ABSORPTION

The process by which toxicants cross body membranes to enter the bloodstream is referred to as absorption.

There are no specific systems or pathways for the sole purpose of absorbing toxicants.

Xenobiotics penetrate membranes during absorption by the same processes as do biologically essential substances such as oxygen, foodstuffs, and other nutrients. The main sites of absorption are the GI tract, lungs, and skin.

Absorption of Toxicants by the Gastrointestinal Tract

The GI tract is one of the most important sites where toxicants are absorbed.

Many environmental toxicants enter the food chain and are absorbed together with food from the GI tract.

This site of absorption is also particularly relevant to toxicologists because accidental ingestion is the most common route of unintentional exposure to a toxicant (especially for children) and intentional overdoses most frequently occur via the oral route.

Absorption of toxicants can take place along the entire GI tract, even in the mouth and the rectum.

If a toxicant is an organic acid or base, it tends to be absorbed by simple diffusion in the part of the GI tract where it exists in its most lipid-soluble (nonionized) form.

Because gastric juice is acidic (pH about 2) and the intestinal contents are nearly neutral, the lipid solubility of weak organic acids or bases can differ markedly in these 2 areas of the GI tract.

The Henderson– Hasselbalch equations determine the fraction of a toxicant that is in the nonionized (lipid-soluble) form and estimate the rate of absorption from the stomach or intestine.

$$pH = pK_a + \log \frac{[\text{ionized}]}{[\text{nonionized}]}$$

$$pH = pK_a - \log \frac{[\text{nonionized}]}{[\text{ionized}]}$$

However, the Henderson–Hasselbalch calculations are not an absolute determination of absorption because other factors—including the mass action law, surface area, and blood flow rate—have to be taken into consideration in examining the absorption of weak organic acids or bases.

The mammalian GI tract has numerous specialized transport systems (carrier-mediated) for the absorption of nutrients and electrolytes.

The absorption of some of these substances is complex and depends on several additional factors.

For example, iron absorption is determined by the need for iron and takes place in 2 steps.

Iron accumulates within the mucosal cells as a protein–iron complex termed ferritin. When the concentration of iron in blood drops below normal values, some iron is liberated from the mucosal stores of ferritin and transported into the blood.

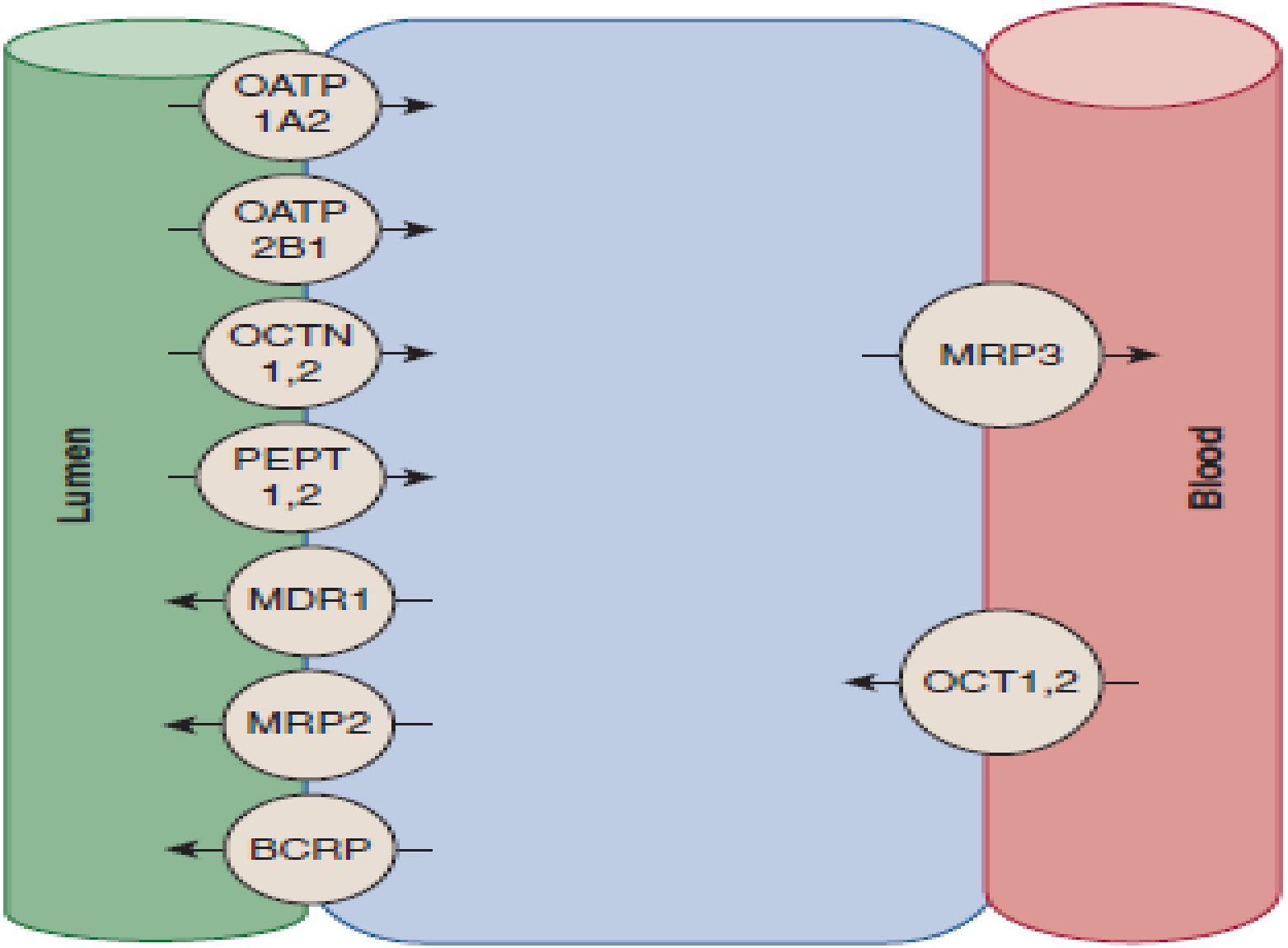
Calcium is also absorbed by a 2-step process: absorption from the lumen followed by exudation into the interstitial fluid. Vitamin D is required for both steps of calcium transport.

Some xenobiotics are absorbed by the same specialized transport systems for nutrients, thereby leading to potential competition or interaction.
For example, 5-fluorouracil is absorbed by the pyrimidine transport system, thallium utilizes the system that normally absorbs iron, lead can be absorbed by the calcium transporter, and cobalt and manganese compete for the iron transport system.

Numerous xenobiotic transporters are expressed in the GI tract where they function to increase or decrease absorption of xenobiotics.
In humans, OATP1A2 and OATP2B1 are the most abundant and important members of this family that are expressed in the intestine, although OATP3A1 and OATP4A1 have also been identified.

OCTN1 and OCTN2 are also present in the intestine, with OCTN2 specifically involved in the uptake of carnitine. The peptide transporter, PEPT1 is highly expressed in the GI tract and mediates the transport of peptide-like drugs such as antibiotics, particularly those containing a β-lactam structure. The OCTs, particularly OCT1 and OCT2, also contribute to xenobiotic uptake into enterocytes, but are expressed on the basolateral membrane.
The primary active efflux transporters such as MDR1, MRP2, and BCRP are also expressed on enterocyte brush-border membranes where they function to excrete their substrates into the lumen, thereby decreasing the net absorption of xenobiotics. MRP3 is also found in the intestine, but is localized to the basolateral membrane.
The expression of the intestinal transporters varies across the GI tract.
For example, MDR1 expression increases from the duodenum to colon, whereas MRP2 and most of the uptake transporters are expressed most highly in the duodenum and decrease to in the terminal ileum and colon.

Figure: Schematic model showing the important xenobiotic transport systems present in the human gastrointestinal tract.


OATP 1A2
OATP 2B1
OCTN 1,2
PEPT 1,2
MDR1
MRP2
BCRP
MRP3
OCT1,2
Lumen
Blood

Particles and particulate matter can also be absorbed by the GI epithelium. In this case, particle size is a major determinant of absorption, whereas factors such as the lipid solubility or ionization characteristics are less important.
For particles, size is inversely related to absorption such that absorption increases with decreasing particle diameter.

This explains why metallic mercury is relatively nontoxic when ingested orally and why powdered arsenic was found to be significantly more toxic than its coarse granular form. Large particles (greater than about 20 μm in diameter) enter intestinal cells by pinocytosis, a process that is much more prominent in newborns than in adults.

Additionally, surface characteristics of nanoparticles contributes to their absorption, with hydrophobic, nonionized particles being more extensively absorbed than those modified to possess an ionized surface as is the case with larger particles, the gut-associated lymphoid tissue appears to be the predominant absorption pathway for nanoparticles from the GI tract.

Overall, the absorption of a toxicant from the GI tract depends on its physical properties, including lipid solubility and its dissolution rate.

In addition to the characteristics of the compounds themselves, there are numerous additional factors relating to the GI tract itself that influence the absorption of xenobiotics.

These factors include pH, the presence of food, digestive enzymes, bile acids, and bacterial microflora in the GI tract, along with the motility and permeability of the GI tract.

A toxicant may be hydrolyzed by stomach acid, biotransformed by enzymes in the GI tract or modified by the resident microflora to new compounds with a toxicity different from that of the parent compound.

For example, snake venoms, which are proteinaceous moieties, are much less toxic by the oral route relative to intravenous exposure because they are degraded by digestive enzymes of the GI tract.?

Intestinal microflora can also influence absorption and toxicity of compounds.

For example, a variety of nitroaromatic compounds are reduced by intestinal bacteria to potentially toxic and carcinogenic aromatic amines.

It has also been shown that ingestion of well water with high nitrate content produces methemoglobinemia much more frequently in infants than in adults.

In this case, bacteria in the GI tract convert nitrate to nitrite, increasing the likelihood of methemoglobinemia.

Infants are more susceptible to methemoglobinemia because the higher pH of the neonatal GI tract is permissive for the growth of bacteria (such as *Escherichia coli*) that convert nitrate to nitrite

One example wherein intestinal microflora reduce the potential toxicity is that of the mycotoxin, deoxynivalenol, which is found in numerous grains and foodstuffs. Strict anaerobes detoxify this compound leading to the absorption of a less toxic reductive metabolite.

Agents such as the chelator, ethylenediaminetetraacetic acid (EDTA), increase absorption of some toxicants by increasing intestinal permeability.

Before a chemical enters the systemic circulation, it can be biotransformed by the cells in the GI tract or extracted by the liver and excreted into bile with or without prior biotransformation.

This phenomenon of the removal of chemicals before entrance into the systemic circulation is referred to as presystemic elimination or first-pass effect. Chemicals that have a high first-pass effect will appear to have a lower absorption because they are eliminated as quickly as they are absorbed. Furthermore, metal ions can affect absorption of other ions.

For example, cadmium decreases the absorption of zinc and copper, calcium decreases cadmium absorption, and magnesium decreases absorption of fluoride.

Consumption of grapefruit juice can also influence GI absorption through the actions of naringin, a flavonoid that inhibits the function of several transporters including MDR1 and OATP1A2.

By reducing MDR1-dependent efflux, grapefruit juice increases GI absorption of numerous pharmaceutical agents (such as calcium-channel blockers and cholesterol-lowering agents),

and, in some cases, this effect leads to toxic or adverse reactions resulting from increased exposure to the drugs.

Absorption of Toxicants by the Lungs

Toxic responses to chemicals can occur from absorption following inhalation exposure.

Relevant examples include carbon monoxide poisoning and silicosis, an important occupational disease. These toxicities result from absorption or deposition of airborne poisons in the lungs.

A major group of toxicants that are absorbed by the lungs are gases (eg, carbon monoxide, nitrogen dioxide, and sulfur dioxide),

vapors of volatile or volatilizable liquids (eg, benzene and carbon tetrachloride), and aerosols.