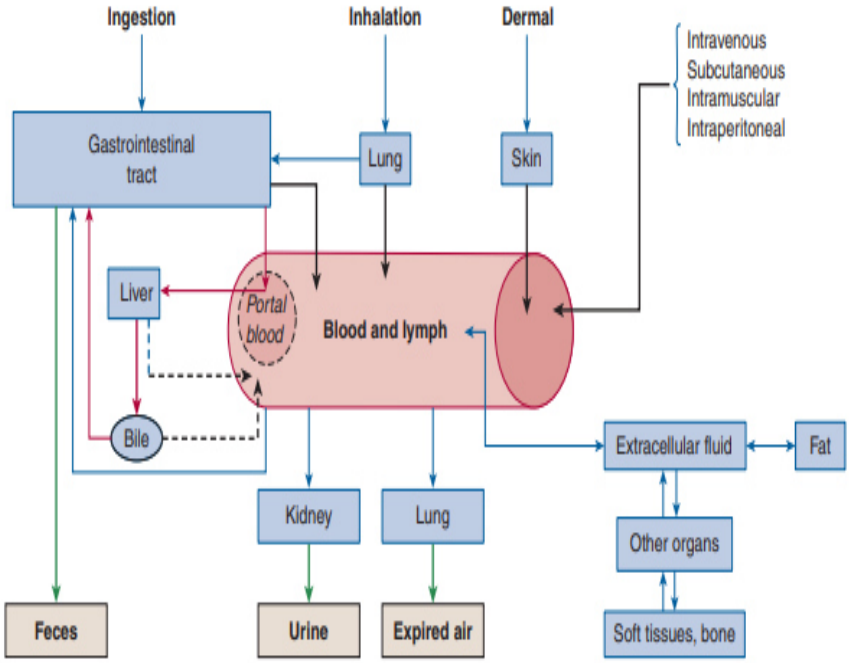
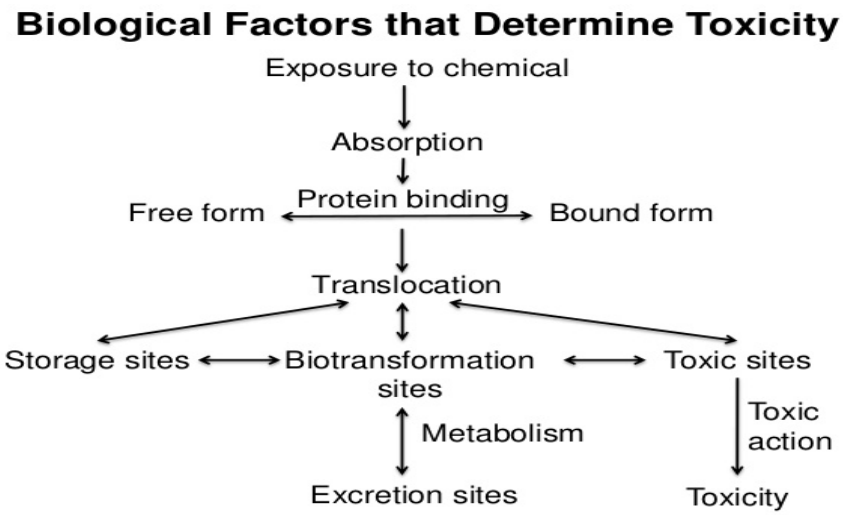
Translocation of Xenobiotics

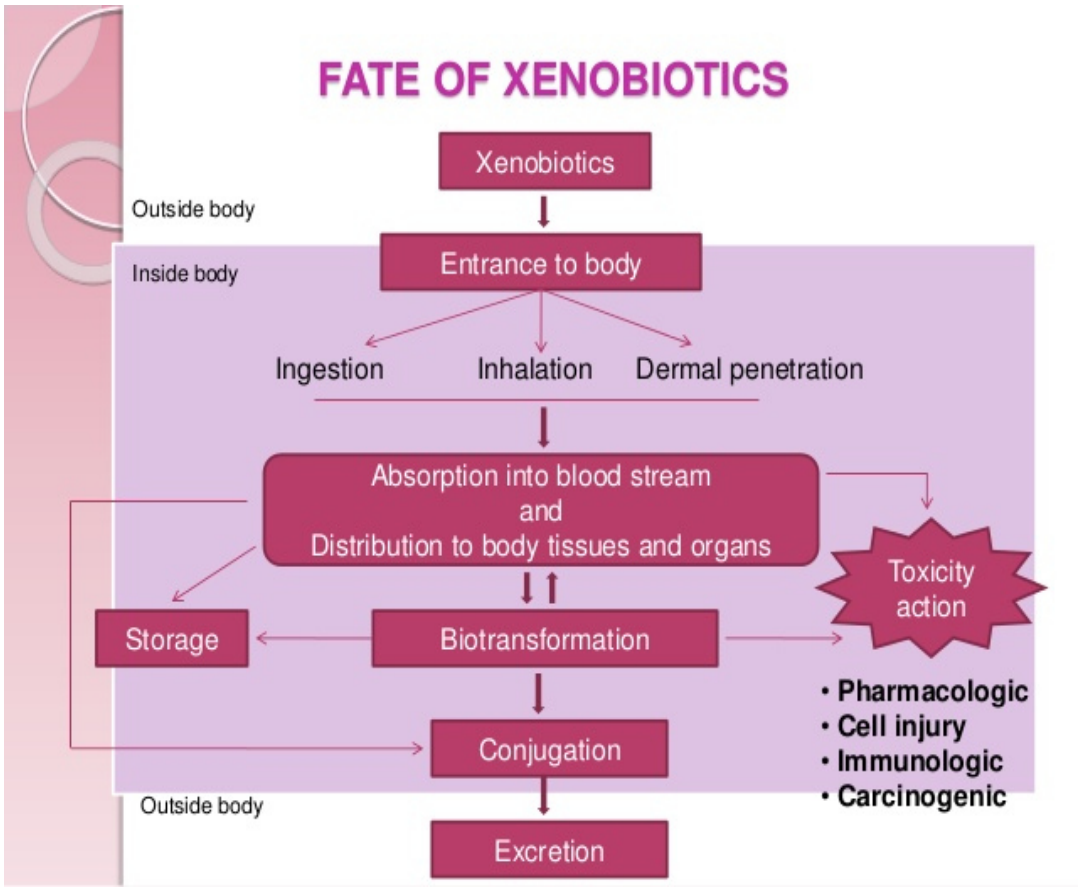
By Dr. Dharam Singh

The process of transport of toxicant molecules from the site of their application to the specific site of action or to storage depots or to the site of biotransformation including their elimination may be termed as translocation of toxicants.

The disposition of a chemical is define as the composite actions of its absorption, distribution, biotransformation, and elimination. The various factors and organs involved in affecting disposition of a toxicant. The toxicity of a substance is directly dependent on the dose, where "dose" is defined as the amount that ultimately reaches the site or sites of action (tissue, cell, or molecular target). Therefore, the disposition of a chemical determines its concentration at the site of action such that the concerted actions of absorption, distribution, and elimination also determine the potential for adverse events to occur. The skin, lungs, and alimentary canal are the main barriers that separate higher organisms from an environment containing a large number of chemicals.

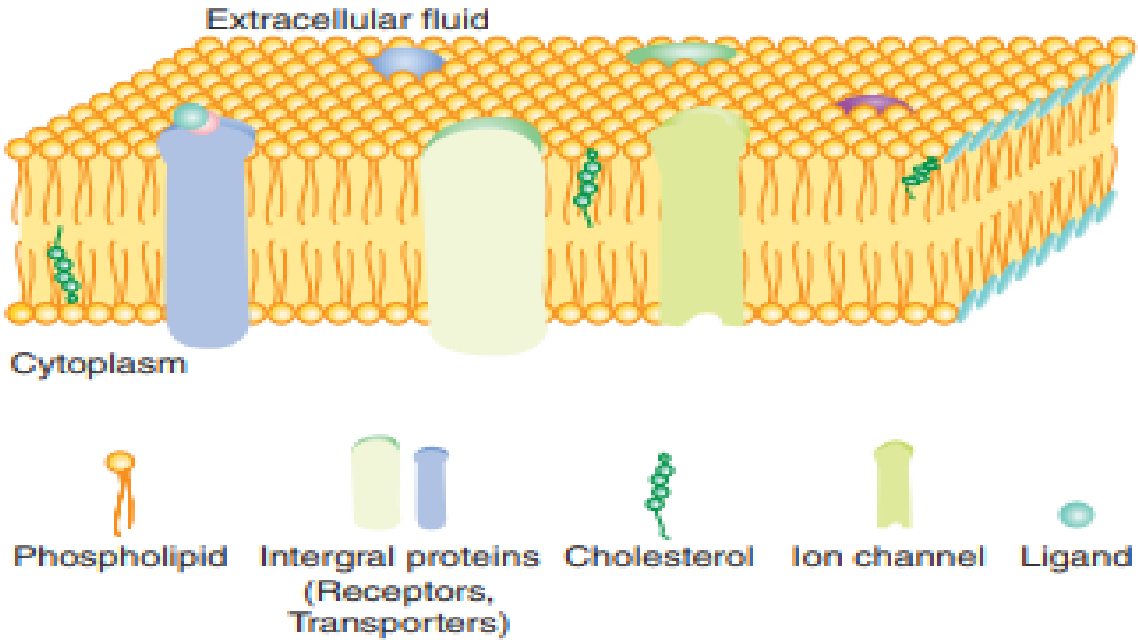






Cell membranes: Toxicants usually pass through a number of cells, such as the stratified epithelium of the skin, the thin cell layers of the lungs or the gastrointestinal (GI) tract, capillary endothelium, and ultimately the cells of the target organ. The plasma membranes surrounding all

these cells are remarkably similar. The basic unit of the cell membrane is a lipid bilayer composed primarily of phospholipids, glycolipids, and cholesterol. The phospholipids, primarily phosphatidylcholine and phosphatidylethanolamine are most abundant. Phospholipids are amphiphilic, consisting of a hydrophilic polar head and a hydrophobic lipid tail. In membranes, the polar head groups are oriented toward the outer and inner surfaces of the membrane, whereas the hydrophobic tails are oriented inward and face each other to form a continuous hydrophobic inner space.



Absorption: The absorption of toxicant define a process by which the toxicants crosses the body membrane and enter the blood stream. The xenobiotics penetrate membranes during absorption by the same processes as do biologically essential substances such as oxygen, foodstuffs, and other nutrients. Toxicant penetrates the body membrane either by passive transport or by specialized transport. The main sites of absorption are the GI tract, lungs, and skin. However, absorption may also occur from other sites, such as the subcutis, peritoneum, or muscle, if a chemical is administered by special routes.

1. Passive transport:

a) Simple diffusion: Most toxicants cross membranes by simple diffusion, following the principles of Fick's law, which establishes that chemicals move from regions of higher concentration to regions of lower concentration without any energy expenditure. For example a small, water-soluble compound such as ethanol is rapidly absorbed into the blood from the GI tract and is distributed just as rapidly throughout the body by simple diffusion from blood into all tissues.

b) Filtration : Substances of low molecular weight, which are readily soluble in water, can pass through the pores of membranes along with sufficient flow of water. Passage of substances through these channels is known as filtration

2. Special transport: These systems are responsible for the transport (both influx and efflux) across cell membranes of many nutrients, such as sugars and amino and nucleic acids, along with numerous foreign compounds.

a) **Active transport:** Substances actively transported across cell membranes presumably form a complex with a membrane-bound macromolecular carrier on one side of the membrane. The complex subsequently traverses to the other side of the membrane, where the substance is released. Afterward, the carrier returns to the original surface to repeat the transport cycle. Active transport is characterized by (1) movement of chemicals against electrochemical or concentration gradients, (2) saturability at high substrate concentrations, (3) selectivity for certain structural features of chemicals, (4) competitive inhibition by chemical cogeners or compounds that are carried by the same transporter, and (5) requirement for expenditure of energy, so that metabolic inhibitors block the transport process.

b) **Facilitated diffusion:** Facilitated diffusion applies to carriermediated transport that exhibits the properties of active transport except that the substrate is not moved against an electrochemical or concentration gradient, and the transport process does not require the input of energy; that is, metabolic poisons do not interfere with this transport. The transport of glucose from the GI tract across the basolateral membrane of the intestinal

epithelium, from plasma into red blood cells, and from blood into the central nervous system (CNS) occurs by facilitated diffusion.

c) Additional transport : Phagocytosis and pinocytosis are proposed mechanisms for cell membranes fl owing around and engulfs particles. This type of transfer has been shown to be important for the removal of particulate matter from the alveoli by phagocytes and from blood by the reticuloendothelial system of the liver and spleen.

3. Following factors involved in absorbing a chemicals:

1. Physicochemical properties of chemicals

a) Hydrophilic / Lipophilic substances

b) Ionized /Non-ionized/ weak acid / base

c) Molecular weight

2. Route of exposure

Mechanism of Absorption

- Takes place by passive transport or by specialized transport

A. Passive Transport

i. Simple diffusion
ii. Filtration

B. Specialised Transport

i. Active transport
ii. Facilitated diffusion
iii. Endocytosis