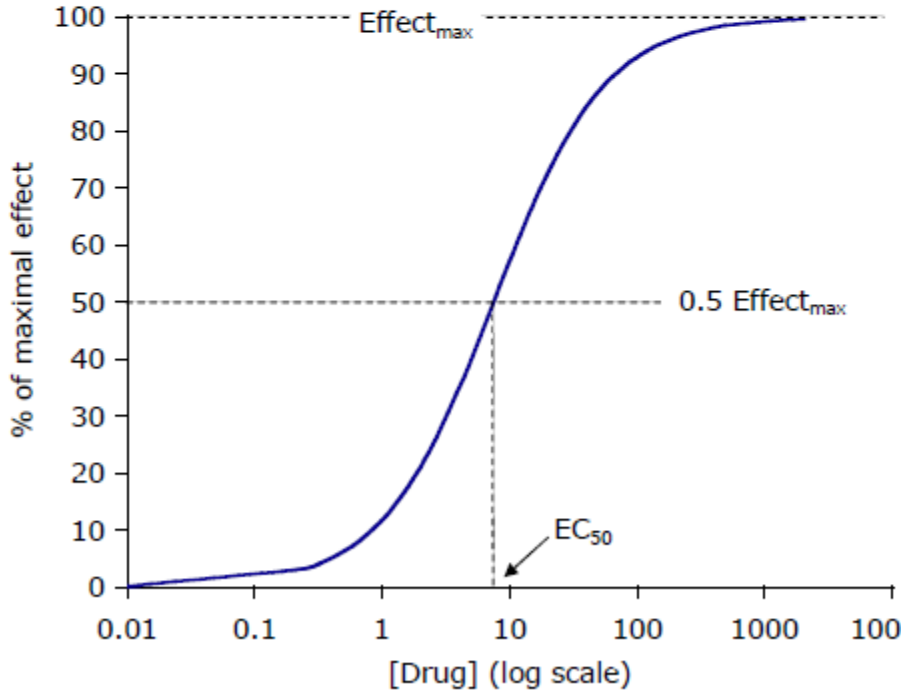
- Dose-response analysis is a method of determining the toxicity of a substance by measuring response to different doses.
- Lab animals are used.
- Responses to doses are plotted on a **dose-response curve.**

Relation between Drug concentration and response

The relation between drug dose and the clinically observed response may be quite complex.

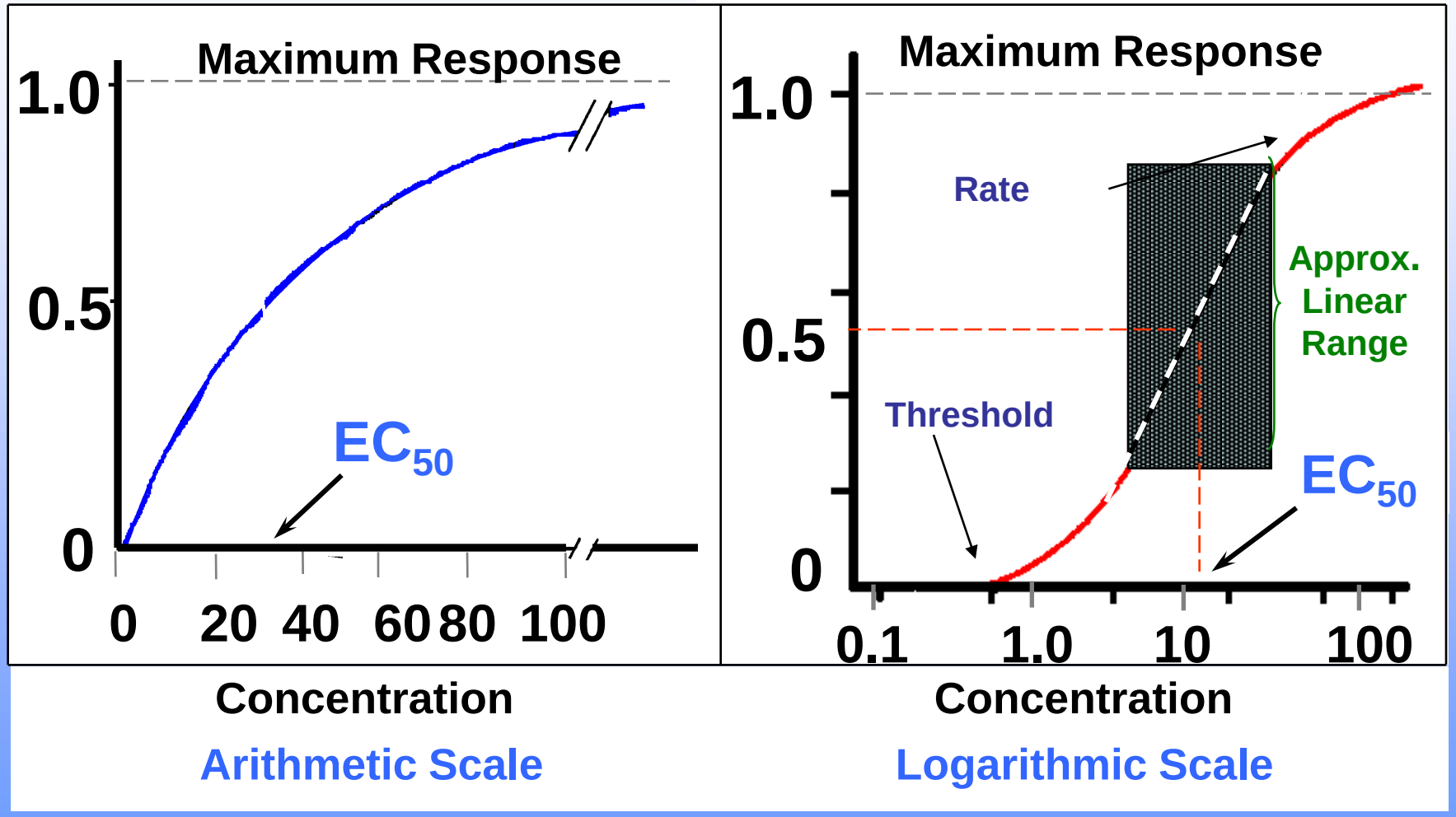
However, in carefully controlled *in vitro* systems, the relationship between drug concentration and its effect is often simple and may be described with mathematical precision.





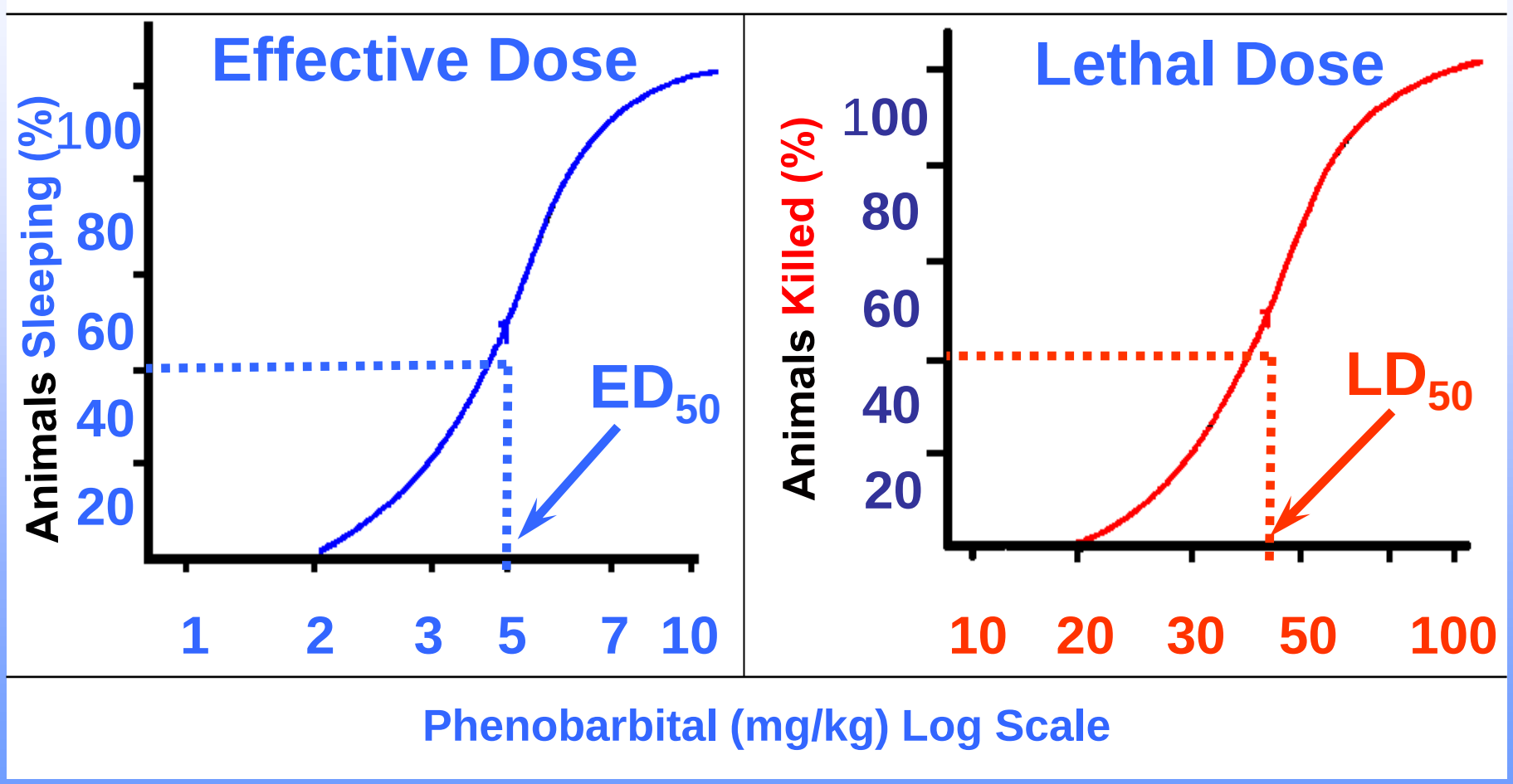
Dose-Response Curves

"The Dose Makes the Poison"



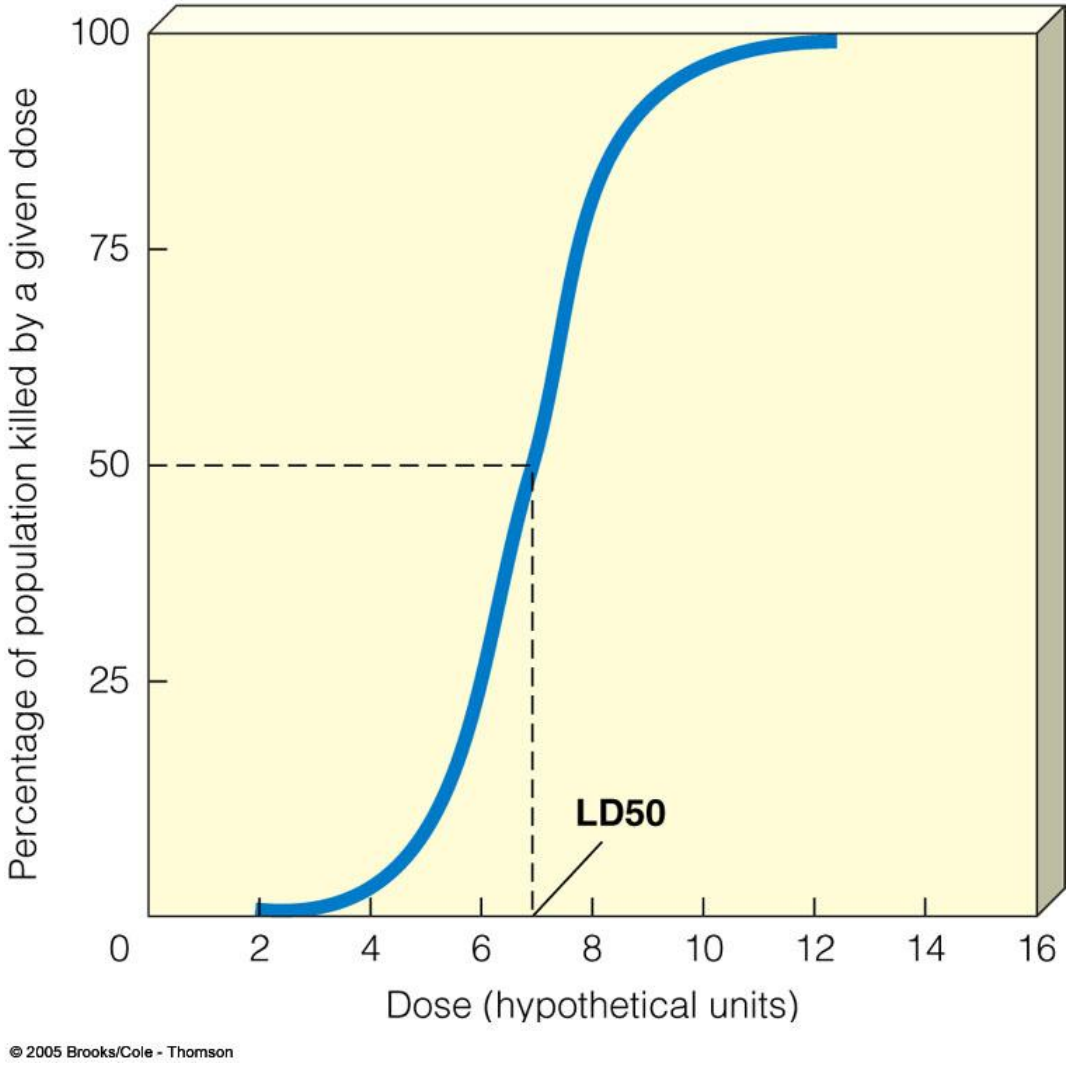
Dose-Response Relationship

"The Dose Makes the Poison"



Poisons

Median lethal dose (LD 50): at what dosage does the toxin kill 50% of animals



LD_{50} is also used to determine the level of toxicity

LD_{50}	Toxicity Level
≤ 1mg	Extremely Toxic
1-50mg	Highly toxic
50-500mg	Moderately toxic
>500mg	Non Toxic

LD_{50} (/Kg body weight	substance
200mg	Caffeine
100ng	Botulinum toxin
40g	Sodium chloride

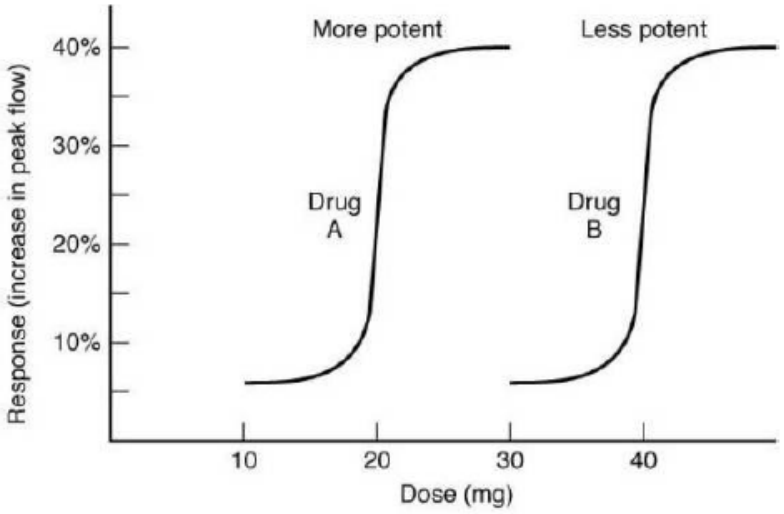
POTENCY and EFFICACY

POTENCY = ED_{50} (Effective Dose 50), EC_{50} (Effective Concentration 50)

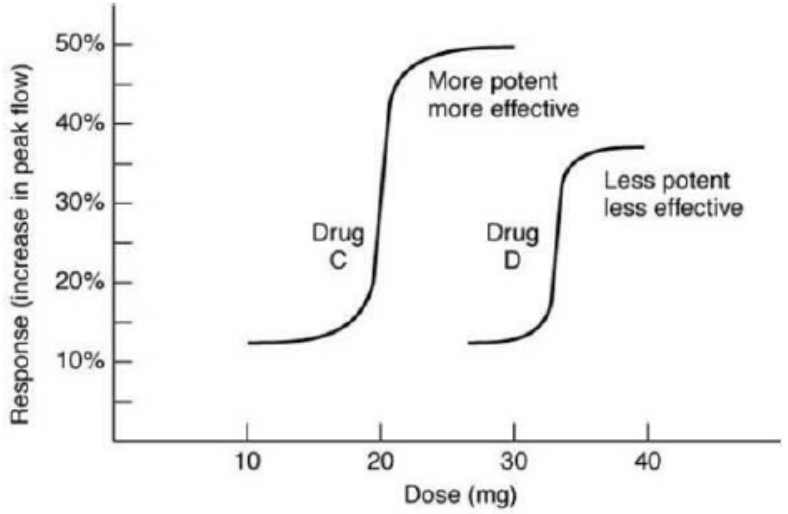
ED50: the drug ***dose*** producing 50% of a maximal effect; or alternatively the dose producing the desired effect in 50% of the population. Which definition is appropriate depends on the context in which the abbreviation is being applied; i.e., referring to the results of a population study, or drug effects on a single animal).

EFFICACY = E_{max} (maximal effect)

(E_{max}) is the maximum response achievable from a drug.



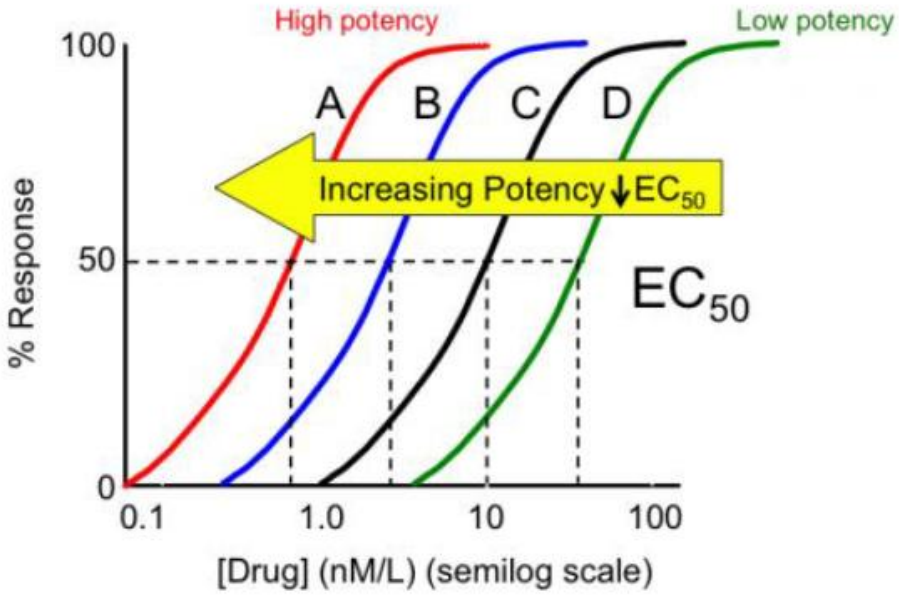
Drug A is more potent than drug B.
Drug A is equal to drug B's efficacy or response.

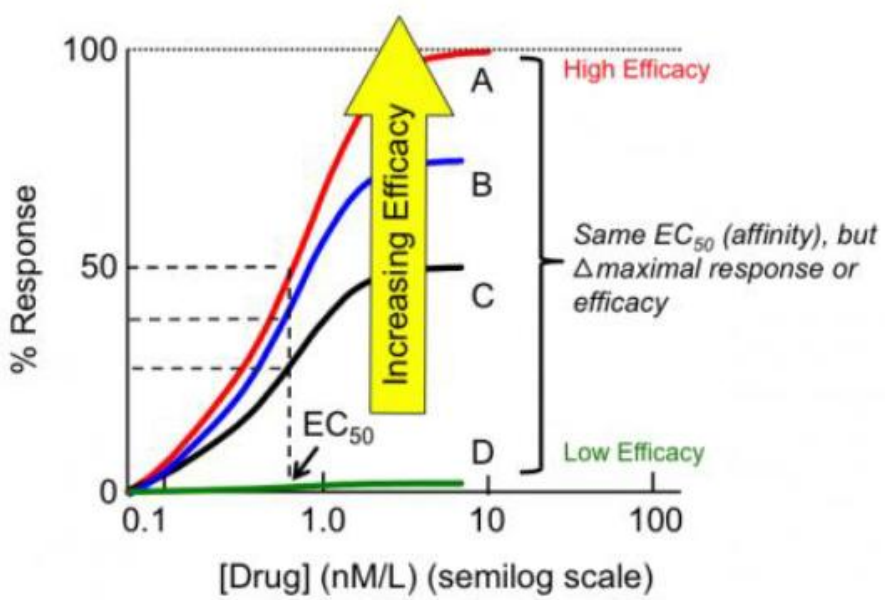


Drug C is more potent than drug D.
Drug C has greater efficacy than Drug D.

POTENCY and EFFICACY

HOW DO WE COMPARE DRUGS?

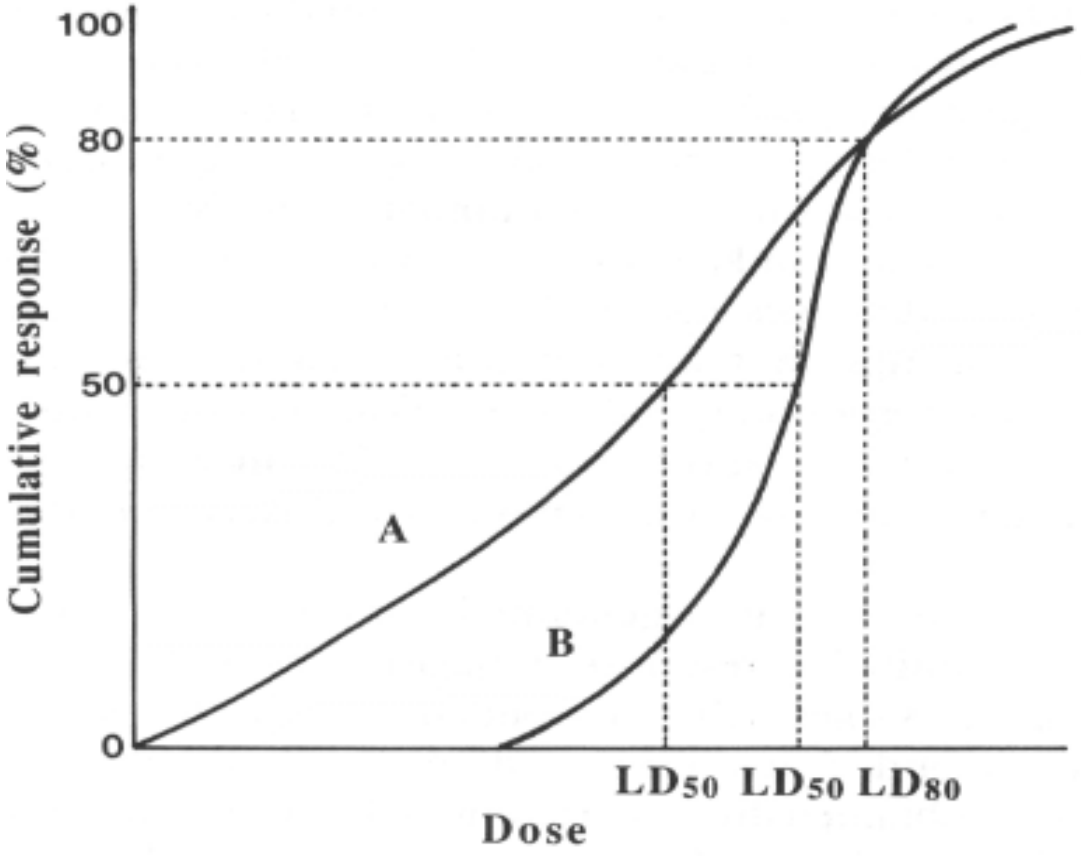




The lower the EC50, the higher the drug potency (less drug to obtain the expected effect).

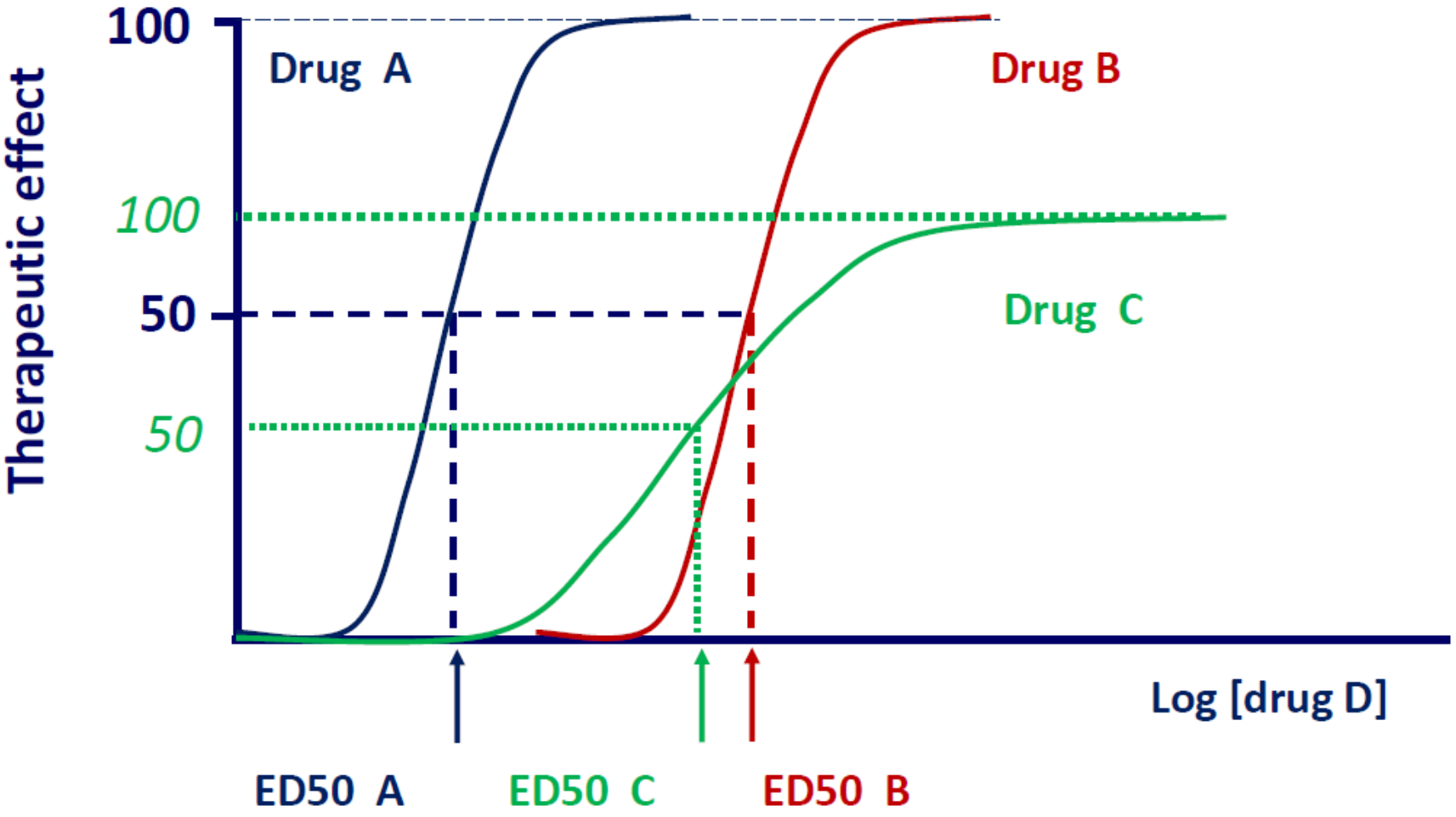
The higher the Emax, the higher the efficacy of the drug to modify the biological activity considered

Cumulative response-curve (compounds A and B)

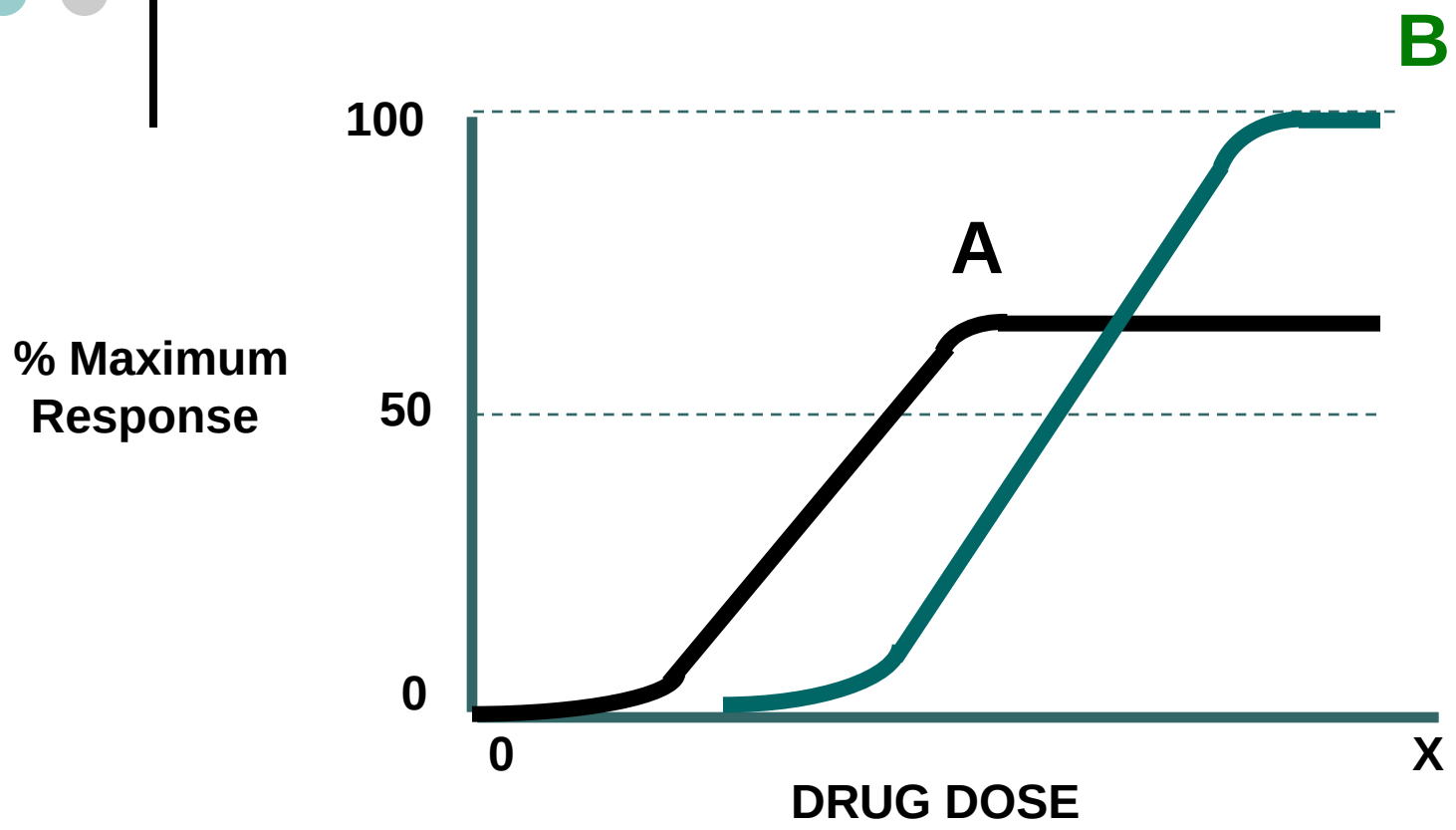


POTENCY and EFFICACY

WHICH DRUG HAS THE HIGHEST POTENCY?



Maximum Efficacy



- B has greater max efficacy than A ~

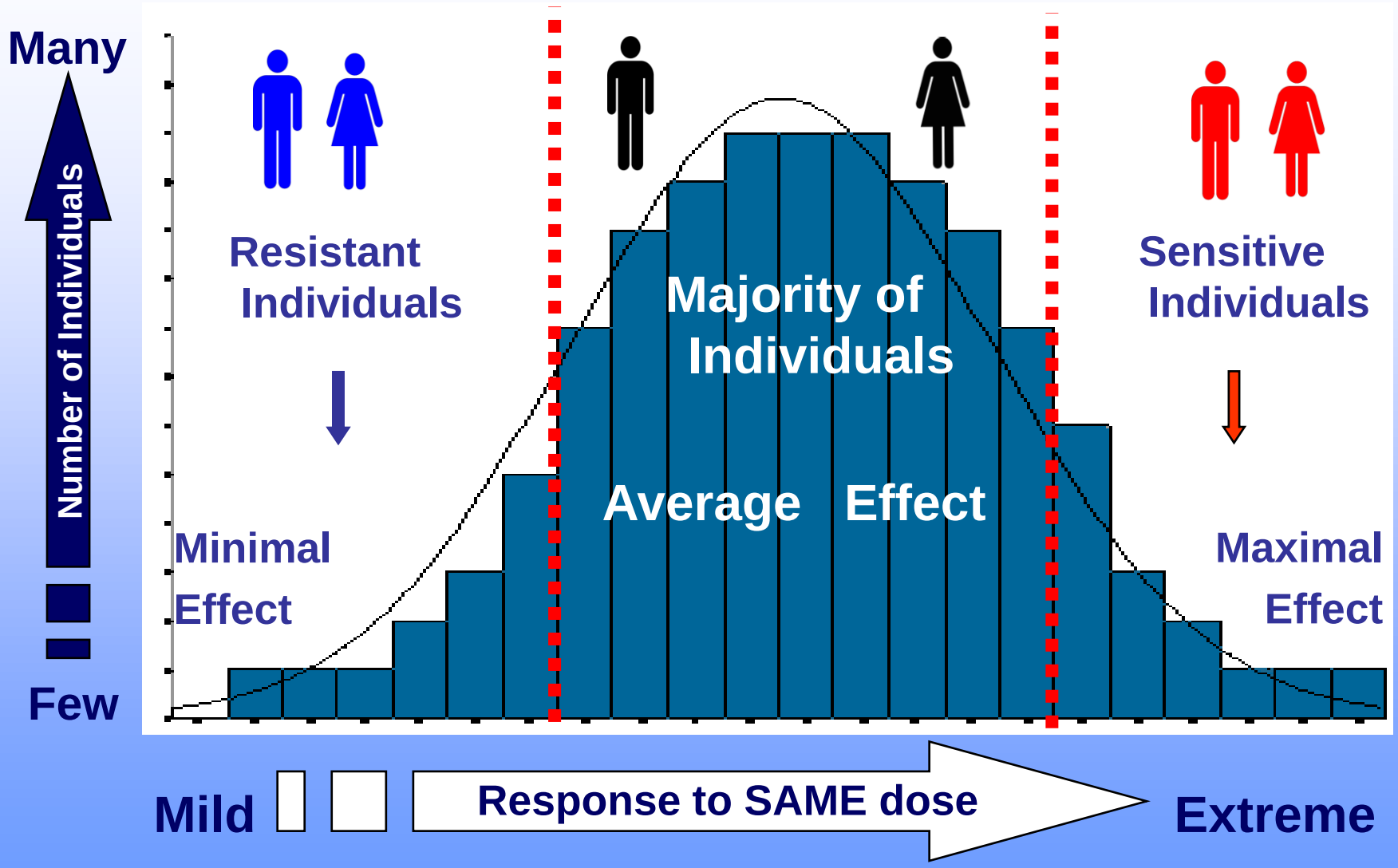
Dose-response curve

- Dose-response curves allow us to predict effects of higher doses.
- Dose levels are usually expressed in mg/kg body weight of the test animal for solids and mg/m^3 or parts per million for aerosols/vapours

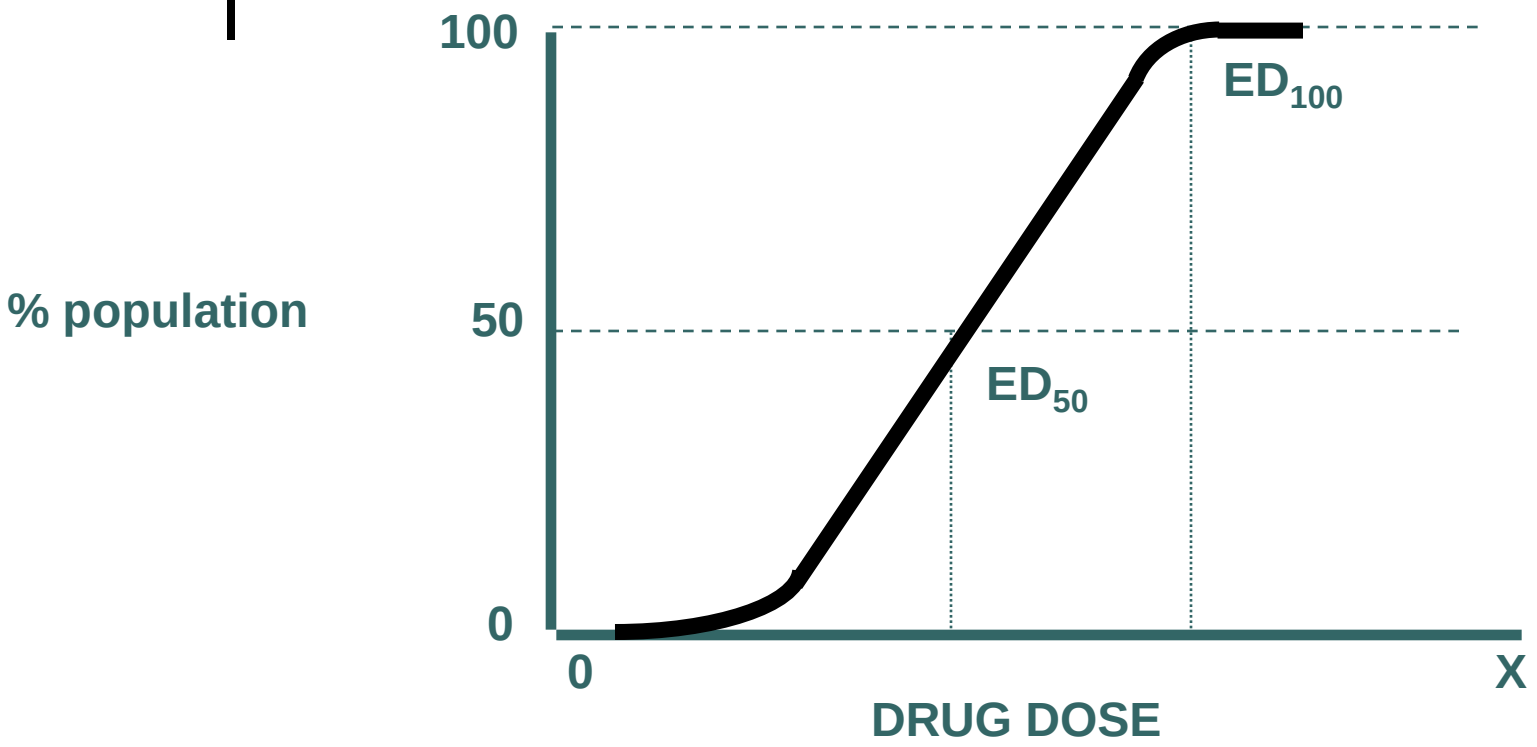
- By extrapolating the curve out to higher values, we can predict how toxic a substance may be to humans at various concentrations.

- In most curves, response increases with dose.
  But this is not always the case; the increase may not be linear. With endocrine disruption, it may *decrease*.

Population Dose-Response

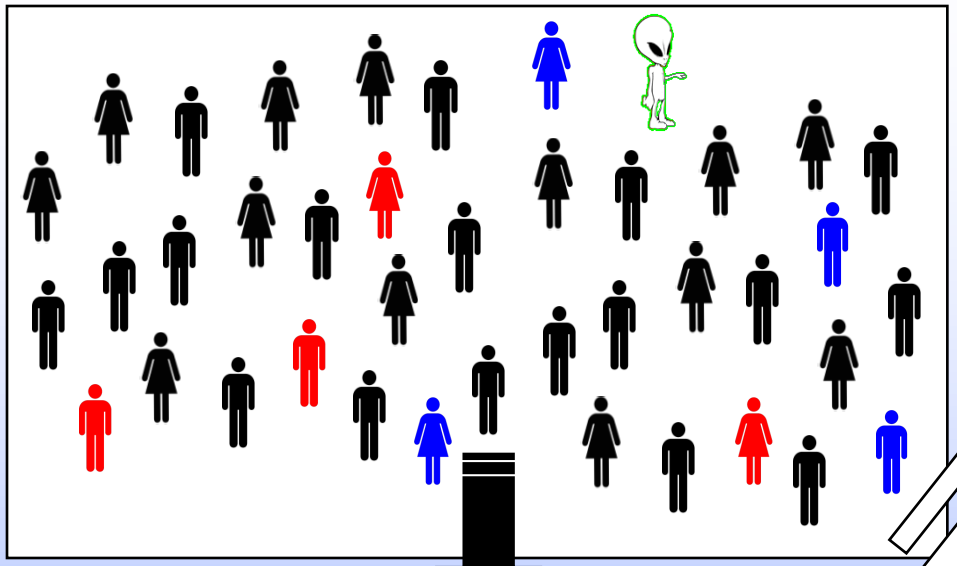


Dose-Response Curve: % Population



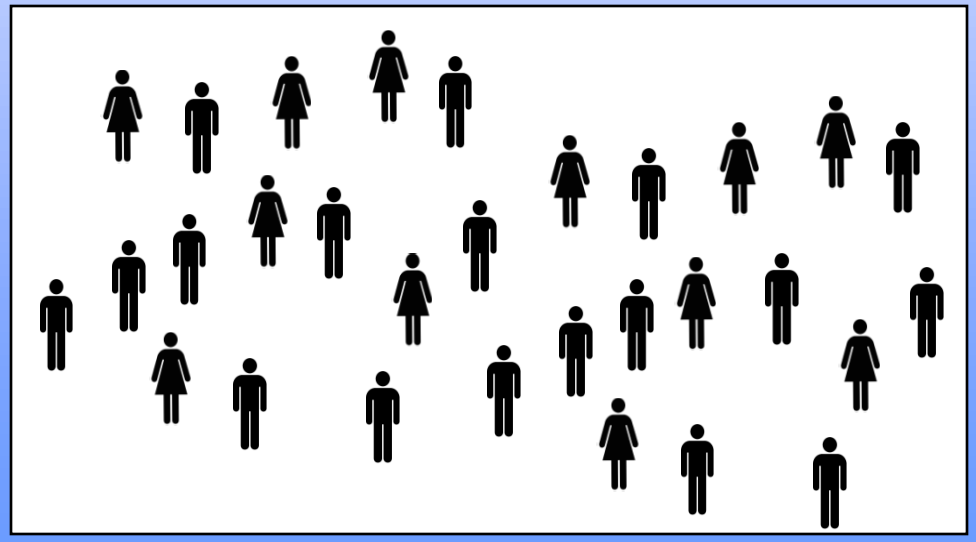
- ED_{50} = effective dose in 50% of population
- **LD_{50} = lethal dose in 50% of population ~**

Typical Population



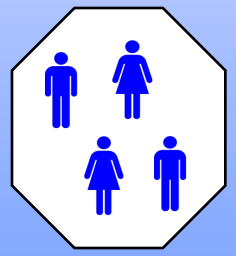
The emerging field of "Pharmacogenomics" or "Toxicogenomics" offers the potential to identify and protect subsets of people predisposed to toxicity from chemicals or drugs

Identify People with "normal" responses

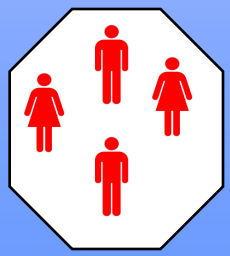


Identify people with different chemical/drug sensitivity

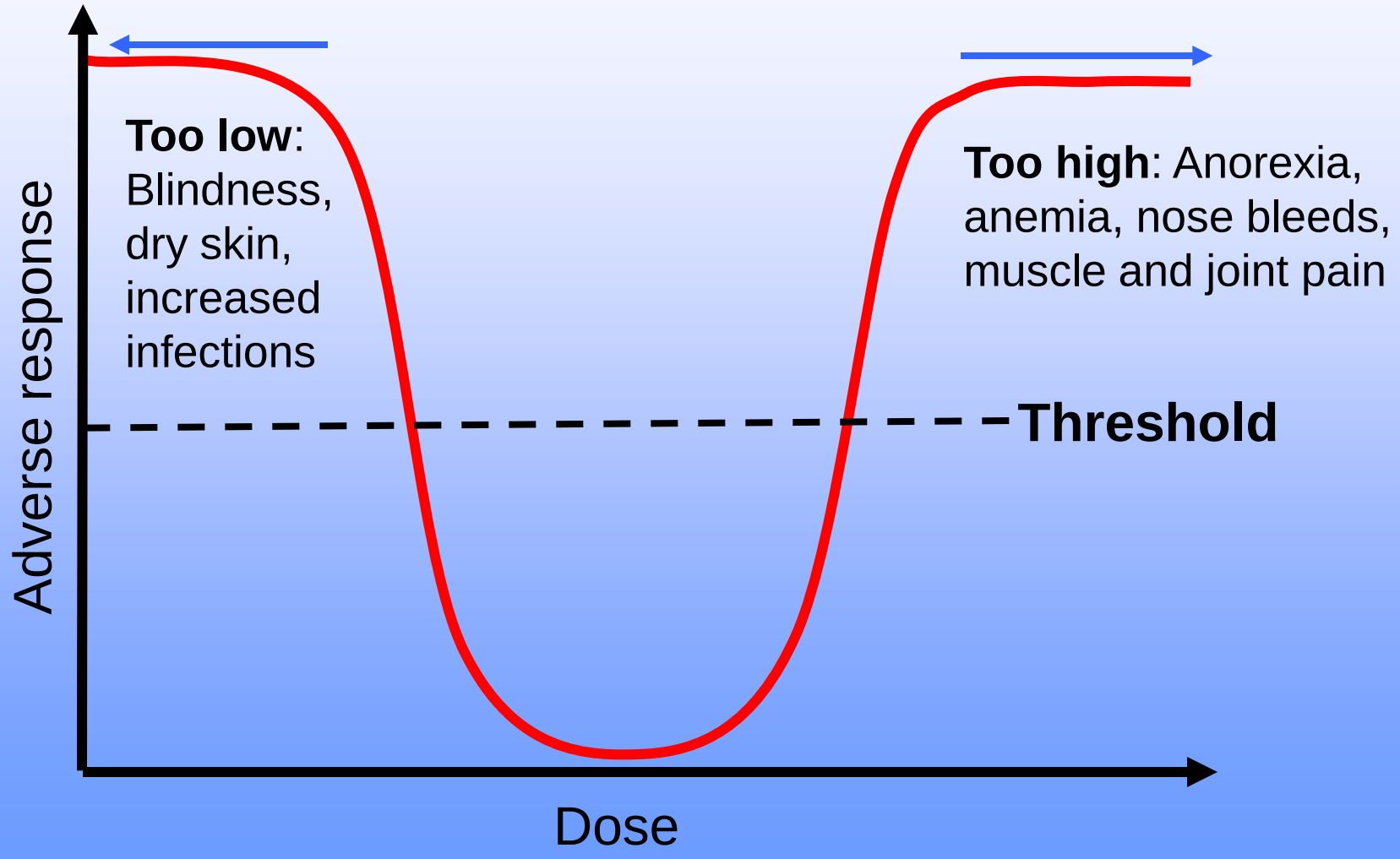
Less Sensitive



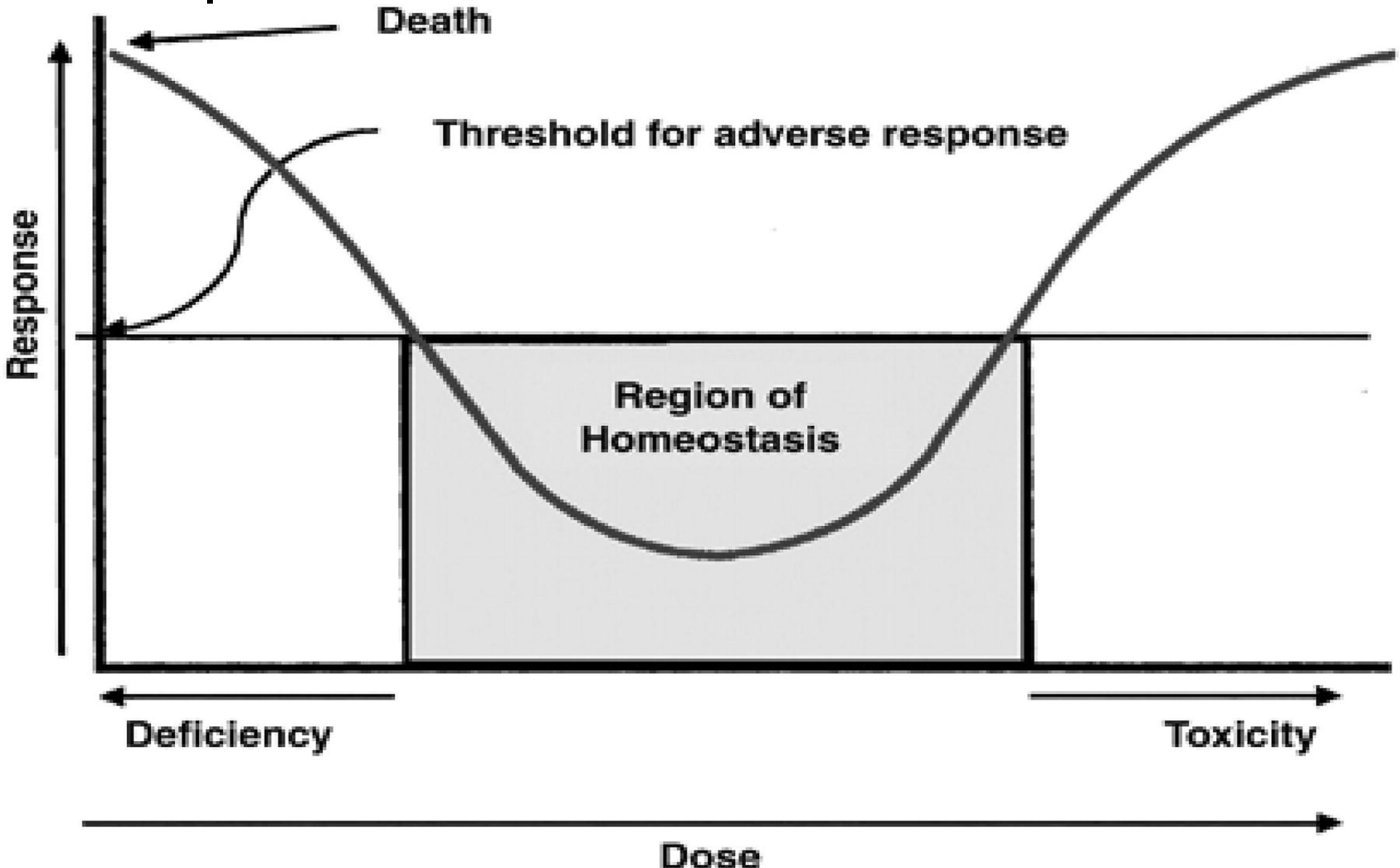
More Sensitive



Some chemicals have both therapeutic and toxic effects: Vitamin A

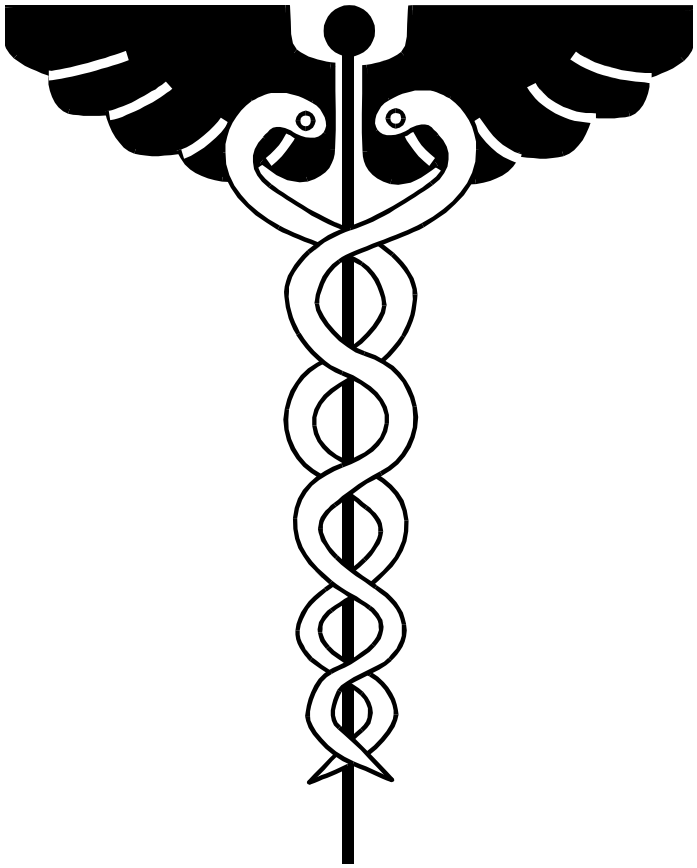


Dose – response curve for an essential nutrient



WHAT CAUSE THE TOXIC COMPOUNDS?

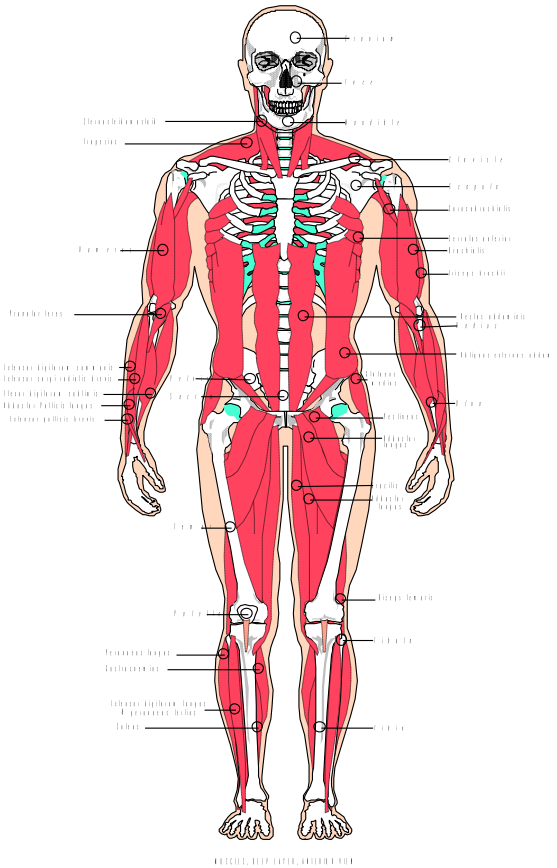
TYPES OF TOXIC EFFECT



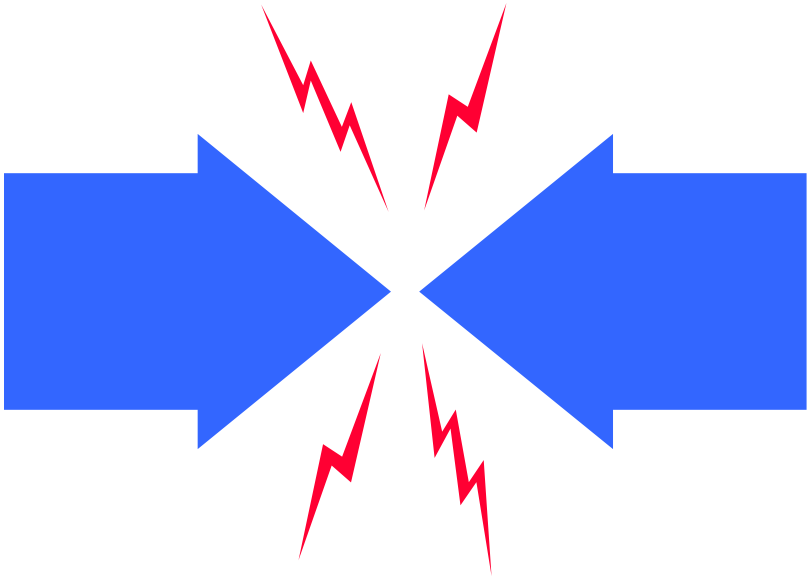
- mortality
- pathological change
- growth rate change
- physiological injury
- biochemical change
- behavioral effects
- reproductive system damage
- mutagenic, etc.

Toxic Effect by Target Organ

- irritant
- asphyxiant
- anesthetic
- hepatotoxic
- nephrotoxic
- neurotoxic
- pulmonary



Factors Influencing Intensity of Toxic Action



- route of entry
- rate of exposure
- age of host prior exposure
- environment
- host factors
  gender, genetics
- other factors

Factors Influencing Intensity of Toxic Action

- ROUTE OF EXPOSURE: route determines how much is absorbed and which organs are exposed to the highest concentrations.
- RATE OF EXPOSURE: **rate** of elimination or the **rate** of detoxification.
- AGE OF HOST: babies and older people most sensitives
- ENVIRONMENT: presence of mixture
- GENDER: some substances are more toxic to one gender than another

Mixtures of toxicants

- Substances may interact when combined together.
- Mixes of toxicants may cause effects greater than the sum of their individual effects.These are called **synergistic effects.**
  A challenging problem for toxicology:
  There is no way to test all possible combinations!
- **The environment contains complex mixtures of many toxicants.**