# Routes of Exposure

# Toxicants take many routes through the environment

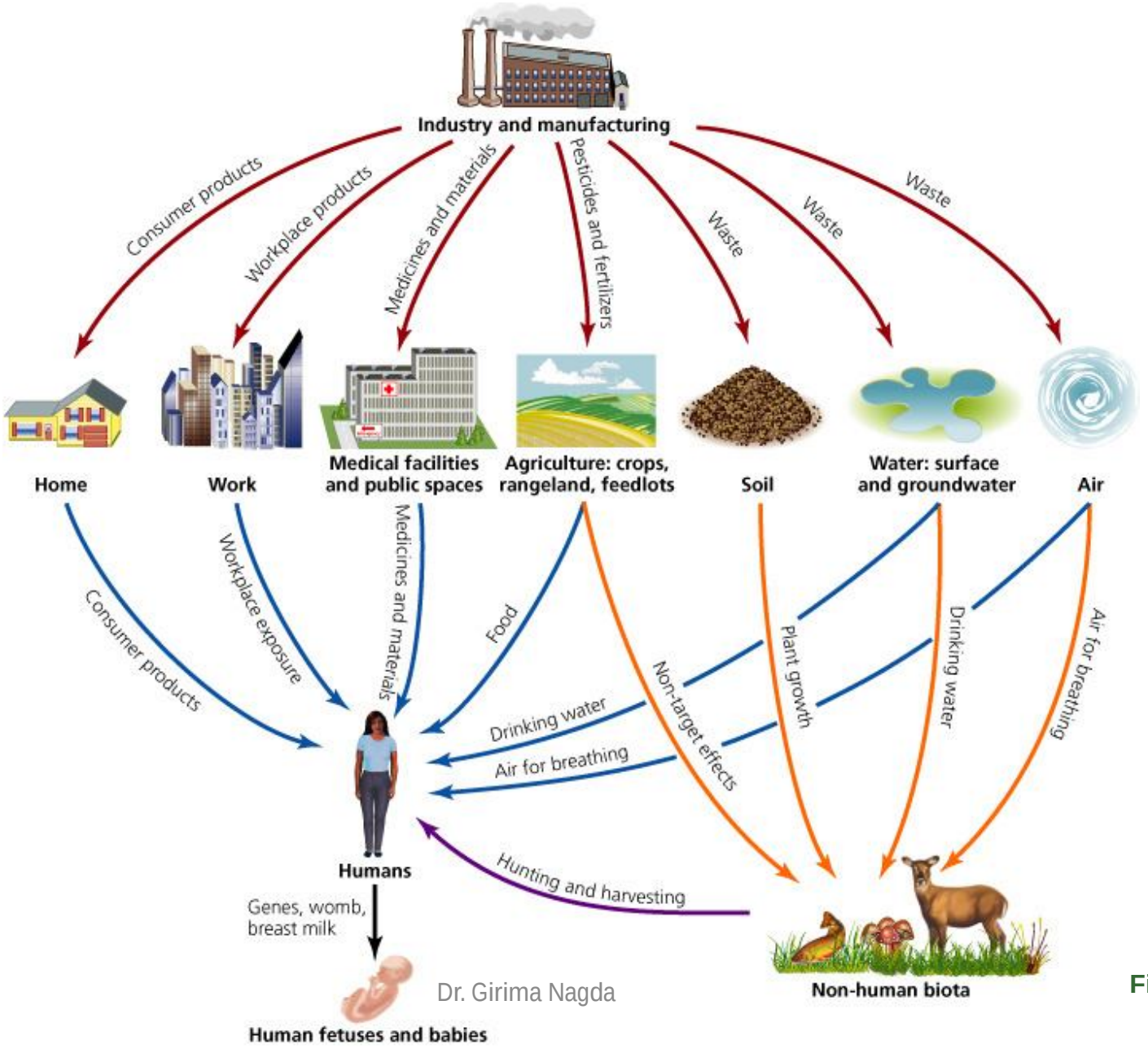
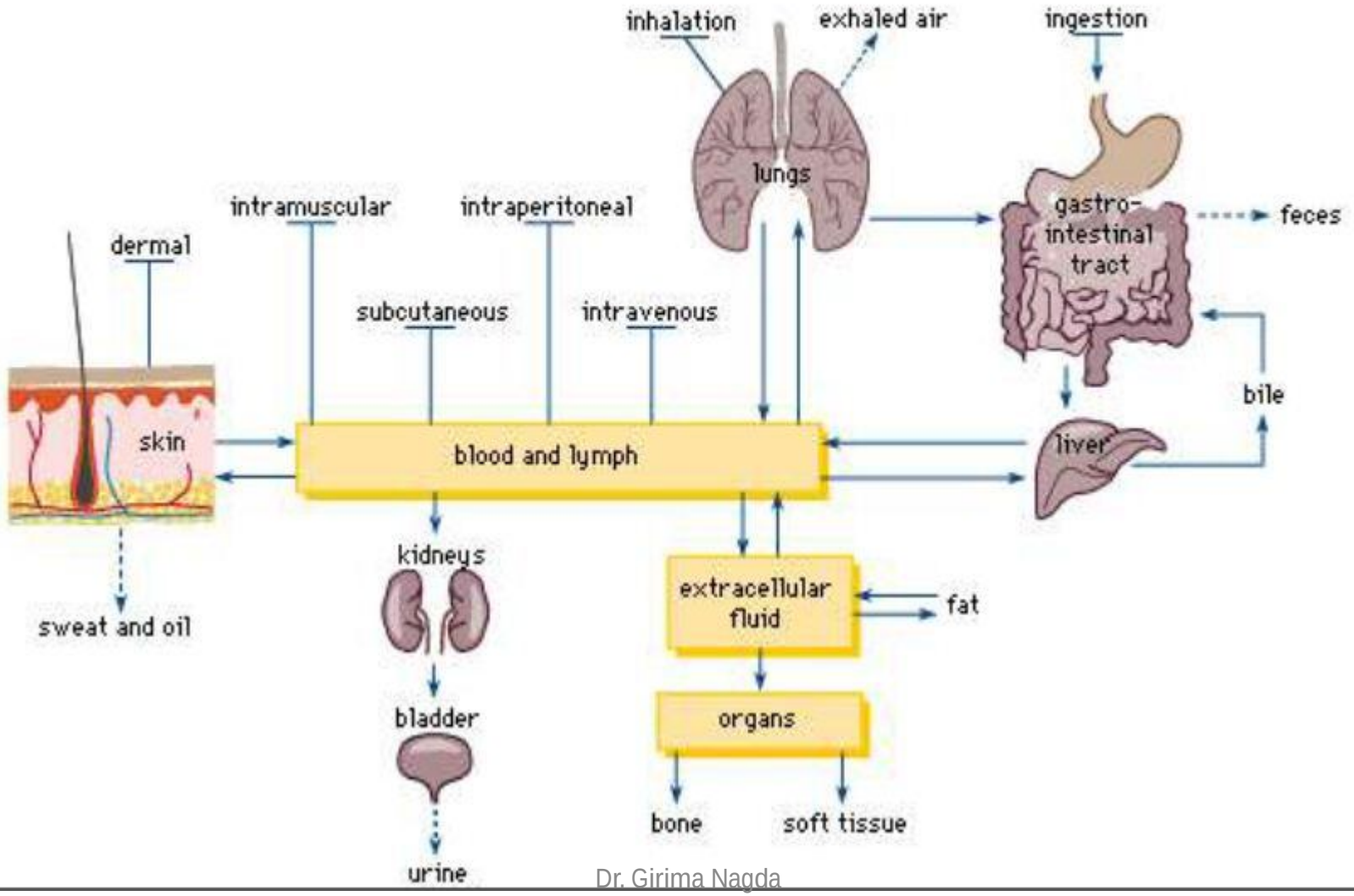




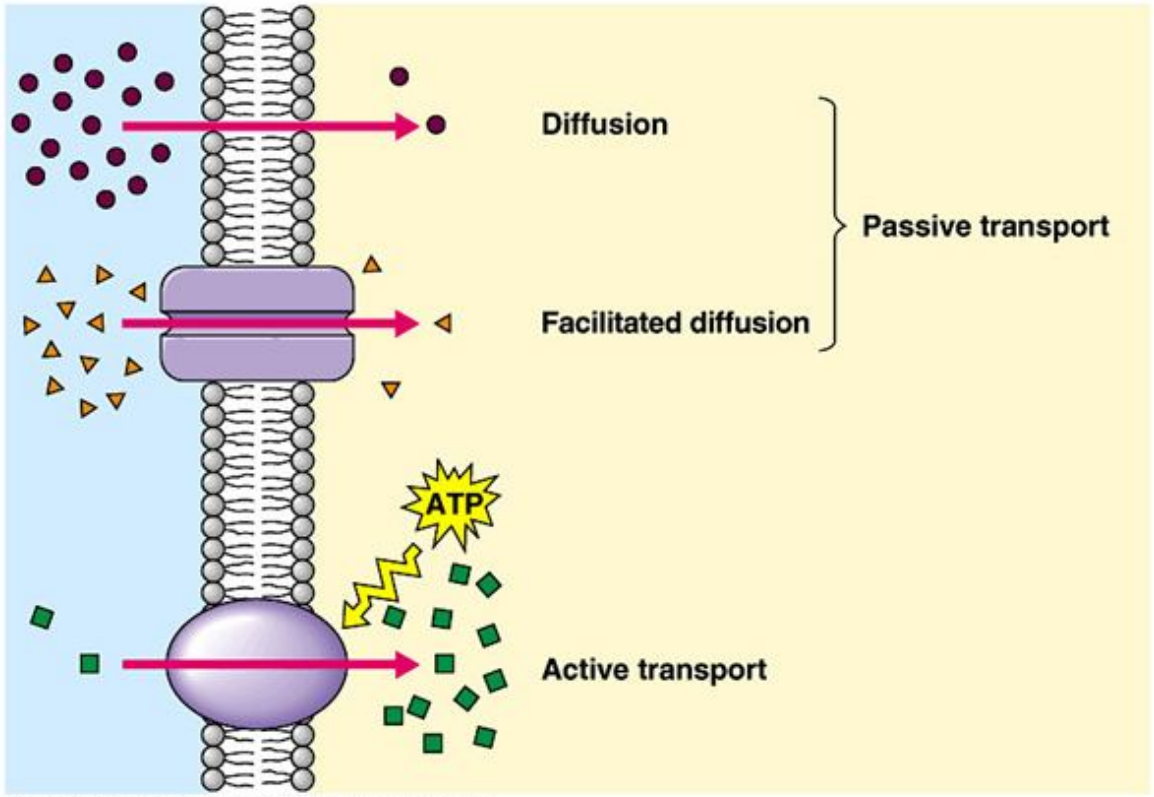

Figure 10.7

# HOW CHEMICALS ENTER THE BODY IS DEPENDENT ON THE PROPERTIES OF THE CHEMICAL AND THE BIOLOGY OF THE ORGANISM.



- In animals the exposure may be
  - Dermal
    - skin
    - Water pollution e.g. swimming in a polluted lake
  - Inhalation
    - lungs
    - air pollutants e.g. ozone, lead, methyl mercury
  - Ingestion
    - intestine
    - pollutant in food; e.g. PCBs in fish we eat
- Immediate and long term effects are directly linked to the mode of entry into the body
  - The most common place of entry in animals is the skin through follicles, sweat glands, and wounds
  - Toxicant has to pass through a series of membranes (tissue, cell, capillary

- Uptake / how to get through a membrane
  - Passive diffusion
  - Facilitated diffusion
  - Active transport




- Lipophilicity ($K_{ow}$) of a compound is important, because it affects adsorption properties

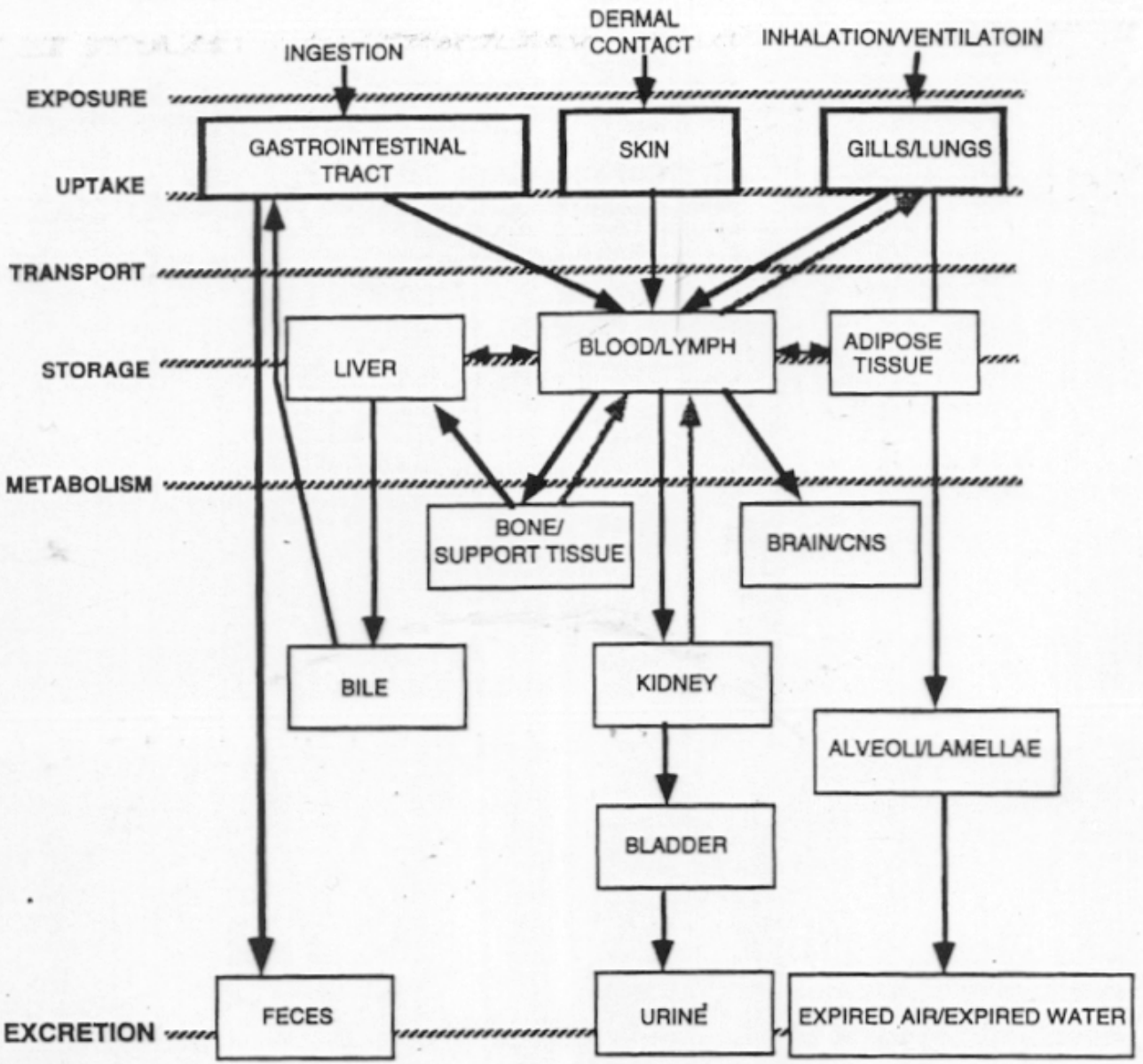



**Figure 5.2** Routes of absorption, translocation, and excretion of toxicants in a vertebrate.

# 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

# FACTORS RELATED TO EXPOSURE

- The toxic compound must come in contact & react with an appropriate site on the organism at a high enough concentration & for a required duration of time.
- The concentration and time required to produce an adverse effect vary with the chemical, species of organism & severity of effect.

# FACTORS AFFECTING EXPOSURE

- Physical & chemical form of toxicant
- Medium in which they are present
- Their mobility in soil
- Biology of organism
- Volatility

# ROUTES OF ENTRY

- THROUGH FOOD
- THROUGH WATER
- THROUGH AIR
- THROUGH SKIN
- THROUGH EGG YOLK & PLACENTA

Table 4.1 Routes, sources and nature of toxicants

| Route | Sources | Nature | Entry point |
|---|---|---|---|
| Food | Natural—plants and animals | Direct | Mouth → gastro intestinal tract |
| | Artificial—contamination and addition | Direct or indirect | Mouth and through gills and skin |
| Water | Natural—minerals and organic compounds | Direct | Mouth → gastro intestinal tract |
| | Artificial—pollution and water discharge | Direct | Mouth → gastro intestinal tract |
| Air | Artificial—emission from various sources | Direct | Lungs |
| Skin | Intentional—medication | Administration | Skin |
| | Unintentional—polluted work place | Direct | Skin |

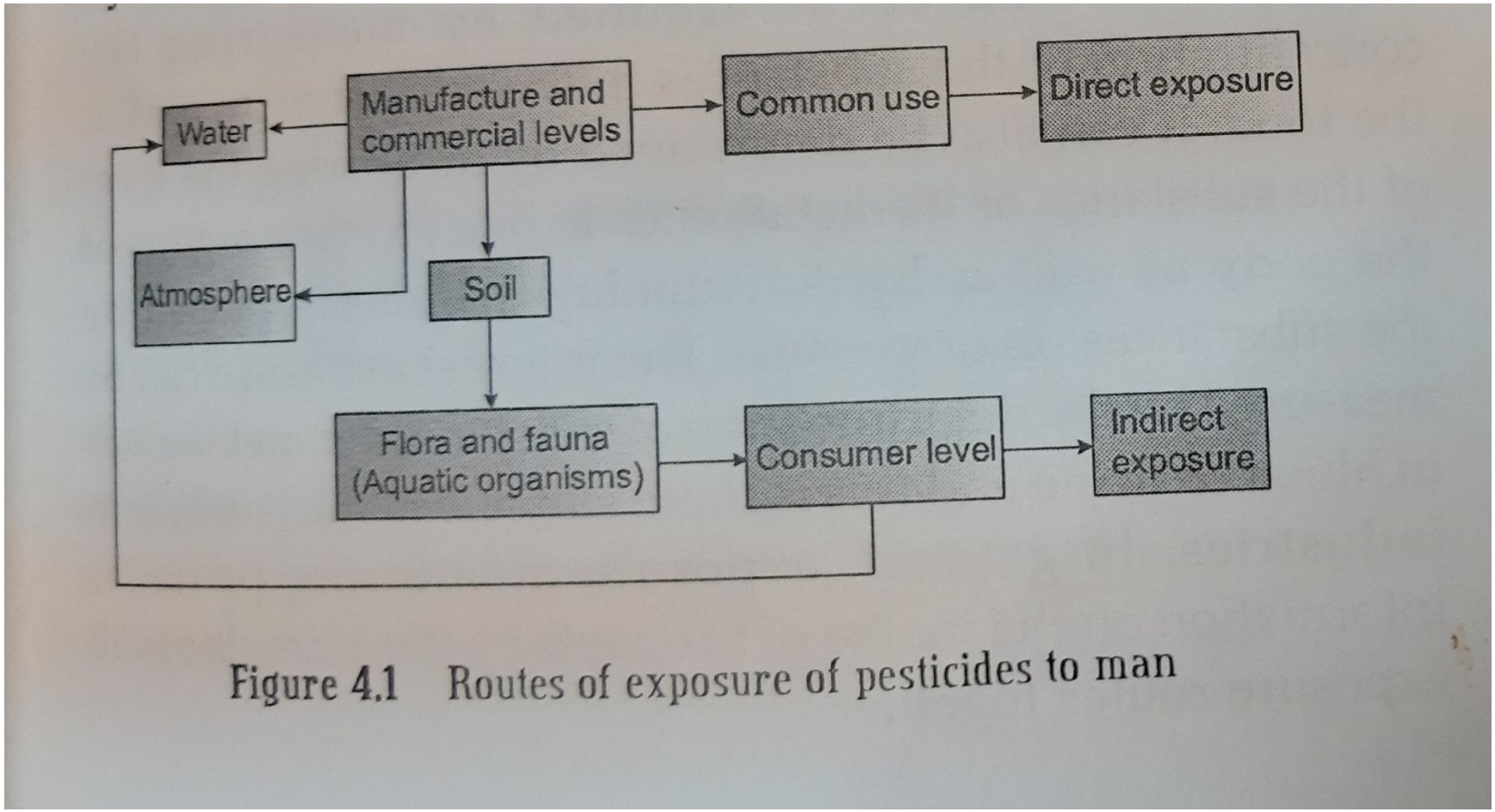



Figure 4.1 Routes of exposure of pesticides to man

# PENETRATION ROUTES IN EXPERIMENTAL ANIMALS

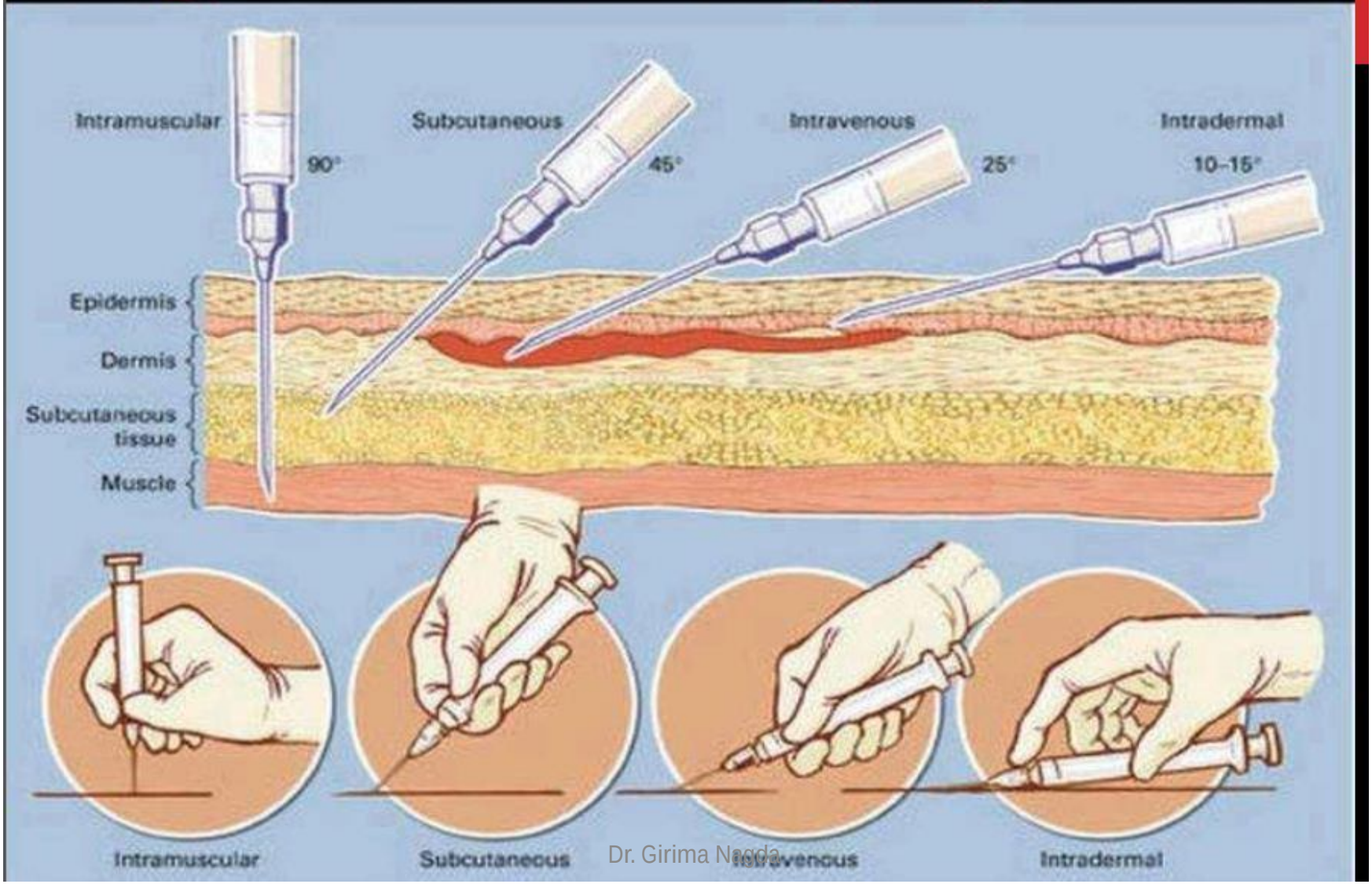
- INHALATION
- TOPICAL APPLICATION
- INJECTION METHOD
- DIPPING METHOD
- ORAL ROUTE THROUGH FEEDING

- There are four primary routes of exposure to chemical contaminants;
  - Injection
  - Ingestion
  - Topical
  - Inhalation

## INJECTION

- It's the only route in which the entire amount exposed is absorbed regardless of the chemical administered, because the chemical is introduced directly into the body. Chemicals may be injected
  - intravenously (directly into a vein),
  - intramuscularly (into a muscle),
  - subcutaneously (under the skin),
  - intraperitoneally (within the membrane lining the organs of the abdomen).

# Angles for inserting injections



- Because the blood is the vehicle of chemical distribution in the body, intravenous injection is the most rapid method of introducing a chemical into the body.
- The almost instantaneous distribution, together with the irreversibility, makes intravenous injection →a dangerous method of chemical exposure, with a fair chance of causing drug overdose if improperly administered.

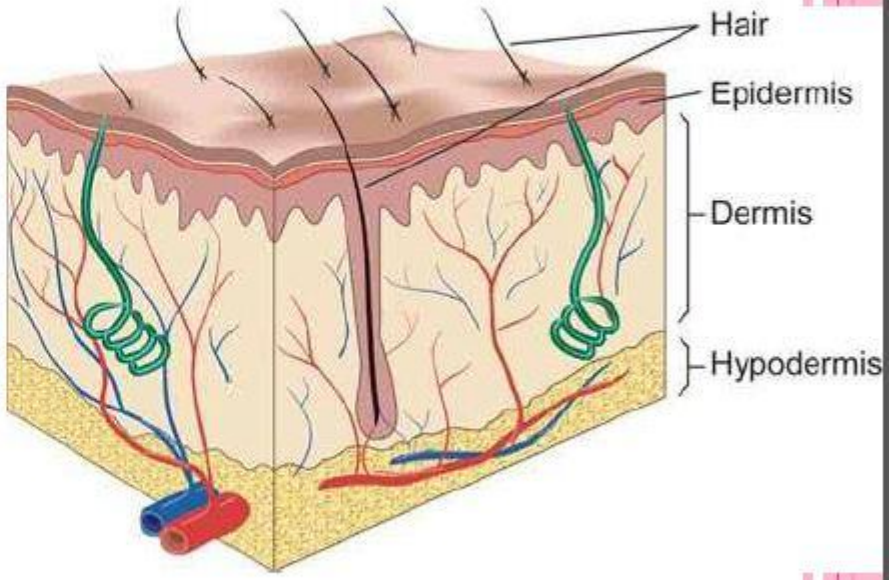
# INGESTION

- is the most common route of exposure to toxic chemicals. Most chemicals diffuse across the cell membrane in the non-ionized form, so that the degree to which the chemical is ionized is important in determining whether a chemical is absorbed.
- Organic acids and bases dissociate into their ionized forms in response to the pH conditions of the environment. Organic acids are in their non-ionized form in an acidic environment (such as the stomach), and they thus tend to diffuse across a membrane, whereas organic bases are non-ionized and thus diffuse across a membrane in a basic environment (such as in the intestine).

- The pH on the mucosal surface of the small intestine is alkaline. Organic bases tend to be in the non-ionized, lipid-soluble form and thus in general are absorbed there.
- The pH of the stomach contents is in the range of 1 to 2 (strongly acidic), and weak organic acids tend to be in the non-ionized, lipid-soluble form. It might be expected that the poisons would be absorbed there, but, because the surface area of the stomach is much smaller than that of the small intestine, often the stomach contents (along with the poisons) are passed to the intestine before the chemicals are absorbed. The acidic environment of the stomach is the main reason for the poor absorption of organic basesy the stomach.

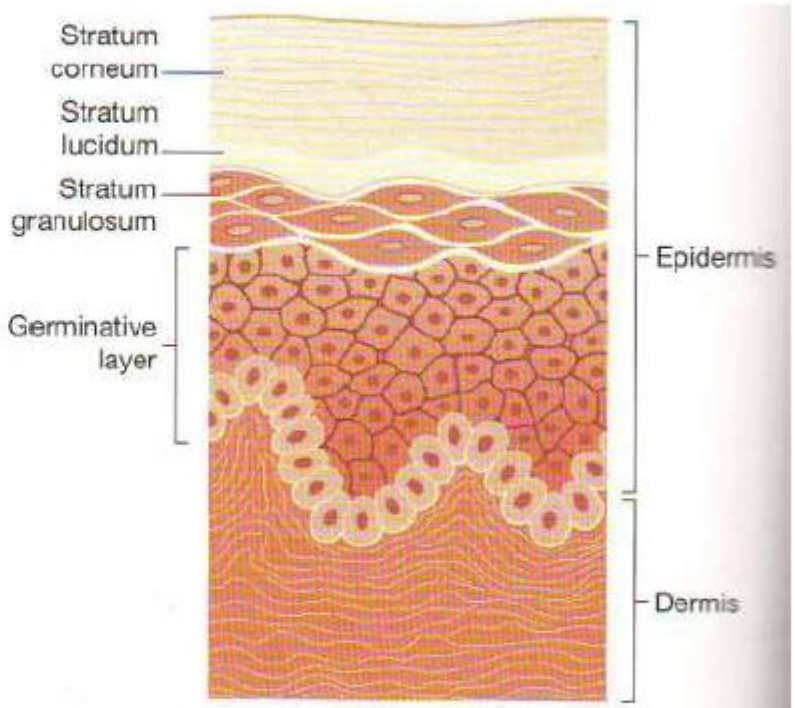
# Topical Exposure

- It happens in Skin
- Skin is consists of two parts, Epidermis and Dermis.



# TOPICAL EXPOSURE

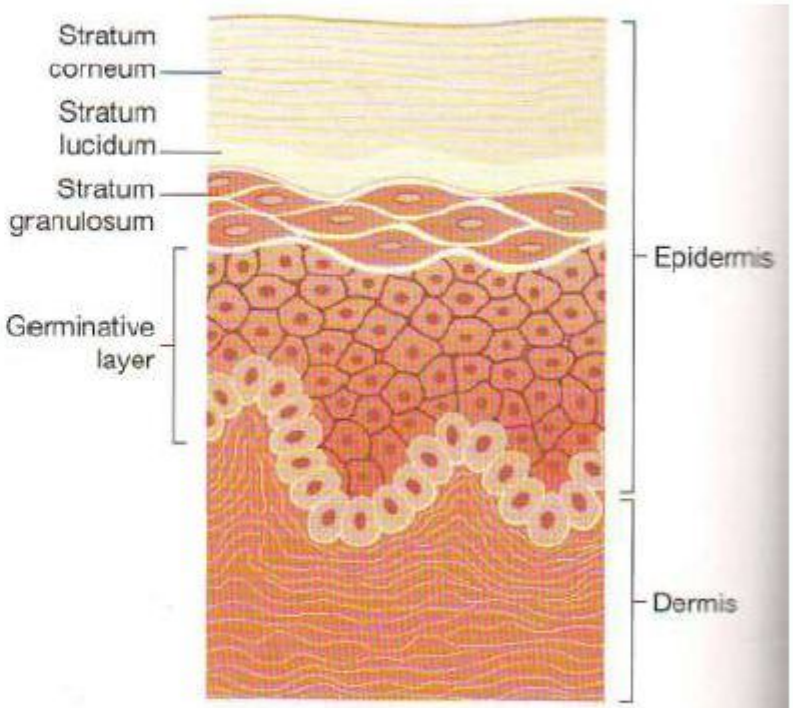
- Epidermis → has Stratum corneum
- Dermis → Connective tissues, elastin fibres, sweat glands, hair follicles, cappilaries




The skin showing the main layers of the epider

# Topical Exposure

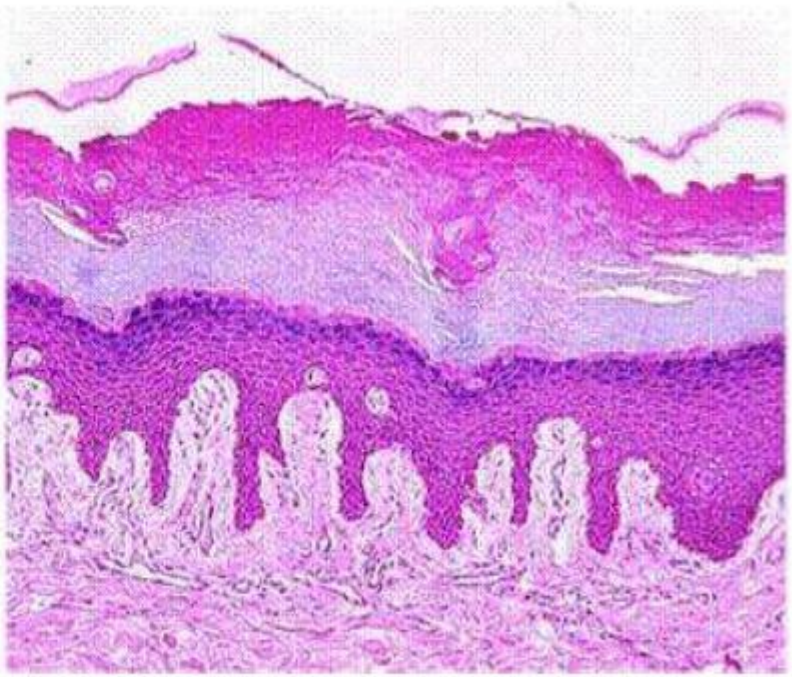
- The absorption is directly proportional with the lipid solubility.
- The absorption is inversely proportional to the Mw.




The skin showing the main layers of the epidermis

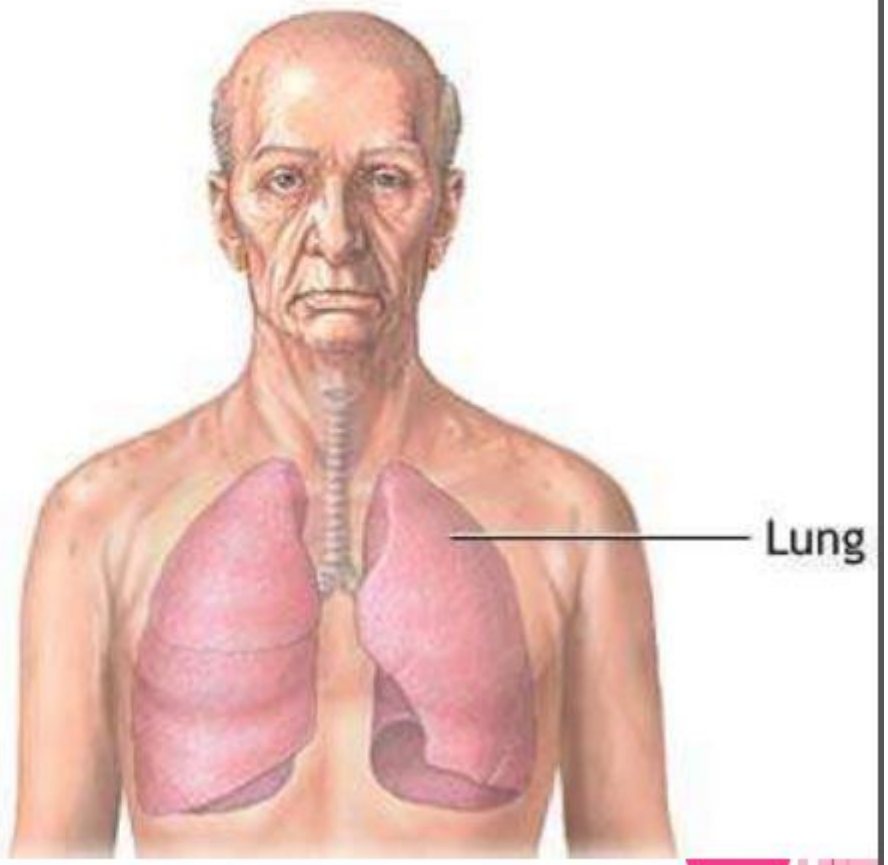
# FACTORS AFFECT THE RATE OF ABSORBTION:

1. The thickness of the layer.
2. The condition.
3. The dryness.
4. The state of the molecules



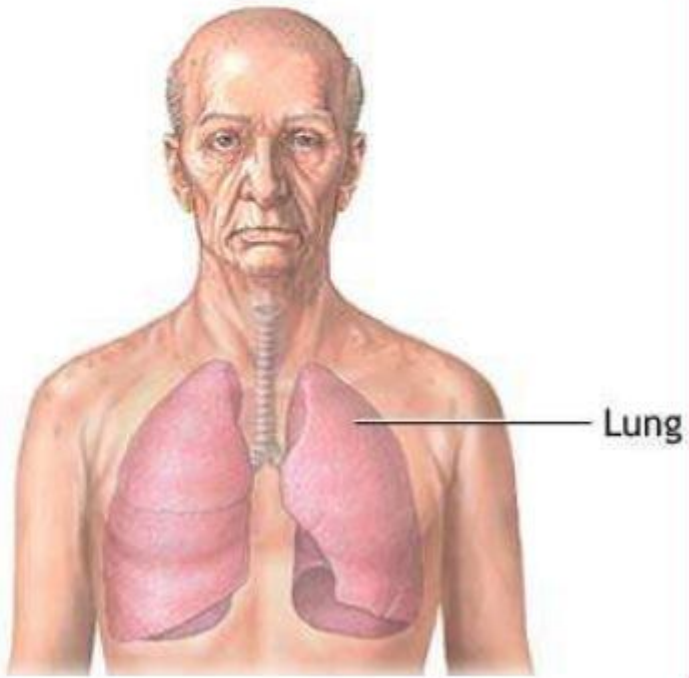
# INHALATION

- For Gases
- In Lungs
- Gas molecules move into the blood by partitioning



# INHALATION

- For aerosols
- particle size and water solubility.
- Aerosols of less than 100 micrometres



## INHALATION

- The larger aerosols (greater than five micrometres) tend to be deposited in the upper respiratory tract, while the smaller ones (less than five micrometres) have a greater chance of being deposited on deeper sites of the lung

# THANK YOU

- Transport
  - Lymphatic system
  - Blood system
  - Transport is usually achieved through blood protein that binds the toxicant – e.g. a lipoprotein
- Storage
  - Liver
  - Lungs
  - Kidneys
  - Bone
  - Adipose (fat) tissue
  - Toxicant may be stored in one reservoir but later transported elsewhere depending on physiological conditions
  - Storage site may or may not be the site of the toxic effect
    - Lead (Pb) is stored in bone, but it's toxic effect is in the liver
    - DDT is stored in adipose tissue but it's effect is through prolonged gradual release

## Metabolism

- Toxicants are metabolized by
  - Lungs
  - Gastrointestinal tract
  - Skin
  - Kidneys
  - Central role : liver
- The liver contains many non-specific enzymes that give it the ability to metabolize a broad spectrum of organic molecules
- Two phases:
  - Phase I involves the addition of reactive polar groups through oxidation, reduction, or hydrolysis; sometimes this makes a non-toxic chemical more toxic
  - Phase II involves conjugation with an endogenous substance to form a complex secondary metabolite which is more water soluble so it can be excreted

- General mechanism of action of xenobiotics
  - Intrinsic activity
  - Activated metabolites
  - Interact with specific site of action to initiate toxic effect
  - Effect can be anywhere in the body
    - Oxidative metabolism
    - Central nervous system
    - DNA replication (cancer and reproduction)
    - Protein synthesis
    - Protein function
  - Effect can be
    - Be terminated by
      - storage
      - transformation
      - Excretion
    - Permanent

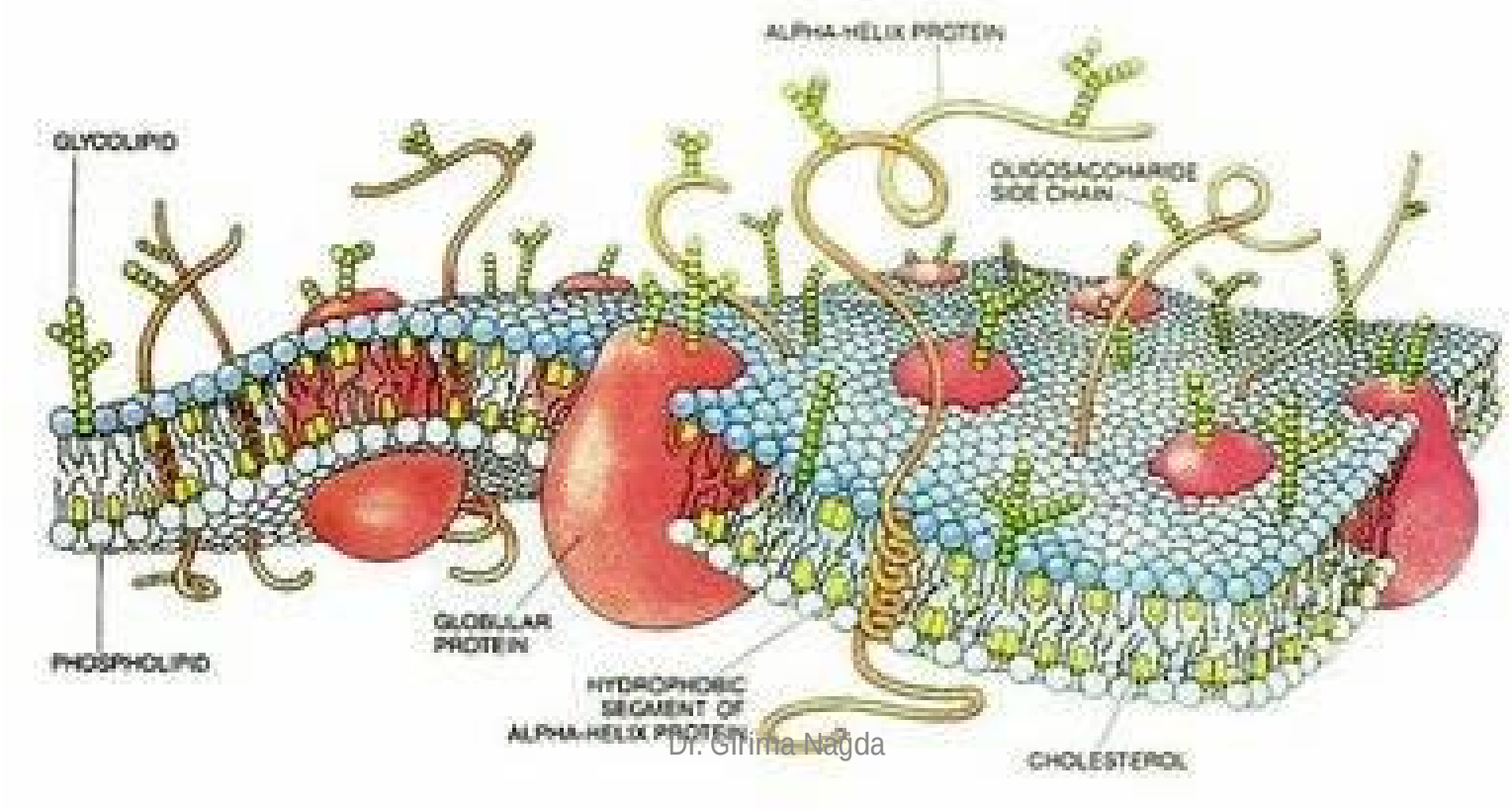
Disruption or destruction of cellular structure

- Structural damage to tissue

- Plants
  - $SO_2$, $O_3$, $NO_2$ and fluoride are for example phytotoxic
  - Feedback: $SO_2$ weakens stomata which lets even more $SO_2$ into cells

- Animals
  - $SO_2$, $O_3$ can cause irritation and damage to the respiratory system pulmonary edema
    - fluid buildup in alveoli due to membrane disruption
  - Industrial solvents can cause narcosis
    - General symptomatic response to toxicants
    - Results from membrane alterations / ion-transport
    - **$\log K_{ow}$** ($\log([\text{octanol}]/[\text{water}])$) is used to asses hydrophobicity of toxicants (correlates with toxicant's ability to cross lipid membranes)

- Narcosis
  - Alteration of physical/chemcial proterties of lipid bilayer
    - Permeability
    - Fluidity
  - Interact with pumps and receptors
  - Affect enzyme function



## Binding to cellular constituents

- Xenobiotics my directly bind to a cellular component and inhibit it's normal function
  - Carbon monoxide (CO) binds to hemoglobin (Hb) in red blood cells and prevent the Hb from binding $O_2$
  - Cadmium; highly toxic heavy metal that binds to metallothionein. This occurs primarily in the kidneys where Ca-metallothionein accumulates and is highly toxic to tubular cells

## Effect on Enzymes

- Enzymes are proteins that are involved in biochemical catalysis i.e. they help transform chemical structures. The purpose of a catalyst is to increase the rate of a reaction
  - Optimal function of enzymes depends on co-factors
  - There are organic and inorganic co-factors = coenzymes
    - vitamin K
    - Mg, Mn, Zn, Ca, Fe, Cu, K, and Na