Absorption and Excretion of Toxicants

Human stratum corneum displays significant differences in structure and chemistry from one region of the body to another, and these differences affect the permeability of the skin to chemicals. The permeability of the skin also depends on both the diffusivity and the thickness of the stratum corneum. There are several factors that can influence the absorption of toxicants through the skin, including:

(1) The integrity of the stratum corneum, removal of this layer by Caustic agents causes a dramatic increase in the permeability of the epidermis for a variety of large or small molecules.

(2) The hydration state of the stratum corneum. Water plays an extremely important role in skin permeability. Under normal conditions, the stratum corneum is partially hydrated, This amount of water increases the permeability of the stratum corneum approximately 10-fold over the permeability that exists when it is completely dry.

(3) Temperature, increased absorption for both lipid-soluble and water-soluble toxicants, and an increase in temperature will increase dermal penetration by increasing dermal blood flow.

(4) Solvents as carriers solvents used to dissolve compounds of interest can also influence dermal penetration. In general, lower absorption will be observed if a toxicant is highly soluble in the vehicle, whereas low solubility of the toxicant in the vehicle will tend to increase dermal penetration. In addition, solvents such as dimethyl sulfoxide (DMSO) facilitate the penetration of toxicants through the skin by increasing the permeability of the stratum corneum. DMSO:

I. removes much of the lipid matrix of the stratum corneum, making holes on artificial shunts in the penetration barrier;
II. reversible configuration changes in integral protein structure of water molecules transporter;
III. produces functions as a swelling agent.

(5) molecular size.

(6) Biotransformation reactions in skin can also facilitate absorption, and the presence of metabolizing enzymes is highly variable across species.

Effect the route of administration on toxicant

The toxicity of a chemical may depend on the route of administration. The most common routes are:

(1) The intravenous route introduces the toxicant directly into the bloodstream, eliminating the process of absorption.

(2) Intraperitoneal injection results in rapid absorption of xenobiotics because of the rich peritoneal and mesenteric blood supply and the relatively large surface area of the peritoneal cavity. Intraperitoneally administered compounds are absorbed primarily through the portal circulation and therefore must pass through the liver before reaching other organ may be completely extracted and biotransformed by the liver with subsequent excretion into bile without gaining access to the systemic circulation.

(3) Subcutaneously and intramuscularly administered toxicants are usually absorbed at slower rates but enter directly into the general circulation. The rate of absorption by these two routes can be altered by changing the blood flow to the injection site. For example, epinephrine causes vasoconstriction and will decrease the rate of absorption if it is coinjected intramuscularly with a toxicant.

DISTRIBUTION

a toxicant is distributed to tissues throughout the body. The rate of distribution to organs or tissues is determined primarily by:

A. blood flow

B. the rate of diffusion out of the capillary bed into the cells of a particular organ or tissue.
C. determined largely by affinity

Volume of Distribution

Total body water is derived from:

- Plasma water
- interstitial water comprise the extracellular compartment
- intracellular water.

total water:	**60% (50-80%)**	**42 L**
intracellular volume:	40%	28L
extracellular volume:	20%	14L
plasma volume:	4%	3L
blood volume:	8%	5.5L

Volume of distribution (Vd) The concentration of a toxicant in blood depends largely on its volume of distribution.

The distribution of toxicants is complex, some toxicants do not readily cross cell membranes and therefore have restricted distribution, whereas other toxicants rapidly pass through cell membranes and are distributed throughout the body. Some toxicants selectively accumulate in certain parts of the body as a result of protein binding, active transport, or high solubility in fat. The toxicants binding to and/or dissolution in various storage sites of the body, such as fat, liver, and bone. The target organ for toxicity may be the site of accumulation, but this is not always the case. If a toxicant accumulates at a site other than the target organ or tissue, the accumulation is likely to be protective because plasma levels reduced and consequently its concentration at the site of action is reduced.

The storage depot of toxicant:

The compartment where a toxicant is concentrated is toxicologically inactive. However, a chemical in a storage depot is also in equilibrium with the free fraction of the toxicant in plasma, so that it is released into the circulation as the unbound fraction of toxicant is eliminated. As a result, the biological half-life of stored compounds can be very long.

Some xenobiotics attain their highest concentrations at the site of toxic action, such as carbon monoxide, which has a very high affinity for hemoglobin, which accumulates in the lungs. Other chemicals concentrate at sites other than the target organ. For example, lead is stored in bone, but manifestations of lead poisoning appear in soft tissues.

❖ Plasma Proteins :

Plasma proteins is the major site of protein binding, and several different plasma proteins bind xenobiotics and some endogenous constituents of the body. Albumin, present in the plasma, is the most abundant protein in plasma and serves as both a depot and multivalent transport protein for many endogenous and exogenous compounds. Protein–ligand interactions occur primarily as a result of hydrophobic forces(hydrogen bonding). Because of their high molecular weight, plasma proteins and the toxicants bound to them cannot cross capillary walls. The interaction of a chemical with plasma proteins is a reversible process, and as unbound chemical diffuses out of capillaries, bound chemical dissociates from the protein until the free fraction reaches equilibrium between the vascular space and the extravascular space

The bound fraction is determined as the difference between the total and unbound fractions. Binding of toxicants to plasma proteins can be assessed through the use of Scatchard analysis in which the ratio of bound to free ligand (toxicant)

The binding of chemicals to plasma proteins is an important concept in toxicology for two reasons.

1. Toxicity is typically manifested by the amount of a xenobiotic that is unbound. Therefore, a compound with a high degree of plasma protein binding may not show toxicity when compared to one that is less extensively bound to plasma proteins.

2. Severe toxic reactions can occur if a toxicant with a high degree of protein binding is displaced from plasma proteins by another agent, increasing the free fraction of the toxicant in plasma, thus concentration of the toxicant in a target organ. For example, if a strongly bound sulfonamide is given concurrently with an antidiabetic drug, the sulfonamide may displace the antidiabetic drug and induce a hypoglycemic coma.

The penicillin–sulfonamide mixture led to much higher mortality than did the tetracycline, because the sulfonamide displaced a considerable amount of bilirubin from albumin. Free bilirubin then diffused into the brain of the newborns (because the blood–brain barrier is not fully developed), causing a severe form of brain damage termed kernicterus.

Liver and Kidney as Storage Depots:

These two organs probably concentrate more toxicants than do all the other organs combined; the distribution is determined primarily by blood flow therefore, a well-perfused organ such as the liver may attain high initial concentrations of a xenobiotic). And active transport or binding to tissue components are likely to be involved. In addition, some proteins serve to sequester xenobiotics in the liver or kidney. For example,

*metallothionein (MT), a specialized metal-binding protein, sequesters both essential and toxic metals including zinc and cadmium (Cd) with high affinities in the kidney and liver. In liver, Cd bound to MT serves to concentrate and sequester the heavy metal while preventing its excretion into bile. In the kidney, however, the Cd–MT complex is very toxic and is mechanistically involved in the chronic toxicity of Cd

* Protein that sequesters certain toxicants in the kidney is α2u-globulin:The chemical-α2u-globulin complex is taken up by the kidney, where it accumulates within the lysosomal compartment and damages the proximal tubule cells.

❖ Fat as Storage Depot

There are many organic compounds that are highly stable and lipophilic, leading to their accumulation in the environment. The lipophilic nature of these compounds also permits rapid penetration of cell membranes and uptake by tissues, that highly lipophilic toxicants are distributed and concentrated in body fat. The environmental accumulation and potential toxicological significance of long-term storage of numerous compounds including the pesticides aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, mirex, and toxaphene, along with polychlorinated and polybrominated biphenyls, dioxins, and furans has led to international treaties controlling the use of these persistent organic pollutants. The potential for these compounds to produce toxicity, including carcinogenic, developmental, and endocrine effects is related to their accumulation and storage in body fat, higher amounts are likely to be retained in obese individuals. Storage lowers the concentration of the toxicant in the target organ such that toxicity is likely to be less severe in an obese person than in a lean individual.but the concern is the possibility that a sudden increase in the concentration of a chemical in blood and the target organ of toxicity may occur if rapid mobilization from fat occurs.

❖ Bone As Storage Depot:

Compounds such as fluoride, lead, and strontium may be incorporated and stored in the bone matrix. Skeletal uptake of xenobiotics is essentially a surface chemistry phenomenon, with exchange taking

place between the bone surface and the fluid in contact with it. The fluid is the extracellular fluid, and the surface is that of the hydroxyapatite crystals of bone mineral. Many of those crystals are very small, resulting in a large surface area relative to the mass of the bone. The extracellular fluid brings the toxicant into contact with the hydration shell of the hydroxyapatite, allowing diffusion through it and penetration of the crystal surface.

Toxicants can be released from the bone by ionic exchange at the crystal surface and dissolution of bone crystals through osteoclastic activity. An increase in osteolytic activity such as that seen after parathyroid hormone administration leads to enhanced mobilization of hydroxyapatite lattice, which can be reflected in an increased plasma concentration of toxicants. Deposition and storage of toxicants in bone may or may not be detrimental. Lead is not toxic to bone, but the chronic effects of fluoride deposition (skeletal fluorosis) and radioactive strontium (osteosarcoma and other neoplasms).

Blood–Brain Barrier

Access to the brain is restricted by the presence of two barriers:

The blood–brain barrier (BBB) and the blood–cerebral spinal fluid barrier (BCSFB). Many toxicants do not enter the brain in appreciable quantities because of these barriers.

Diffusion of more lipophilic compounds through endothelial cell membranes is counteracted by xenobiotic efflux transporters present in the endothelial cells (active transport processes represent a key mechanism that decreases the concentration of xenobiotics in the brain. Including P-gp, Mrp2, Mrp4, and BCRP, these transporters are located on the luminal plasma membrane and function to move xenobiotics absorbed into the capillary endothelial cells out into the blood). Glial cells, particularly astrocytes, contribute to the BBB by secreting chemical factors that modulate endothelial cell permeability, and astrocytes and perivascular microglial cells extend processes that support the integrity of the BBB. For small- to medium-sized water-soluble molecules, the tighter junctions of the capillary endothelium and the lipid membranes of the glial cell processes represent the major barrier.

The blood–cerebral spinal fluid barrier:

Xenobiotic transporters also contribute to removing compounds that may enter the endothelial cells. Furthermore, the protein concentration in CSF is much lower than that in other body fluids. The low protein content of the CSF also limits the movement of water-insoluble compounds by paracellular transport.

Furthermore, in most cases, toxicants achieve concentrations in the CSF that are no higher than the concentration of the unbound toxicant in the plasma. The BCSFB is more of an anatomical entity than a true barrier, but it does provide some protection against the distribution of toxicants to the CNS.

The effectiveness of the blood–brain barrier varies from one area of the brain to another. For example, the cortex, the lateral nuclei of the hypothalamus, the area postrema, the pineal body, and the posterior lobe of the hypophysis are more permeable than are other areas of the brain. this is due to the increased blood supply to those areas, or because the BSCFB represents a more permeable barrier, or both.

The blood–brain barrier is not fully developed at birth, and this is one reason why some chemicals are more toxic in newborns than adults. The example morphine is 3–10 times more toxic to newborn than to adult rats because of the higher permeability of the brain of a newborn to morphine.

Passage of Toxicants Across the Placenta

The main function of the placenta is to protect the fetus against the passage of noxious substances from the mother.

Placentas in which the maximum numbers of cell layers are present (all six layers) most toxic chemicals pass the placenta by simple diffusion. The placenta also has biotransformation capabilities that may prevent some toxic substances from reaching the fetus.

Among the substances that cross the placenta by passive diffusion, more lipid-soluble substances rapidly attain a maternal-fetal equilibrium.

Many foreign substances can cross the placenta, and the same factors that dictate the passage of xenobiotics across biological membranes are important determinants of the placental transfer.

Xenobiotic transporters are differentially expressed in these various cells and contribute to the barrier function that restricts distribution of toxicants to the fetus. In particular, P-gp, Mrp2, and BCRP are expressed on the apical border of the Syncytiotrophoblast in placenta whereas Mrp1 is localized to the basolateral membranes of syncytiotrophoblasts and the fetal capillary endothelial cells.

One important consequence of placental transfer is that of transplacental carcinogenesis. In this case exposing the mother during gestation increases the likelihood of tumor development in the offspring later in life. The most well-known transplacental carcinogen

in humans is diethylstilbestrol(synthetic nonsteroidal estrogen) but other compounds such as the anti-viral drug zidovudine and inorganic arsenic

EXCRETION

Toxicants are eliminated from the body by several routes.

Urinary Excretion

Kidney most important organ for the excretion of xenobiotics because more chemicals are eliminated from the body by this route than by any other. Biotransformation to more water-soluble products to the excretion of xenobiotics through urine by the same mechanisms the kidney uses to remove the endproducts of intermediary metabolism from the body. The degree of plasma protein binding affects the rate of filtration because protein-xenobiotic complexes, particularly those bound to albumin, will not be filtered by the glomerulus. A toxicant filtered at the glomerulus may remain in the tubular lumen and be excreted with urine. Depending on the physicochemical properties of a compound, it may be reabsorbed across the tubular cells of the nephron back into the bloodstream. Toxicants with a high lipid/water partition coefficient are reabsorbed efficiently, whereas polar compounds and ions are excreted with urine. The pH of urine may vary but it is usually slightly acidic. Excretion of acids toxicants at higher urinary pH . For example, the treatment of phenobarbital and salicylate poisoning with sodium bicarbonate. In a similar manner, urinary acidification can be used to increase the excretion of a weak base like phencyclidine (PCP) in drug abusers.

Transport systems in the proximal tubule of the kidney:

Transporters expressed on the basolateral side of the renal

tubules include OATs, OCTs, and selected members of the organic anion transporting polypeptides (OATP). The OAT family mediates the renal uptake of organic acids such as PAH(paminohippurate) and is important in the renal exchange of dicarboxylates.

kidney are incompletely developed at birth the OATs is not fully developed at birth, so that some xenobiotics are eliminated more slowly in newborns than in adults, and therefore may be more toxic to newborns. For example, the clearance of penicillin by premature infants is only about 20% of that observed in older children.

If a toxicant binds to those small proteins, it can be carried into the proximal tubule cells and exert toxicity by pinocytosis at the brush border membrane.

Fecal Excretion

*Elimination of many xenobiotics is through feces Nonabsorbed Ingesta (varying proportions of nutrients and xenobiotics that are present in food or are ingested voluntarily (drugs) pass through the alimentary canal)

*The intestinal can secretion the toxicants in blood, which likely occurs by passive diffusion out of enterocytes or via exfoliation of intestinal cells during the normal turnover of this epithelium.

*Biliary Excretion: The biliary route of elimination is contributing to the fecal excretion of xenobiotics and is even more important for the excretion of metabolites. The liver plays an important role in removing toxic chemicals from blood after absorption from the GI tract. A compound can be extracted by the liver, thereby preventing its distribution to other parts of the body. The liver is also the main site for biotransformation of toxicants, and metabolites may be excreted directly into bile.

Foreign compounds excreted into bile are often divided into three classes on the basis of the ratio of their concentration in bile versus that in plasma.

Class A substances have a ratio of bile to plasma nearly 1and include sodium, potassium, glucose, mercury, thallium, cesium, and cobalt.

Class B substances have a ratio of bile to plasma greater than 1 Include bile acids, bilirubin, lead, arsenic, manganese, and many other xenobiotics.

Class C substances have a ratio of bile to plasma below 1 (e.g., inulin, albumin, zinc, iron, gold, and chromium).

Compounds rapidly excreted into bile are usually class B substances. However, a compound does not have to be highly concentrated in bile for biliary excretion to be of quantitative importance. For
example, mercury is not concentrated in bile, yet bile is the main route of excretion for this slowly eliminated substance.
Biliary excretion is regulated predominantly by xenobiotic transporters present on the canalicular membrane. Transporters present on the sinusoidal membranes of hepatocytes also contribute to hepatic uptake and efflux, and thereby contribute to hepatobiliary clearance of xenobiotics. There are four known transporters expressed on the canalicular membrane that are directly involved in biliary excretion. These include P-gp, Mrp2, BCRp, and BSEP.

P-gp, Mrp2, and Bcrp are important in the biliary excretion of many xenobiotics, whereas BSEP is critical for the secretion of bile and the regulation of bile flow. Mrp2 is extremely important in biliary excretion because it is largely responsible for the transport of organic anions including the glucuronide and glutathione conjugates of many xenobiotics. BCRP has particular affinity for sulfated conjugates of toxicants, whereas P-gp primarily transports cationic substrates into bile.

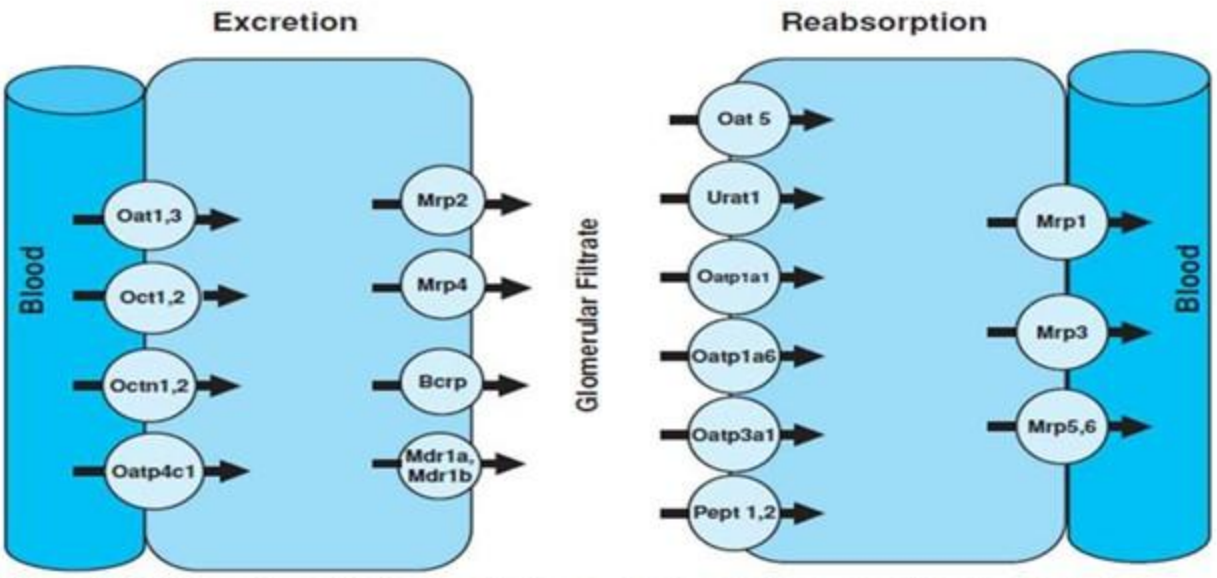

Figure 5-13. Schematic model showing the transport systems in the proximal tubule of the kidney.