

Toxicokinetics

. Is the quantitation of the time course of toxicant in the body during the processes of absorption, distribution, metabolism, and excretion, **ADME**.

Toxicokinetics

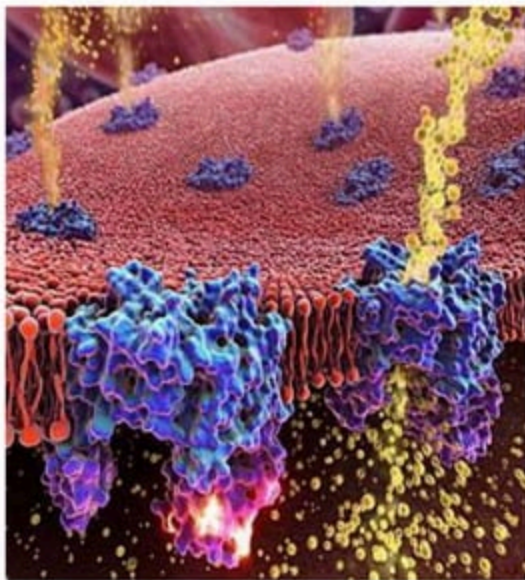
- Toxicokinetics describes how the body handles a toxicant, as a function of dose and time, in terms of ADME:
- The rate of chemical absorption from the site of application into the blood stream (Absorption)
- The rate and extent of chemical movement out of blood into the tissue (Distribution)
- The rate and extent of chemical biotransformation into metabolites (i.e. Metabolism)
- The rate of chemical removal from the body (Excretion)

Absorption of toxicants

- Absorption is the transfer of the parent chemical from the site of administration into the general circulation
- Absorption is also used to describe the extent to which the radioactivity from a radiolabelled chemical is transferred from the site of administration into the excreta and/or expired air.
- To exert a toxic effect on internal organs a toxicant must be absorbed, although such local toxicity as irritation, may occur.

Absorption

- Transfer of chemicals from the gut lumen, lungs, or skin into the general circulation involves movement across cell membranes, and **simple passive diffusion** of the unionized molecule, down a concentration gradient **is the most important mechanism**.
- Lipid-soluble molecules tend to cross cell membranes easily and are absorbed more rapidly than water-soluble ones.



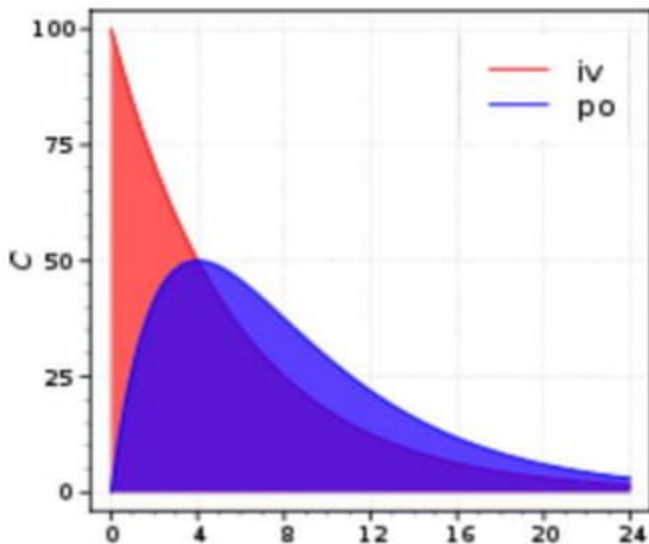
Extent of absorption

- IT is often useful to determine how much of the toxicant actually penetrates the membrane barriers (e.g skin or GIT) and gets into the blood stream.
- The area under the curve (AUC) of the concentration- time profiles for oral or dermal routes is compared with the AUC for IV ROA.
- The ratio of these (AUC) values is absolute bioavailability.

Bioavailability

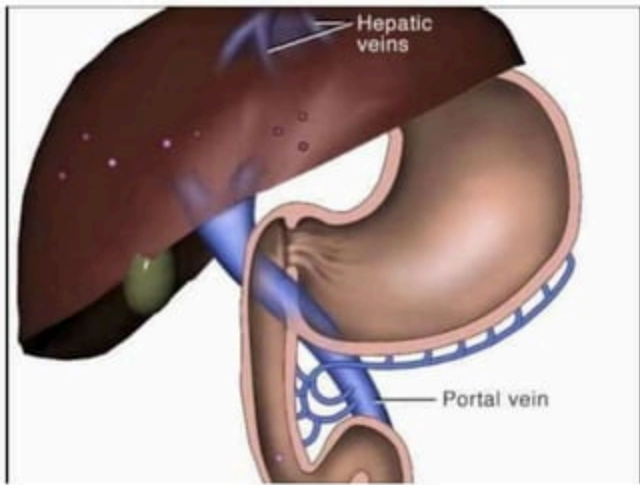
Is used to describe the extent and rate of absorption for a xenobiotic ,which enters the systemic circulation from the exposure site.

$$F = \text{AUC}_{\text{oral}} / \text{AUC}_{\text{iv}}$$



First pass effect

- A phenomenon of toxicant metabolism whereby concentration of a drug is greatly reduced before it reaches the systemic circulation, is termed **first-pass metabolism** or **pre-systemic metabolism**.

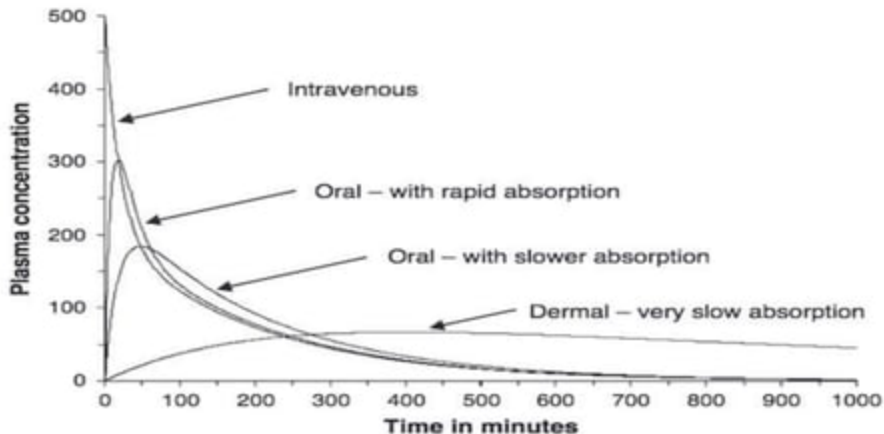


Rate of absorption

- The rate of absorption may be of toxicological importance because it is a major determinant of the peak plasma concentration and, therefore, the likelihood of acute toxic effects.
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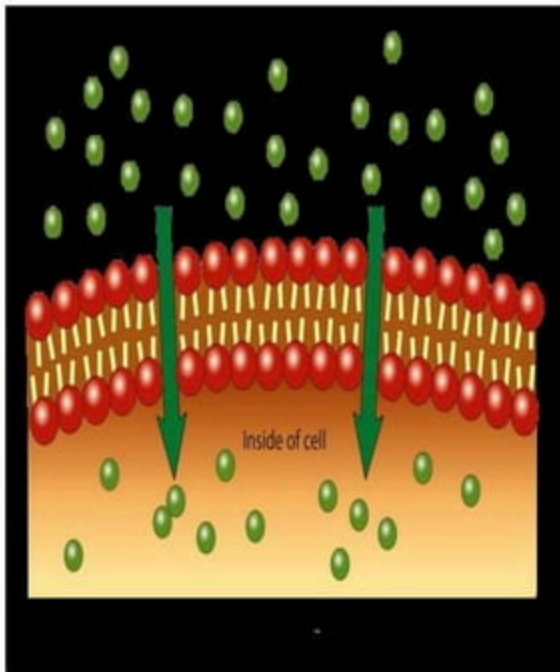


Types of transport

- 1- Simple diffusion
- 2- Facilitated diffusion
- 3- Active transport
- 4-Endocytosis(Pinocytosis&phagocytosis)
- 5- Filtration

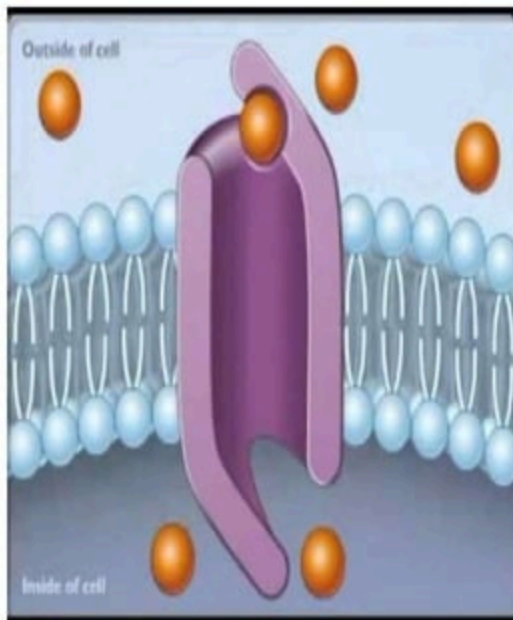
Simple diffusion

- Chemicals traverse from regions of higher concentration to regions of lower concentration
- Transport is not saturable .
- No structural specificity.
- No energy requirement.



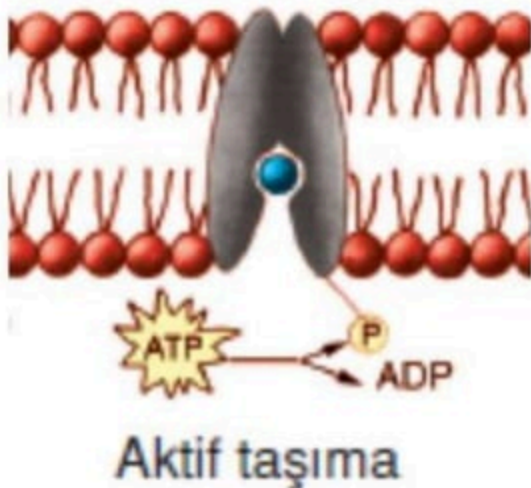
Facilitated diffusion

- 1-Carrier protein mediated transport
- 2-Not occur against concentration or electrical Gradient
- 3- Does not require ATP



Active transport

- Movement of chemicals **against** electrochemical or concentration gradients with expenditure of energy.
- **saturability** at high substrate concentrations.
- **Selectivity** for certain structural features of chemical.
- **competitive inhibition** by chemical or compounds that are carried by the same transporter.



Active transport

- E.g lead ,thallium and paraquat herbicide are transported across the intestinal wall by active transport system.

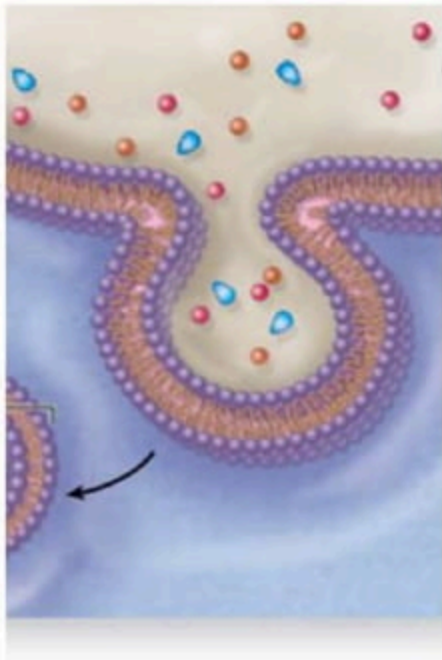
Pinocytosis

Pinocytosis :

In pinocytosis, fluid or particles are engulfed by a cell.

The cell membrane , encloses **the fluid or particles**, then fuses again, forming a vesicle that later detaches and moves to the cell interior.

Energy expenditure is required.



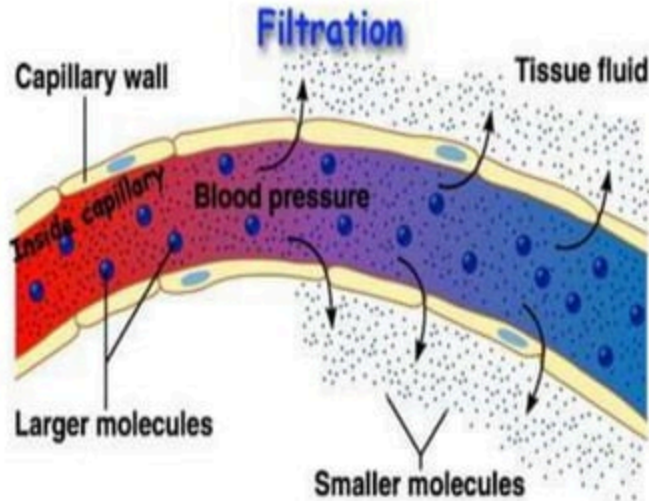
Phagocytosis

- Phagocytosis: large particles suspended in the extracellular fluid are engulfed and either transported into cells or are destroyed within the cell.



filtration

- filtration involves the movement of water and solutes across the cell membrane due to hydrostatic pressure

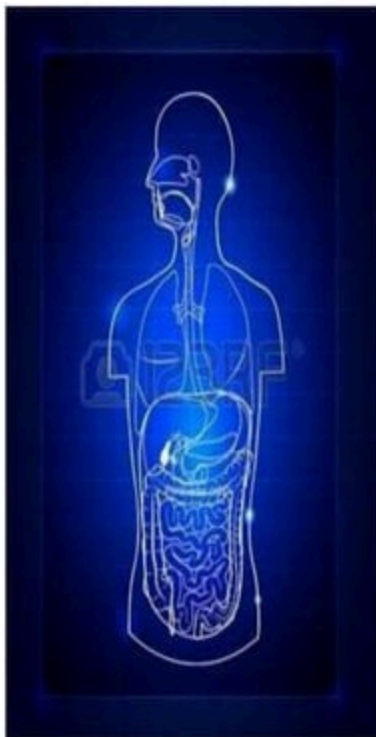


Routes of exposure

- 1. Ingestion
- 2. Inhalation
- 3. Dermal
- 4. Intravascular
- 5. Ophthalmic

Gastric absorption

- Absorption of toxicants can take place along the entire GI tract, even in the mouth and the rectum.
- Absorption of toxic substances in the digestive tract occurs primarily in the small intestine.



Gastrointestinal absorption

- Absorption of a toxicant from the GI tract depends on its
- physical properties, including lipid solubility, its dissolution rate, , particle size etc.
- It is also affected by the local factors in GI tract:
 - pH
 - Motility.
 - Presence of Food.
 - Digestive enzymes.
 - Microbial flora.

Gastrointestinal absorption

- Weak acids and bases will be absorbed by simple diffusion to a greater extent in the part of the GI tract in which they exist in the most lipid-soluble (non-ionized) form.
- The stomach, having high acidity (pH 1-3), is a significant site for absorption of weak organic acids, which exist in nonionised and lipid soluble form.
- Chemically, the stomach acidity may break down some substances.

- Organic bases would be absorbed more readily in the small intestine (pH 5.0 to 8.0).
- Small lipid soluble substances generally enter the mucosal epithelial cells by passive diffusion.
- Particulate toxicants can be absorbed via vesicular transport, either by pinocytosis or phagocytosis.
- Highly hydrophobic compounds may be absorbed into
- the lymphatic system via chylomicrons and drained into
- venous circulation near the heart

Gastric absorption

- Some xenobiotics are absorbed by the same specialised transport systems, thereby leading to potential competition or interaction (Iron inhibits lead and cadmium intestinal uptake due to shared absorption mechanism; conversely, toxic metals may inhibit essential element absorption).
- 5-fluorouracil absorbed by the pyrimidine transport system.
- thallium by iron transport system.
- Lead by calcium transporter

- Chemicals given via the gastrointestinal tract may be subject to a wide range of pH values and metabolizing enzymes in the gut lumen or gut wall, toxicant may be transformed to a more toxic product e.g. the formation of carcinogenic nitrosamines from non-carcinogenic amines.

Respiratory absorption

- Lungs have between 30 and 100 m² of surface area, large blood flow of 2000 km of capillary beds; thin physical chemical barrier between air and blood of 0.8 ~m - nice barrier for toxicants.
- gases and vapours come into equilibrium with blood in the alveolar capillaries almost instantaneously.



Respiratory tract absorption

. Gases and particles, which are water-soluble (and thus blood soluble), will be absorbed more efficiently from the lung alveoli.

Water-soluble gases and liquid aerosols can pass through the alveolar cell membrane by **simple passive diffusion**.

The absorption of airborne particles is dependent upon particle size ,regardless of solubility.

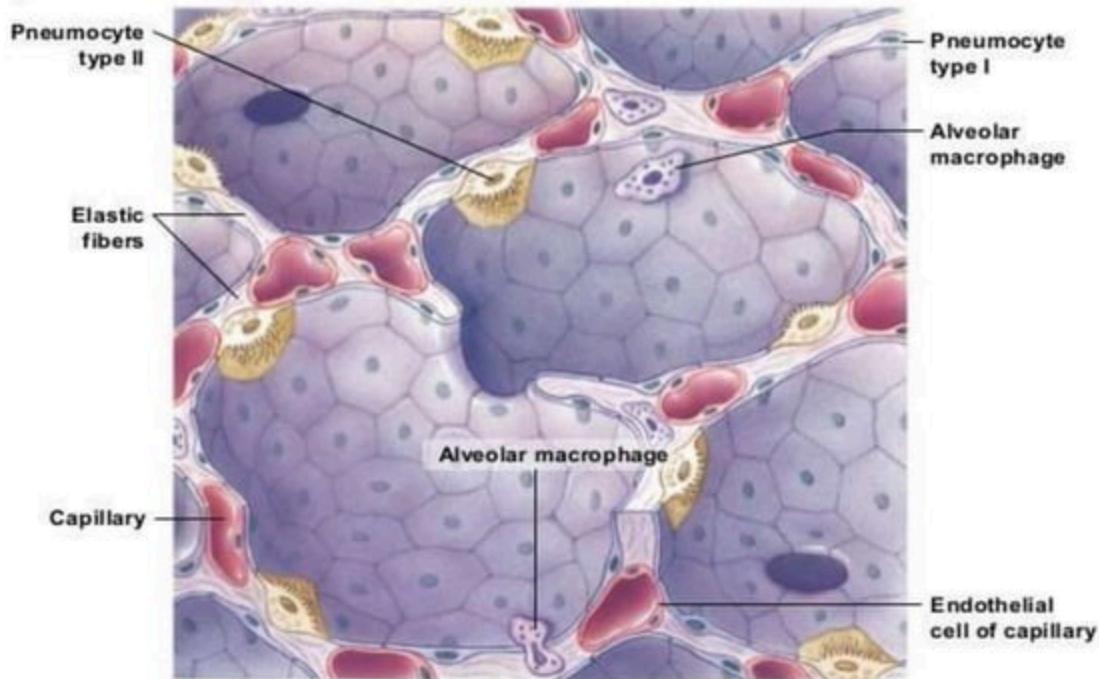
Respiratory tract absorption

- Large particles ($>5\ \mu\text{M}$) are generally deposited in the nasopharyngeal region with little absorption.
- Particles $2\text{-}5\ \mu\text{M}$ can penetrate into the tracheobronchial region.
- Very small particles ($<1\ \mu\text{M}$) are able to penetrate deep into the alveolar sacs where they can deposit and be absorbed.

Respiratory tract absorption

- Pulmonary macrophages exist on the surface of the alveoli.
- They are not fixed and not a part of the alveolar wall.
- They can engulf particles just as they engulf and kill microorganisms.
- Some non-soluble particles are scavenged by these alveolar macrophages and cleared into the lymphatic system .

Figure 23-11b Alveolar Organization



b A diagrammatic view of alveolar structure. A single capillary may be involved in gas exchange with several alveoli simultaneously.

Examples of Toxicant Gases or Volatile Liquids

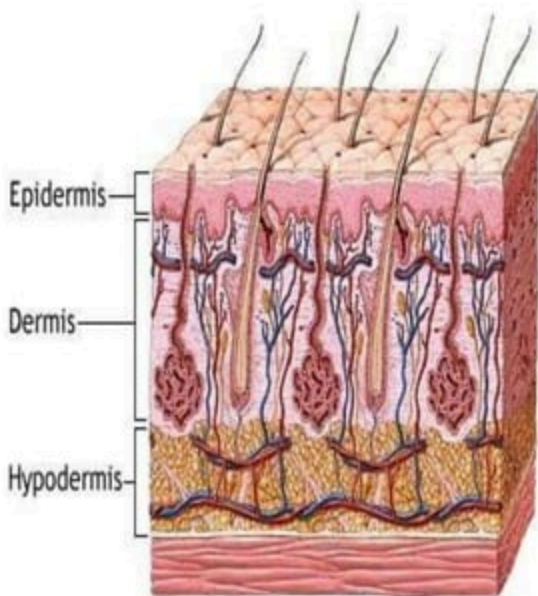
- 1. Sarin gas**—chemical warfare agent ,that causes excessive neuronal excitation, convulsions, seizures, tearing, salivation, suffocation, and death through inhibition of acetylcholinesterase
- 2. Carbon tetrachloride**—volatile liquid used widely as a cleaning agent and refrigerant, currently banned—greenhouse gas and carbon tetrachloride can be bioactivated in the liver to produce a potent hepatotoxin
- 3. Benzene**—largely found in crude oil, but also found in tobacco smoke and used to be found in glues, paints, and detergents—benzene metabolism leads to bioactivated carcinogens that cause leukemia

Non-absorbed foreign material can also cause severe toxic reactions within the respiratory system. This may cause:

- 1- chronic bronchitis.
- 2- alveolar breakdown (emphysema).
- 3- fibrotic lung disease.
- 4- lung cancer.
- In some cases, the toxic particles can kill the alveolar macrophages, which results in a lowering of the bodies' respiratory defense mechanism.

Dermal absorption

- The epidermis (and particularly the **stratum corneum**) is the only layer that is important in regulating penetration of a skin contaminant.



Dermal absorption

- The skin is a complex, multilayer tissue. For this reason, it is relatively impermeable to most ions as well as aqueous solutions.
- It represents, a barrier to most xenobiotics.
- Some notable toxicants, however, can gain entry into the body following skin contamination

Dermal absorption

- Toxicants move across the stratum corneum by passive diffusion.
- water soluble ,(polar) compounds appear to diffuse through the outer surface of the hydrated keratinized layer .
- Lipid-soluble ,(nonpolar)dissolve and diffuse through the lipid material between the keratin filaments .
- Once the substance penetrates through the Stratum corneum ,it enters lower layers of the epidermis(dermis and subcutaneous tissues.
- toxicant then can readily enter the circulation via the large number of venous and lymphatic capillaries in the dermis.

Dermal absorption

- In addition to the stratum corneum, small amounts of chemicals may be absorbed through the sweat glands, sebaceous glands, and hair follicles.

Exampels :

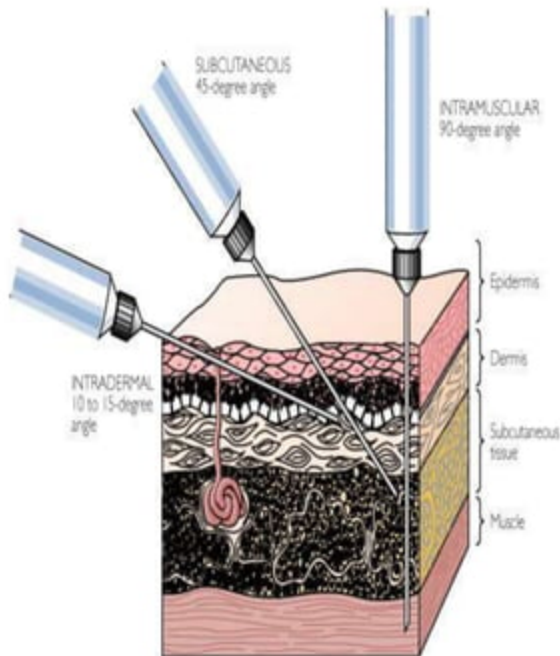
- The neurological warfare agent, **Sarin**, readily passes through the skin and can produce quick death to exposed persons.
- Several industrial solvents can cause systemic toxicity by penetration through the skin .
- e.g **carbon tetrachloride** penetrates the skin and causes liver injury.
- e.g **hexane** can pass through the skin and cause nerve damage.

Example:

- Paraben esters(used in the majority of skin care cosmetics) are absorbed through the skin, and increase female breast cancer incidence ,interfere with male reproductive function ,and to influence development of malignant melanoma .

Intravascular

- Intravenous (I.V)
- INTRAMUSCULAR(I. M)
- SUBCUTANEOUS (S.C)
- Intraperitoneal (I.P)



Thank you