Toxicology

- Definitions
- Toxicological studies
- Dose-response correlations
- Threshold limit values
- Examples

Hazardous

- Denotes the probability of injury or illness from contact or use
- Industrial Hazards
  - Toxicityالسمية
  - Explosivityالتفجيرات
  - Ignitabilityالحرائق
  - Reactivityالتفاعل

Toxic Substance

- Capacity of a substance to produce injury or illness
- Acute Effects
  - Short term, appear shortly after exposure. Can be from single exposure
- Chronic Effects
  - There is a latency, long period of time before you see effect

Three Types of Toxic Hazardous Materials

- Chemical Agents (poisons)
- Physical Agents (dusts, fibers, heat, noise, corrosive)
- Biological Agents (pathogens)

Definitions

- Toxicology is the quantitative and qualitative study of the adverse effects of toxicants on biological organisms

- Toxicant is a chemical or physical agent that produces adverse effects on biological organisms.

So Toxicology is the study of:

- How toxicants enter the organism
- How toxicants effect the organism
- How toxicants are eliminated from (leave) the organism

All substances are toxic if taken in the wrong quantities

INTRODUCTION TO TOXICOLOGY

Definition of Toxicology

- the basic science of poisons (old)
- the study of the adverse effects of chemical agents on biological systems (new)

INTRODUCTION TO TOXICOLOGY

WHAT TOXICOLOGISTS DO

-involved in the recognition, identification, and quantitation of hazard

-develops standards and regulations to protect health and the environment

- involved in safety assessment and use of data as basis for regulatory control of hazards

- determines risk associated with use of chemicals

INTRODUCTION TO TOXICOLOGY

RISK ASSESSMENT

- Hazard identification
- Dose Response Assessment
- Exposure Assessment
- Risk Characterization

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INTERRELATED COMPONENTS OF THE RISK ASSESSMENT

- chemical or physical agent
- biological system
- effect or response
- exposure situation

How toxicants enter organism

- Inhalation (mouth or nose to lungs) then into blood(+*)
- Ingestion (mouth to stomach) then into blood(+)
- Injection (cuts, punctures in skin) into blood
- Dermal absorption (through skin) into blood(+*)

+ Involve membrane transport

* Greatest threats in industry

INTRODUCTION TO TOXICOLOGY

RISK AND SAFETY

-RISK; the probability that harm will occur under specified conditions

-SAFETY; the probability that harm will not occur under specified conditions

INTRODUCTION TO TOXICOLOGY

MAJOR FACTORS THAT INFLUENCE TOXICITY

-route of administration

-duration and frequency of exposure

-dose or concentration

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RAPIDITY OF RESPONSE WITH RESPECT TO ROUTE OF EXPOSURE

-intravenous
-inhalation
-intraperitoneally
-subcutaneous
-intramuscular
-intradermal
-topical

INTRODUCTION TO TOXICOLOGY

INTERACTION OF CHEMICALS

- Additive
- Synergistic
- Potentiation
- Antagonism (functional, chemical, dispositional, receptor)

INTRODUCTION TO TOXICOLOGY

DOSE RESPONSE

-ASSUMPTIONS

-response is due to chemical administered

-the response is related to the dose

-there is a receptor site with which the chemical interacts

Effects of Toxicants

Irreversible Effects

- Carcinogen - causes cancer
- Mutagen - causes chromosome damage
- Reproductive hazard - damage to reproductive system
- Teratogen - causes birth defects

Effects of Toxicants

May or may not be reversible

- Dermatotoxic – affects skin
- Hemotoxic – affects blood
- Hepatotoxic – affects liver
- Nephrotoxic – affects kidneys
- Neurotoxic – affects nervous system
- Pulmonotoxic – affects lungs

Definitions

- Pharmacokinetics – the absorption, distribution, metabolism and excretion of chemicals through the (human) system.

- Bioaccumulation – things such as lead, mercury,, carbon tetrachloride that build up in organs and have low excretion rate. Low exposure over a long time leads to response

Elimination of toxins

- Excretion through kidneys, liver and lungs
- Detoxification is the biotransformation of chemicals into something less harmful
- Storage in fatty tissue

Toxicological Studies

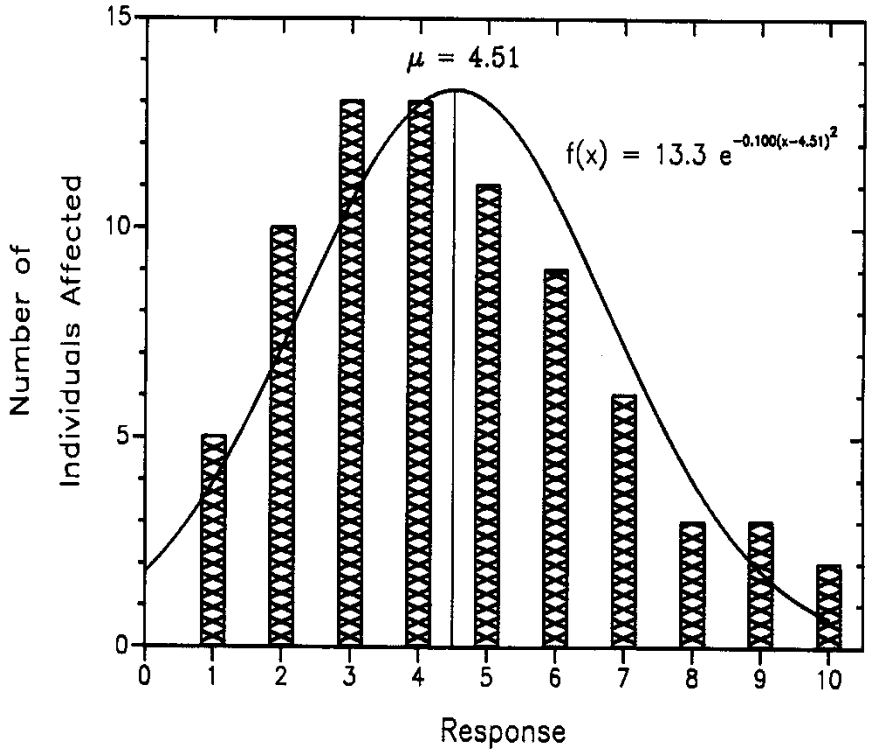
- Baseline study with no toxicant
- Toxicology study to quantify response to toxicants in specified physical state

Difficulties in Toxicological studies

- Baseline study required (control group)
- Response not necessarily numerical
- Specificity of individual response
  - Allergy or immunity
  - Statistical study required
  - Organism specific response, not applicable to humans
  - Dosage response
  - Response time, latency, acute versus chronic
  - Difficulty in measuring intended variable (lead in liver measured by lead in blood)

Dose versus Response

- Run test on “large” population
- Given same dose (usually in dose/body mass)
- Determine the number or fraction of individuals that have a response



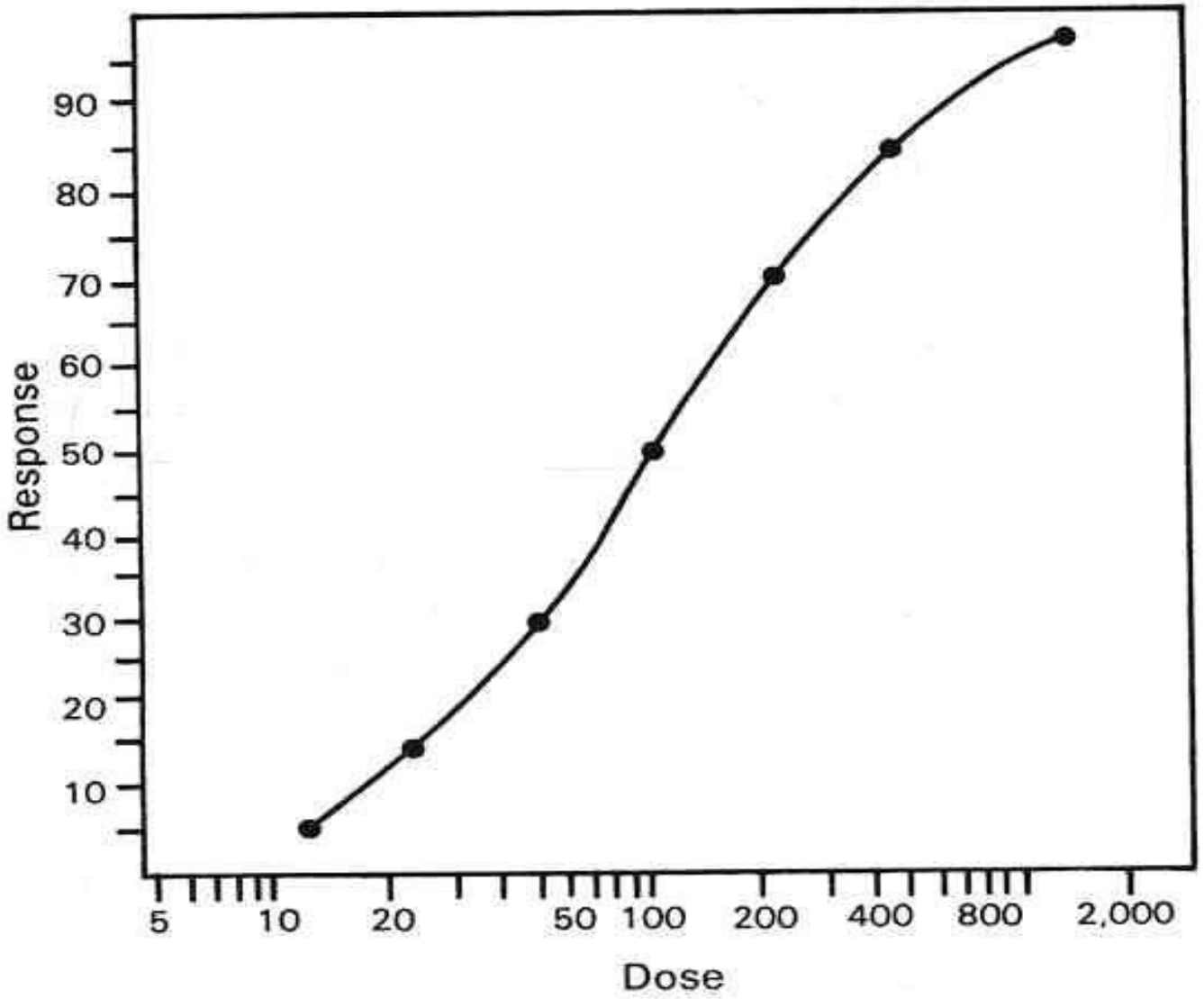


Figure 2–2. Diagram of dose-response relationship. Dosage is most often expressed as mg/kg and plotted on a log scale.

From Casarett & Doull's, Toxicology
3rd Edition, 1986

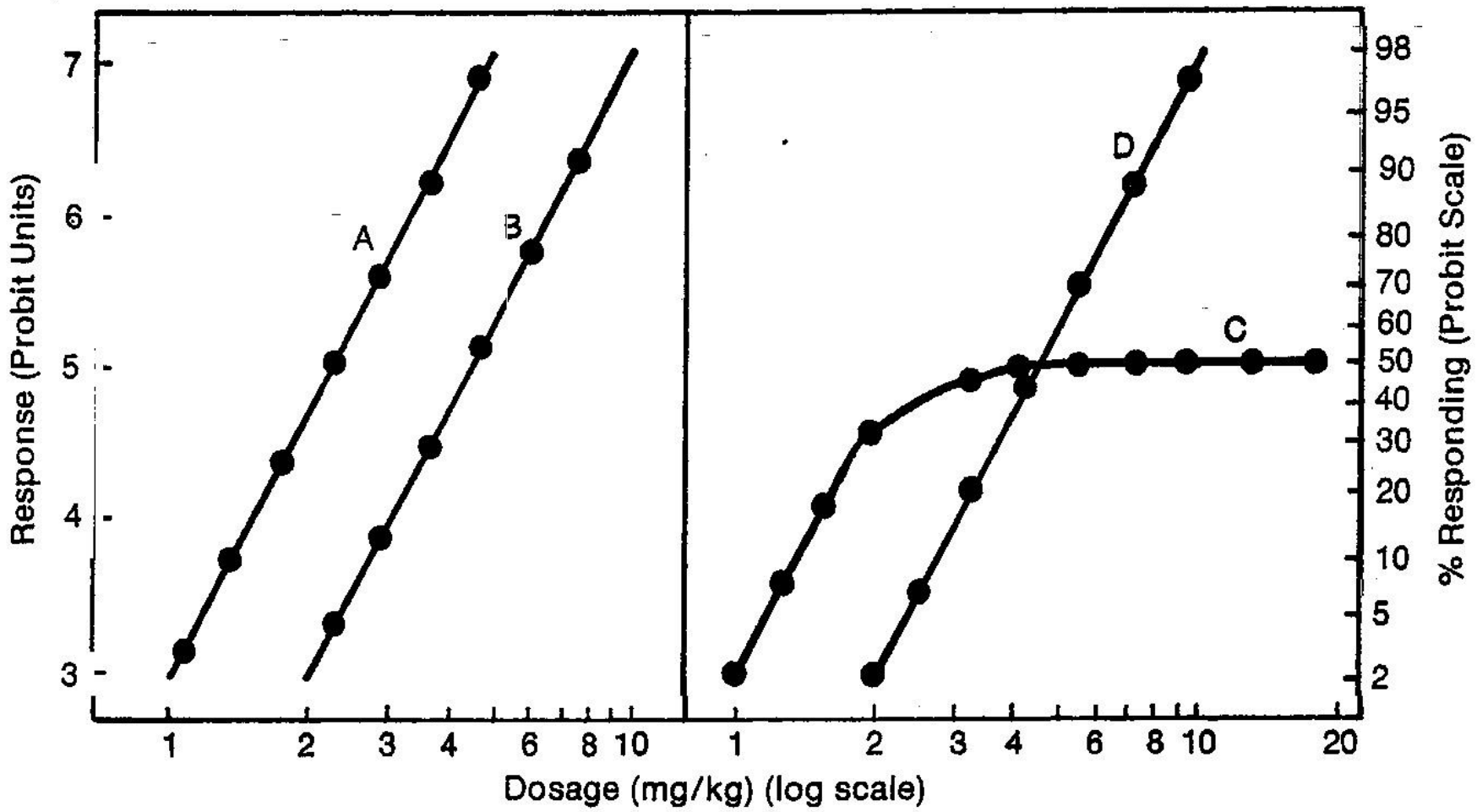


Figure 2–7. Schematic representation of the difference in the dose-response curves for four chemicals (*A–D*), to illustrate the difference between potency and efficacy (see text).

Table 2–1. APPROXIMATE ACUTE LD50'S OF SOME REPRESENTATIVE CHEMICAL AGENTS

AGENT	LD50 (mg/kg)*
Ethyl alcohol	10,000
Sodium chloride	4,000
Ferrous sulfate	1,500
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

* LD50 is the dosage (mg/kg body weight) causing death in 50 percent of the exposed animals.

From Casarett & Doull's, Toxicology
3rd Edition, 1986

You Know ?

92% of all poisonings happen at home.

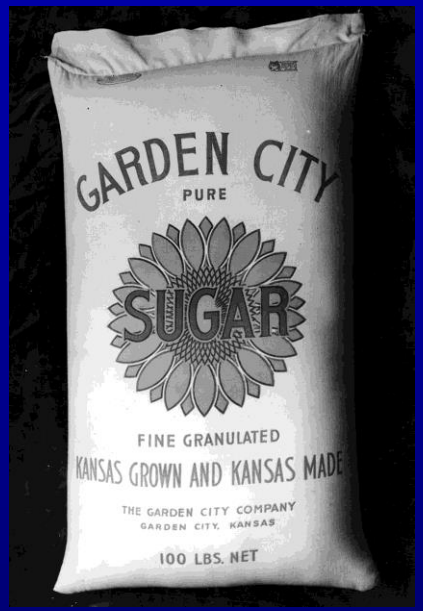
The household products implicated in most poisonings are: cleaning solutions, fuels, medicines, and other materials such as glue and cosmetics.

Certain animals secrete a xenobiotic poison called venom, usually injected with a bite or a sting, and others animals harbor infectious bacteria.

Some household plants are poisonous to humans and animals.

The Dose Makes the Poison

An apparently nontoxic chemical can be toxic at high doses. (Too much of a good thing can be bad).



Highly toxic chemicals can be life saving when given in appropriate doses. (Poisons are not harmful at a sufficiently low dose).

The study of the adverse effects of a toxicant on living organisms

- Adverse effects
  - any change from an organism's normal state
  - dependent upon the concentration of active compound at the target site for a sufficient time.
- Toxicant (Poison)
  - any agent capable of producing a deleterious response in a biological system

What is a Poison?

All substances are poisons;
there is none that is not a poison.
The right dose
differentiates a poison and a remedy.

INTERACTION OF CHEMICALS

- Additive
- Synergistic –**physicians treat bacterial infection with ampicillin and gentamicin**
- Potentiation drugs can interact to alter the absorption ,distribution,metabolism or excretion of drug or interact in a syn.or antag. Fashion altering their pharmacodynamics
- Antagonism (functional, chemical, dispositional, receptor) substance **that stops**

- The effect of another substance ex. Drug that blocks the stimulating effect of estrogen on tumor cell is called (**estrogen receptor antagonist)**

Dose

The amount of chemical entering the body

This is usually given as

mg of chemical/kg of body weight = mg/kg

The dose is dependent upon

* The environmental concentration
* The properties of the toxicant
* The frequency of exposure
* The length of exposure
* The exposure pathway

What is a Response?

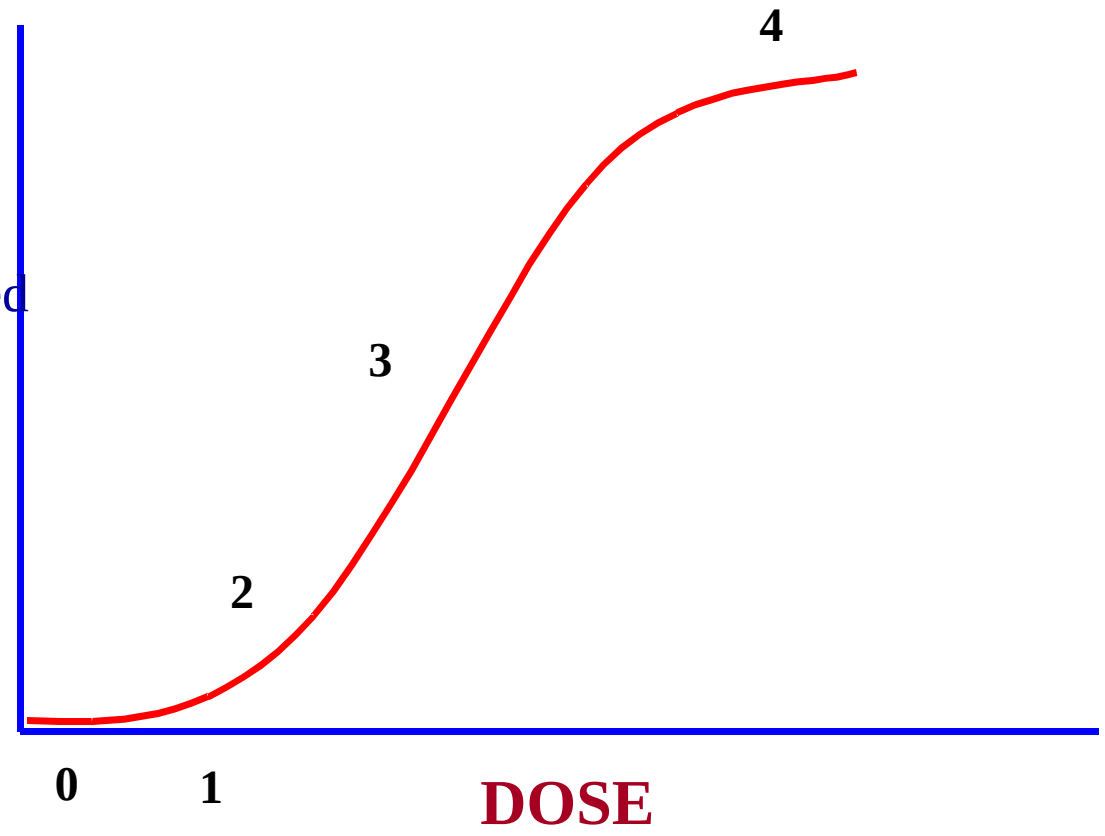
The degree and spectra of responses depend upon the dose and the organism--describe exposure conditions with description of dose

- Change from normal state
  - could be on the molecular, cellular, organ, or organism level--the symptoms
- Local vs. Systemic
- Reversible vs. Irreversible
- Immediate vs. Delayed
- Graded vs. Quantal
  - degrees of the same damage vs. all or none

Dose-Response Relationship:

As the dose of a toxicant increases, so does the response.

0-1 NOAELNo observed Adverse effect level
2-3 Linear Range
4 Maximum Response



DOSE DETERMINES THE BIOLOGICAL RESPONSE

LD_{50}

- Quantal responses can be treated as gradient when data from a population is used.
- The cumulative proportion of the population responding to a certain dose is plotted per dose--10-30 fold variation w/in a population
- If Mortality is the response, the dose that is lethal to 50% of the population LD_{50} can be generated from the curve
- Different toxicants can be compared--lowest dose is most potent

LD_{50} Comparison

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

Exposure: Pathways

- Routes and Sites of Exposure
  - Ingestion (Gastrointestinal Tract)
  - Inhalation (Lungs)
  - Dermal/Topical (Skin)
  - Injection
    - intravenous, intramuscular, intraperitoneal

- Typical Effectiveness of Route of Exposure

  iv > inhale > ip > im > ingest > topical

Exposure: Duration

Acute	< 24hr	usually 1 exposure
Subacute	1 month	repeated doses
Subchronic	1-3mo	repeated doses
Chronic	> 3mo	repeated doses

Over time, the amount of chemical in the body can build up, it can redistribute, or it can overwhelm repair and removal mechanisms

ADME: Absorption, Distribution, Metabolism, and Excretion

- Once a living organism has been exposed to a toxicant, the compound must get into the body and to its target site in an active form in order to cause an adverse effect.
- The body has defenses:
  - Membrane barriers
    - passive and facilitated diffusion, active transport
  - Biotransformation enzymes, antioxidants
  - Elimination mechanisms

Absorption:

ability of a chemical to enter the blood (blood is in equilibrium with tissues)

- Inhalation--readily absorb gases into the blood stream via the alveoli. (Large alveolar surface, high blood flow, and proximityقرب of blood to alveolar air)
- Ingestion--absorption through GI tract stomach (acids), small intestine (long contact time, large surface area--villi; bases and transporters for others)
  - 1st Pass Effect (liver can modify)
- Dermal--absorption through epidermis (stratum corneum), then dermis; site and condition of skin

Distribution:

the process in which a chemical agent translocates throughout the body

- Blood carries the agent to and from its site of action, storage depots, organs of transformation, and organs of elimination
- Rate of distribution (rapid) dependent upon
  - blood flow
  - characteristics of toxicant (affinity for the tissue, and the partition coefficient)
- Distribution may change over time

Distribution: Storage and Binding

- Storage in Adipose tissue--Very lipophylic compounds (DDT) will store in fat. Rapid mobilization of the fat (starvation) can rapidly increase blood concentration
- Storage in Bone--Chemicals analogous to Calcium--Fluoride, Lead, Strontium
- Binding to Plasma proteins--can displace endogenous compounds. Only free is available for adverse effects or excretion

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
- Kidney--high blood flow, concentrates chemicals
- Lung--high blood flow, site of exposure
- Neurons--oxygen dependent, irreversible damage
- Myocardium--oxygen dependent

Target Sites: Mechanisms of Action

- Adverse effects can occur at the level of the molecule, cell, organ, or organism
- Molecularly, chemical can interact with

  Proteins Lipids DNA
- Cellularly, chemical can
  - interfere with receptor-ligand binding
  - interfere with membrane function
  - interfere with cellular energy production
  - bind to biomolecules

Excretion:

Toxicants are eliminated from the body by several routes

- Urinary excretion
  - water soluble products are filtered out of the blood by the kidney and excreted into the urine
- Exhalation
  - Volatile compounds are exhaled by breathing
- Biliary Excretion via Fecal Excretion
  - Compounds can be extracted by the liver and excreted into the bile. The bile drains into the small intestine and is eliminated in the feces.
- Milk Sweat Saliva

Metabolism:

adverse effect depends on the concentration of active compound at the target site over time

- The process by which the administered chemical (parent compounds) are modified by the organism by enzymatic reactions.
  - decrease lipid solubility
    --> decrease amount at target
  - increase ionization
    --> increase excretion rate --> decrease toxicity
- Bioactivation--Biotransformation can result in the formation of reactive metabolites

Individual Susceptibility

--there can be 10-30 fold difference in response to a toxicant in a population

- Genetics-species, strain variation, interindividual variations (yet still can extrapolate between mammals--similar biological mechanisms)
- Gender)
- Age--young (old too)
  - underdeveloped excretory mechanisms
  - underdeveloped biotransformation enzymes
  - underdeveloped blood-brain barrier

Individual Susceptibility

- Age--old
  - changes in excretion and metabolism rates, body fat
- Nutritional status
- Health conditions
- Previous or Concurrent Exposures
  - additive --antagonistic
  - synergistic

Toxicology

- Exposure + Hazard = Risk
- All substances can be a poison
- Dose determines the response
- Pathway, Duration of Frequency of Exposure and Chemical determine Dose
- Absorption, Distribution, Metabolism & Excretion
- The extent of the effect is dependent upon the concentration of the active compound at its site of action over time
- Bioactivation: compounds to reactive metabolites
- Individual variation of the organism will affect ADME