TOXICOTHERAPY

INTRODUCTION TO TOXICOKINETICS

Xenobiotic Absorption and Toxicokinetic Processes:

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Toxicotherapy PHAR 421

Semester one

Week number 3

27/10/2024

Objectives

The students will be able to

1.Understand the ADME Framework

1. Students will be able to define and explain the four key processes of toxicokinetics: absorption, distribution, metabolism, and excretion, and understand their significance in determining the toxic effects of substances in the body.

2.Identify Mechanisms of Xenobiotic Absorption

1. Students will learn the different pathways of xenobiotic absorption, including passive diffusion, active transport, facilitated transport, and pinocytosis, and how these mechanisms affect the onset and extent of toxicity.

Objectives

The students will be able to

1.Explain the Factors Affecting Distribution

Students will recognize the factors that influence how xenobiotics are distributed throughout the body, such as tissue perfusion, molecular size, plasma protein binding, and the concept of volume of distribution (Vd).

2.Describe Metabolic Pathways in Toxicology

Students will be able to differentiate between Phase I and Phase II metabolic reactions, understand the role of the liver and other organs in xenobiotic metabolism, and explain how biotransformation affects toxicity.

3.Analyze the Processes of Excretion and Elimination

Students will learn the various routes of xenobiotic excretion (renal, hepatic, pulmonary, etc.) and the principles of first-order and zero-order elimination, with the ability to apply these concepts in clinical and toxicological contexts.

Definition Clinical toxicology :

•**Clinical toxicology** is the study of the toxic or adverse effects of agents, such as drugs and chemicals, in the body. Most of these agents are usually given to individuals in order to give relief for symptoms or to treat and prevent diseases.

•Or

In clinical toxicology,

- In clinical toxicology, understanding the factors related to both the **patient** and the **poison** is crucial for proper **diagnosis and treatment.**

- Understanding these factors helps clinicians make informed decisions on antidotes, supportive care, and treatment plans for poisoned patients.

: Introduction to Xenobiotics

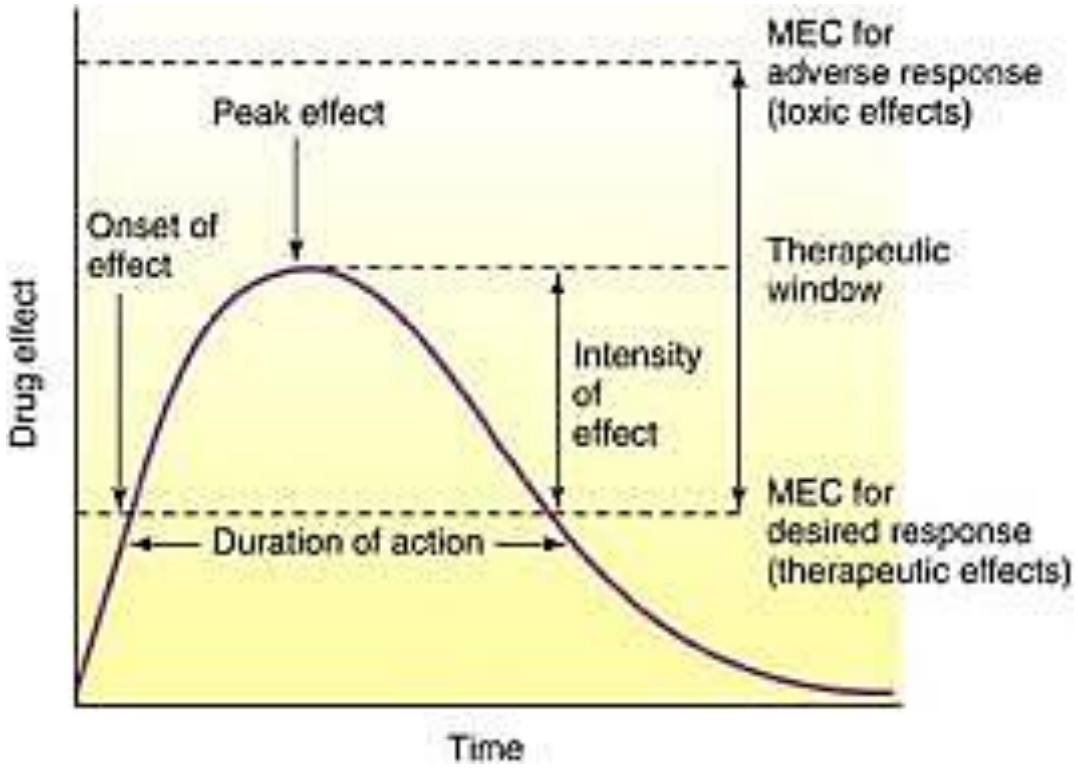
- **Definition**: Xenobiotics are foreign substances not naturally produced in the body.

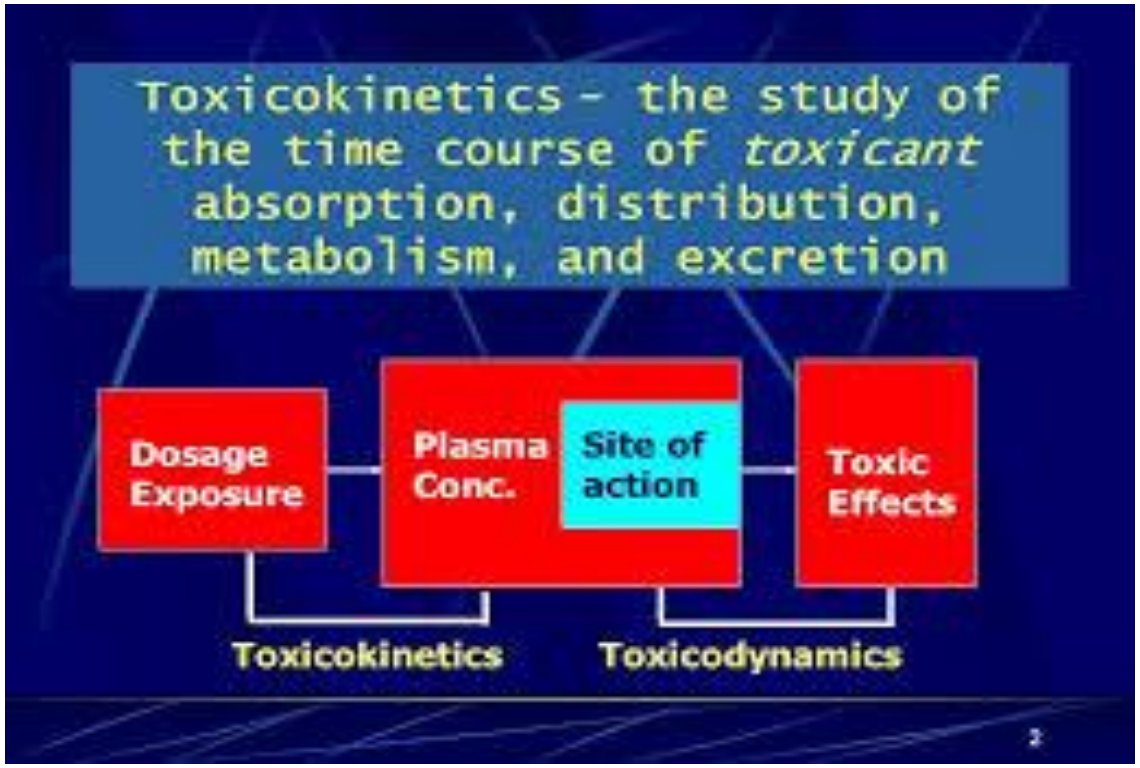
- **Examples**: Drugs, environmental pollutants, food additives.

- **Importance**: Studying absorption helps predict a xenobiotic’s behavior, potential toxicity, and therapeutic impact.

Outline

- **Introduction to Toxicokinetics**
- Definition: Study of the time course of toxicant absorption, distribution, metabolism, and excretion (ADME)
- Key Concepts: Dosage, Exposure, Toxic Effects, Plasma Concentration, Site of Action

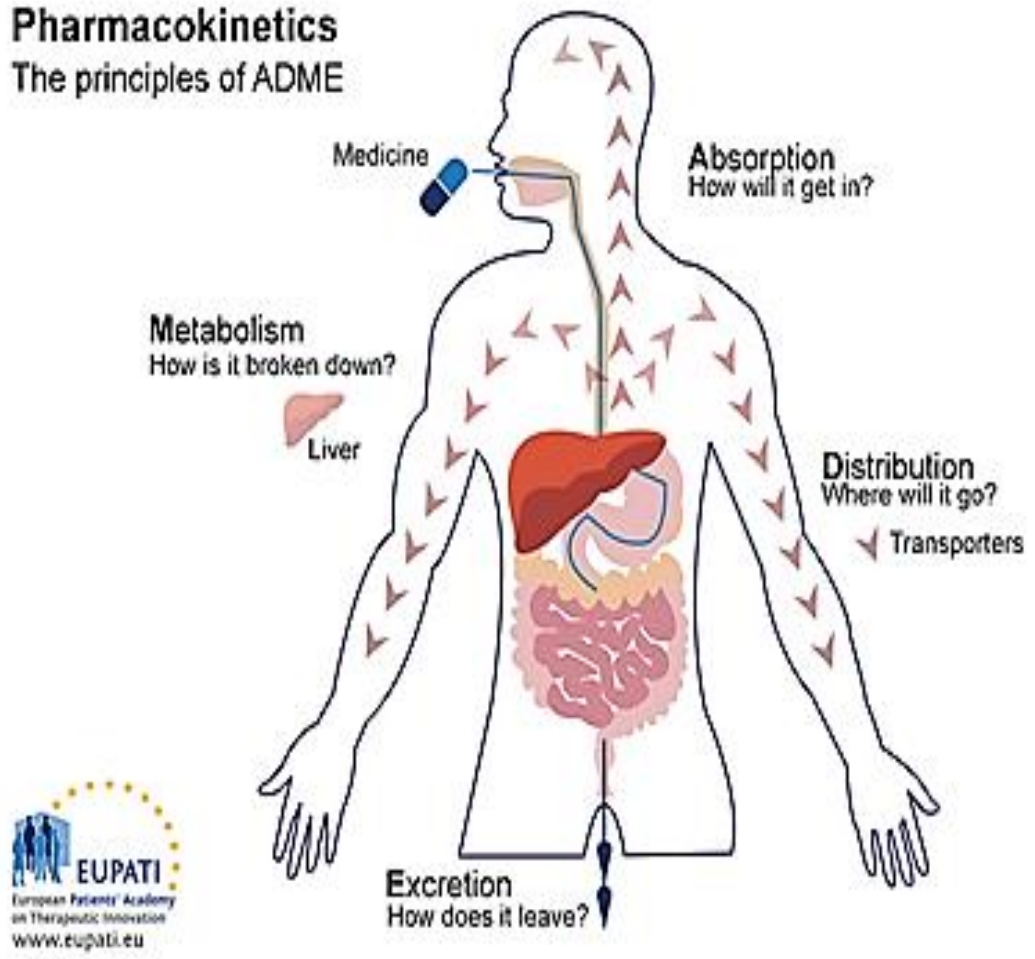




. Definition and Importance

- Understanding the time course of toxicant absorption, distribution, metabolism, and excretion (ADME).

- Key concepts:
- Dosage, Exposure, Toxic Effects, Plasma Concentration, Site of Action.



Pharmacokinetics

- **Introduction to Pharmacokinetics**
- Pharmacokinetics is the branch of pharmacology that studies how drugs move through the body. It encompasses four main processes: absorption, distribution, metabolism, and excretion (ADME).

Pharmacokinetics is the study of how drugs move through the body and encompasses the processes of **ADME**:

- **Absorption:** The process by which a drug enters the bloodstream from its site of administration.
- **Distribution**: The dispersion of the drug throughout the body's fluids and tissues.
- **Metabolism:** The chemical transformation of the drug, primarily in the liver, to facilitate its elimination.
- **Excretion:** The removal of the drug from the body, mainly via the kidneys (urine) or bile (feces).
- These principles help determine the onset, duration, and intensity of a drug's action.

Toxicokinetics Key Concepts

- Relationship between dose and plasma concentration.
- Impact of toxicokinetics on toxic effects and therapeutic interventions.
- By understanding **Toxicokinetics**, healthcare professionals can optimize drug dosing, enhance therapeutic outcomes, and minimize potential side effects, ensuring safe and effective treatment for patients.

Toxicokinetics,

- Toxicokinetics, which involves the ADME processes for toxic substances, affects the way toxic effects manifest and how interventions are planned.

- The absorption, distribution, metabolism, and excretion of toxins determine their concentration in target tissues and the duration they stay in the body, influencing their toxic impact.

Understanding Toxicokinetics

- Understanding toxicokinetics helps in developing effective therapeutic strategies, such as:
- **Optimizing antidotes or treatments** that can enhance metabolism or excretion.
- **Adjusting the timing and dosage** of interventions to counteract toxic effects efficiently.
- **Identifying vulnerable populations** (e.g., pregnant women) and specific tissues protected by barriers (e.g., blood-brain barrier).
  - This knowledge supports the development of targeted and safe therapeutic responses to toxic exposures.

Absorption of Xenobiotics

- **Toxicokinetic Processes**
  - **ADME Framework**: Absorption, Distribution, Metabolism, Excretion.
- **Mechanisms of Absorption**
  - **Membrane Barriers**: Skin, Gastrointestinal (G.I.) Tract, Lungs.
  - **Permeation Methods**: Passive Diffusion, Active Transport, Facilitated Transport, Pinocytosis.
- **Factors Influencing Absorption**
  - Permeability factors: Lipid solubility, pH, pK, Concentration Gradient.
  - Physical factors: Blood flow, Dissolution, Gastric stability.
  - **Bioavailability**: Fraction of administered dose reaching systemic circulation.
  - **First Pass Effect**: Metabolism differences between gastric and intestinal absorption.

- **Title**: Xenobiotic Absorption

- Understanding How Foreign Compounds Enter the Body

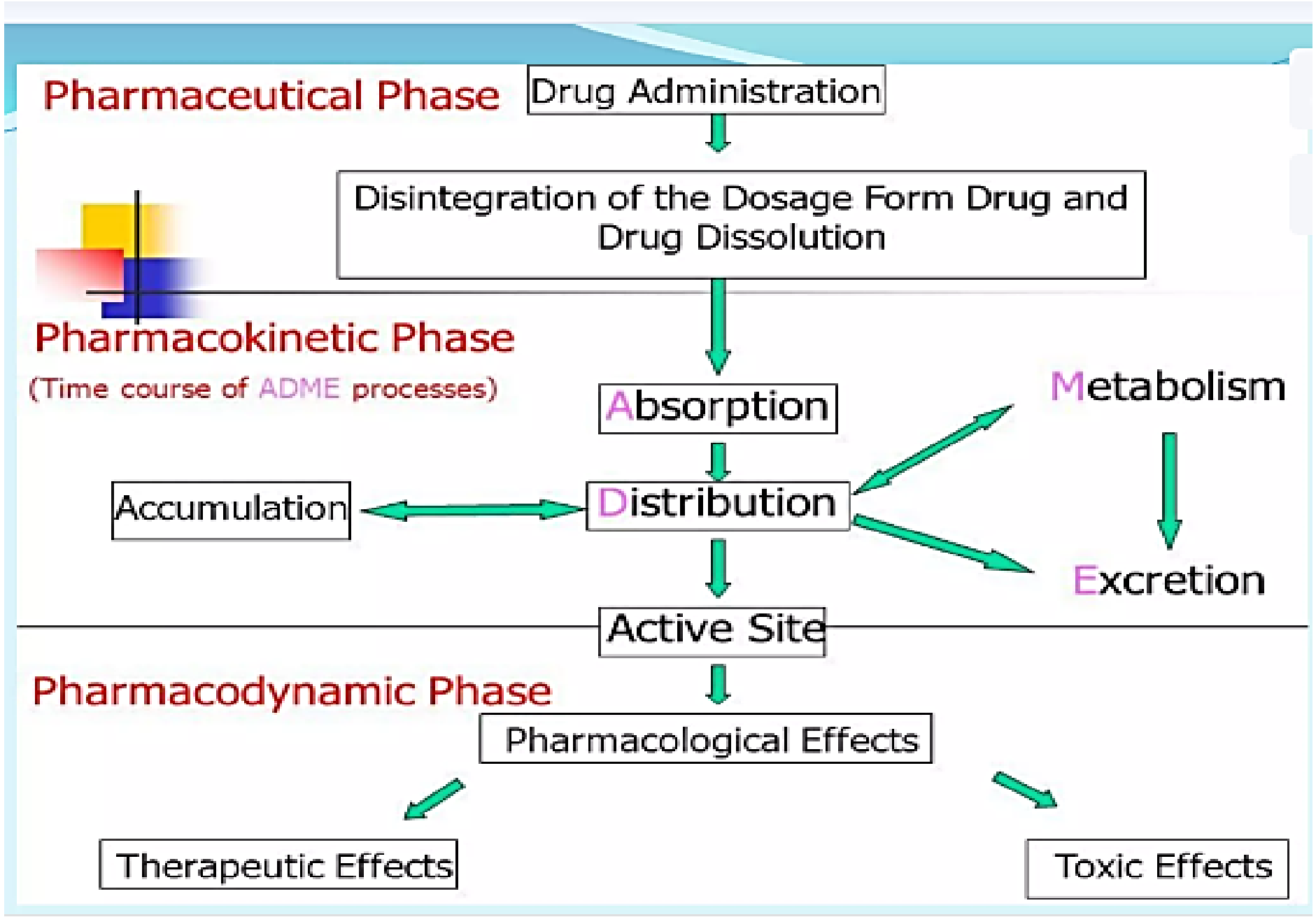
  - **Mechanisms of Absorption**: Absorption mechanisms refer to how substances move into the bloodstream after exposure. This can happen through various membrane barriers:

Mechanisms of Absorption

- **Passive Diffusion**: Movement along concentration gradient; common for lipid-soluble xenobiotics.

- **Active Transport**: Carrier proteins assist some compounds that resemble natural molecules.

- **Facilitated Diffusion**: Transport across membranes with protein assistance.


Pharmaceutical Phase
Drug Administration
Disintegration of the Dosage Form Drug and Drug Dissolution
Pharmacokinetic Phase
(Time course of ADME processes)
Absorption
Metabolism
Accumulation
Distribution
Excretion
Active Site
Pharmacodynamic Phase
Pharmacological Effects
Therapeutic Effects
Toxic Effects

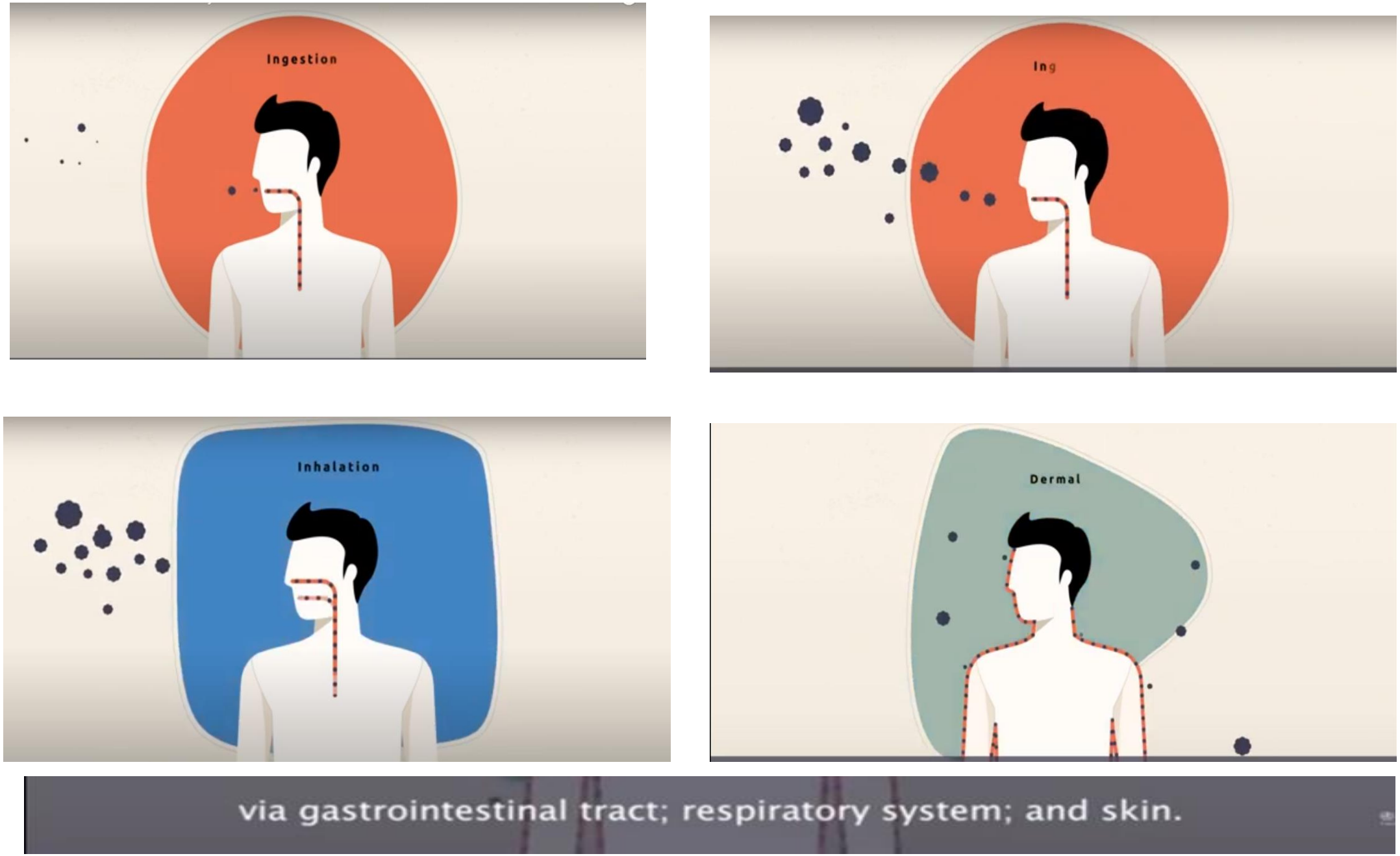


Image Illustration of absorption pathways (e.g., lungs, skin, GI tract)

Mechanisms of Absorption:

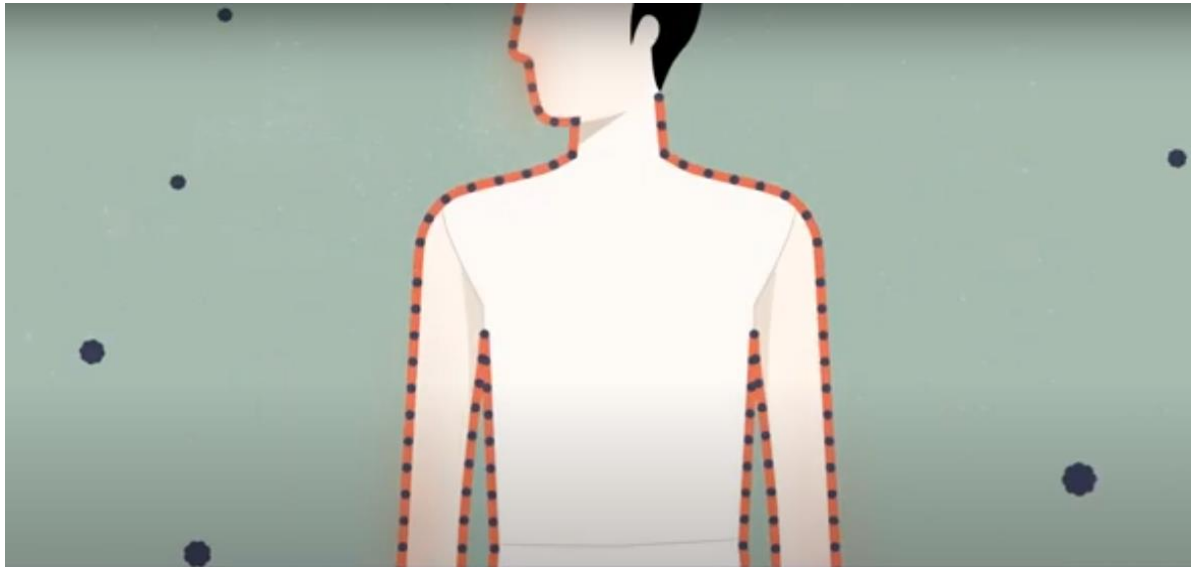
1. **Skin**: Acts as a protective barrier, but certain toxins can penetrate via diffusion, especially if they are lipid-soluble or the skin is damaged.
2. **Gastrointestinal (G.I.) Tract**: Substances taken orally can be absorbed through the intestinal lining, where active transport and passive diffusion help toxins pass through the gut wall.
3. **Lungs**: Gaseous or airborne toxins can be absorbed via the alveoli in the lungs, which have a thin membrane and rich blood supply, facilitating rapid entry into the bloodstream.

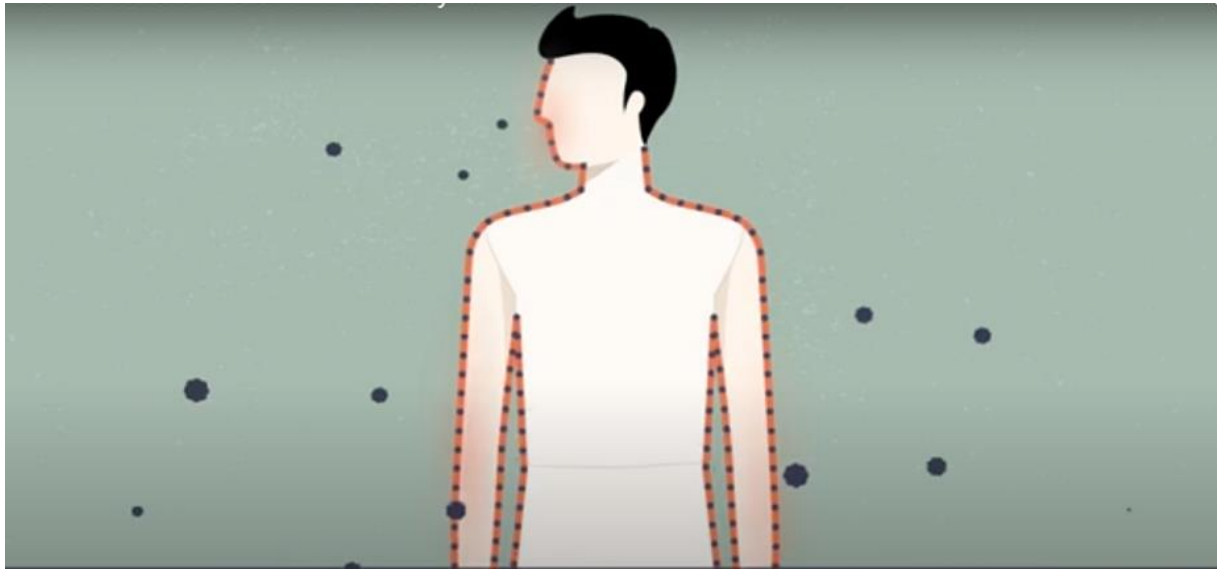
1. Skin route of absorption

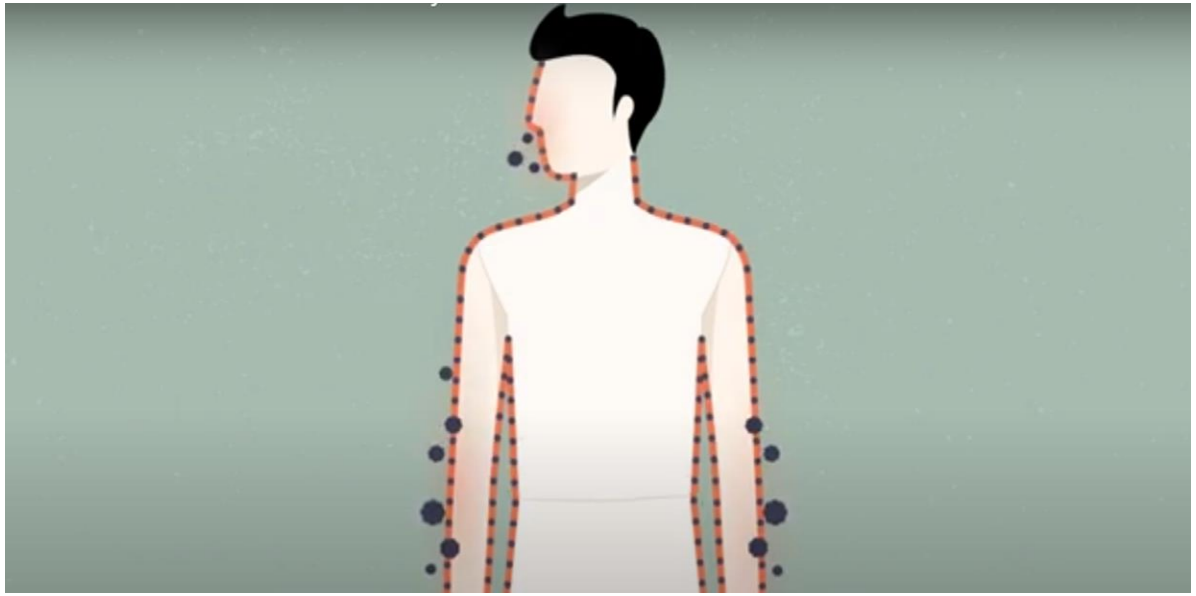
- The dermal route of absorption provides one of the most effective cellular barriers to external substances due to the structure of the skin, especially the outermost layer, the stratum corneum.

- This layer is composed of tightly packed dead skin cells surrounded by lipids, which create a barrier that is difficult for most substances to penetrate. However, certain chemicals, particularly those that are lipid-soluble or small in size, can penetrate this barrier and be absorbed into the bloodstream.

- The skin's barrier function plays a crucial role in protecting against potential toxins and pathogens.

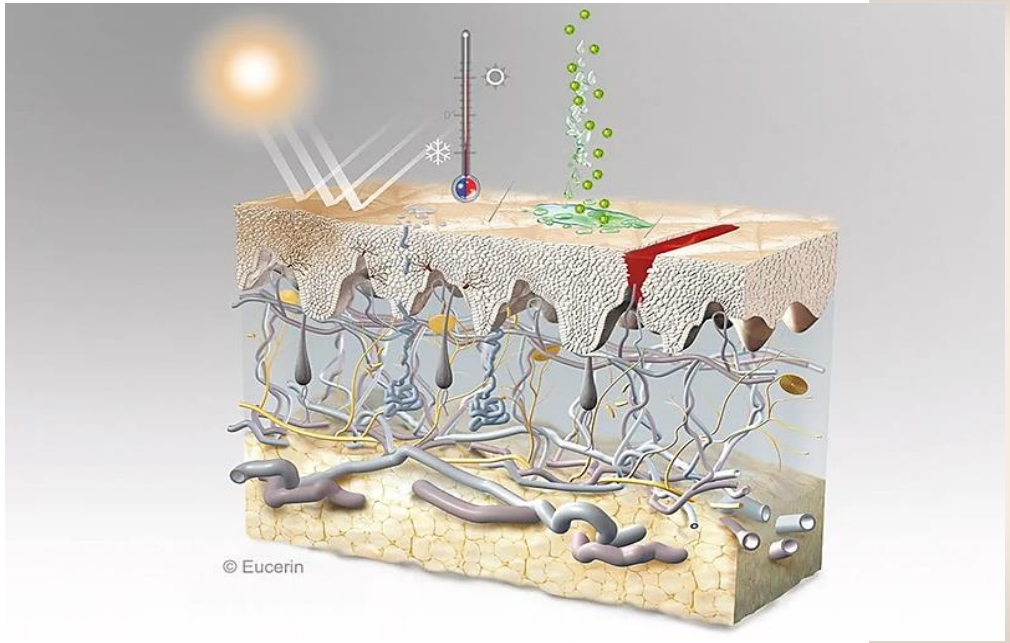


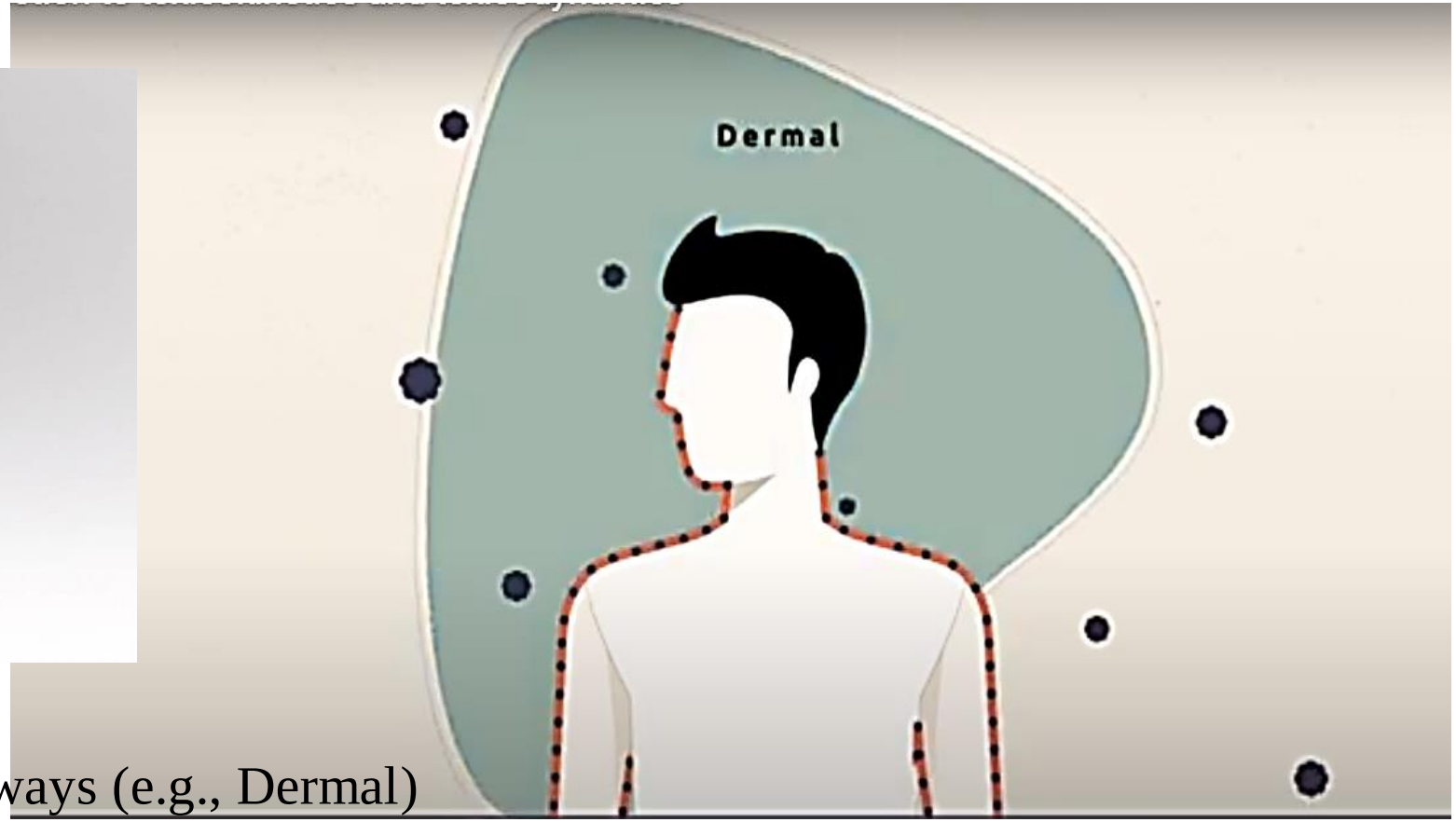




- Images: illustration the dermal root of absorption of provide the greatest cellular barrier

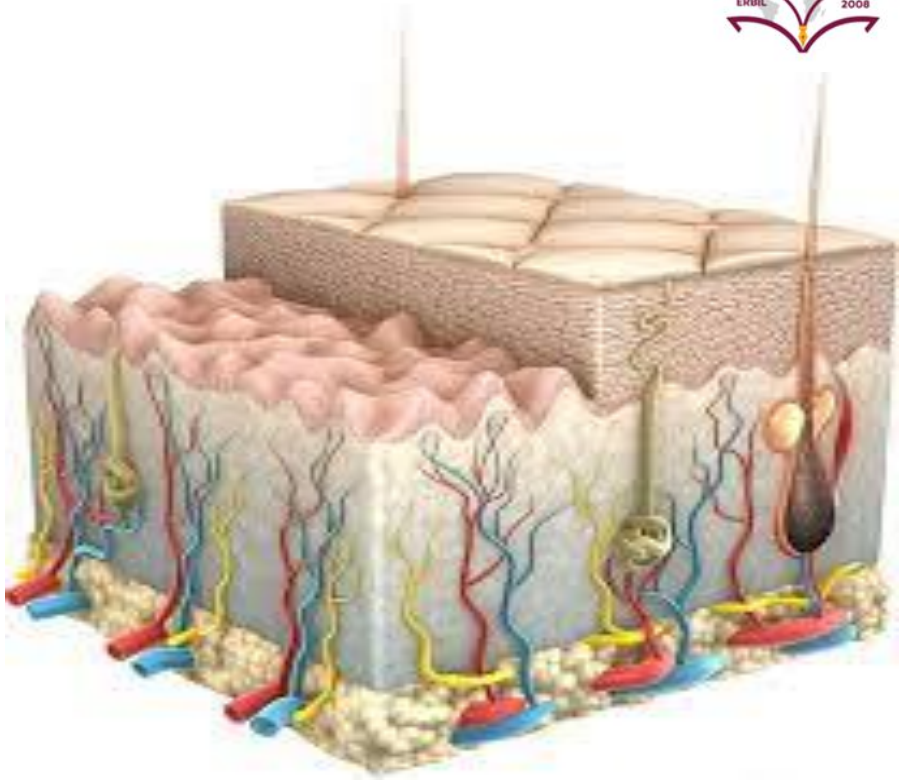
- **1. Skin as a Protective Barrier**: The skin acts as the body's first line of defense, preventing the entry of most harmful substances. Its structure includes multiple layers, such as the outermost **stratum corneum**, which is composed of tightly packed dead cells with a lipid matrix, making it highly effective at blocking water-soluble substances.





- **Image**: Illustration of absorption pathways (e.g., Dermal)

Skin as a Protective Barrier:



- However, **lipid-soluble toxins** can penetrate this barrier more easily because they dissolve in and pass through the lipid layers of the skin. If the skin is damaged or compromised (e.g., through cuts or abrasions), it becomes more permeable, allowing more substances, including potentially harmful toxins, to pass through via **diffusion**.

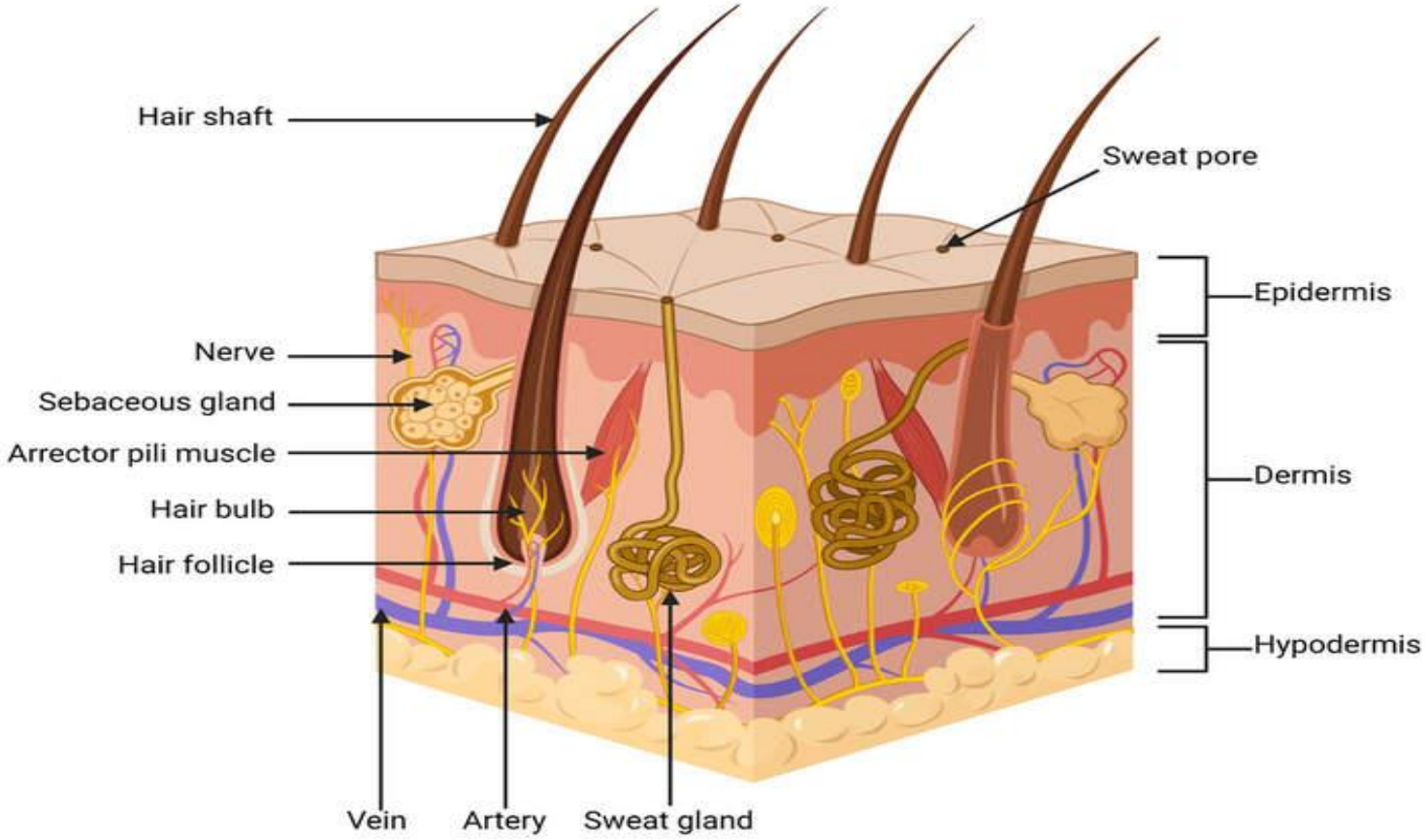


Image: illustration the layers of the skin

Factors Influencing Penetration of the Stratum Corneum

1. Thickness

- The thickness of the stratum corneum varies greatly with regions of the body.

- The stratum corneum of the palms and soles is very thick (400-600 μM) whereas that of the arms, back, legs, and abdomen is much thinner (8-15 μM). The stratum corneum of the axillary (underarm) and inguinal (groin) regions is the thinnest with the scrotum especially thin.

- As expected, the ability of toxicants to penetrate that stratum corneum inversely relates to the thickness of the epidermis.

2. Damage

- Any process that removes or damages the stratum corneum can enhance penetration of a xenobiotic.

- Abrasion, scratching, or cuts to the skin will make it more penetrable.

- Some acids, alkalis, and corrosives can injure the stratum corneum and make it easier for agents to penetrate this layer.

- The most prevalent skin conditions that enhance dermal absorption are skin burns and dermatitis.

3. Passive Diffusion

- Toxicants move across the stratum corneum by passive diffusion. There are no known active transport mechanisms functioning within the epidermis.

- Polar and nonpolar toxicants diffuse through the stratum corneum by different mechanisms:
- **Polar compounds,** which are water soluble, appear to diffuse through the outer surface of the hydrated keratinized layer.

- **Nonpolar compounds,** which are lipid soluble, dissolve in and diffuse through the lipid material between the keratin filaments.

4. Water

Water plays an important role in dermal absorption. Normally, the stratum corneum is partially hydrated (approximately 7% by weight).

Penetration of polar substances is about 10 times more effective than when the skin is completely dry.

Additional hydration on the skin's surface increases penetration by 3–5 times, which further increases the ability of a polar compound to penetrate the epidermis.

Other Sites of Dermal Absorption

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

- However, since these structures represent only a very small percentage of the skin's total surface area, they are not ordinarily viewed as important contributors to dermal absorption.

Transdermal drug delivery (TDD).

- For transdermal drug delivery (TDD), the big challenge is the barrier property of skin, especially the stratum corneum (SC). Different methods have been developed to enhance the penetration of drugs through the skin, with the most popular approach being the use of penetration enhancers (PEs), including natural terpenes.
- Terpenes, a large and diverse class of organic compounds produced by a variety of plants, are a very safe and effective class of PEs.
- **Limonene** is one example of a terpene used as a penetration enhancer. The main mechanism for the penetration enhancing action of terpenes is the interaction with SC intercellular lipids. The key factor affecting the enhancement is the lipophilicity of the terpenes and the drug molecules.

Dermis and Subcutaneous Tissue

- *Key Point*: The skin's deeper layers facilitate easier diffusion, leading to systemic absorption.

- **Skin Absorption Pathway**
- Once a substance penetrates the **stratum corneum**, it advances into:
  - **Lower epidermis, dermis, and subcutaneous tissue**.
- These layers:
  - Are less resistant to further diffusion.
  - Contain a **porous, nonselective aqueous medium**.
  - Allow penetration via **simple diffusion**.
- Toxicants that pass through the stratum corneum:
  - Readily diffuse through the remaining skin.
  - Enter the **circulatory system** via:
    - **Venous and lymphatic capillaries** in the dermis.

Dermal Exposure to Semivolatile Organic Compounds (SVOCs)

•**Key Insight: Understanding dermal exposure mechanisms helps assess total SVOC absorption and its health implications.**

•**SVOCs Exposure**:

•Dermal absorption is a significant route for SVOCs.
•**Air-to-skin uptake** can be similar to or exceed inhalation intake for many indoor SVOCs.

•**Examples of SVOCs**:

1, Butylated hydroxytoluene (BHT)
2. Chlordane
3. Chlorpyrifos
4. Diethyl phthalate
5. Nicotine (free-base form) and some **Other chemicals**

Image illustration Examples of SVOCs from consumer goods

Importance of Dermal Exposure to SVOCs in Health Assessments

- *Key Insight*: Understanding dermal exposure and its distinct impact compared to other pathways is crucial for accurate health risk assessments.

- **Undervalued Pathway**:
  - **Dermal exposure** to indoor SVOCs has been historically underestimated in exposure assessments.
- **Growing Awareness**:
  - Increased recognition by **exposure scientists, risk assessors,** and **public health officials** regarding its significance and health impacts.
- **Pathway-Specific Health Implications**:
  - **Direct skin absorption** allows SVOCs to bypass gastrointestinal detoxification (e.g., stomach, intestines, liver).
  - **Potential for higher toxicity** due to unfiltered entry into the bloodstream compared to ingestion.

Homework

- Write short assignment about the flowing titles

1. The effect of **particles and dust** on dermal exposure.
2. Clothing and bedding as transport vectors.
3. Hair follicles as potential shunts for transport through the epidermis.

Homework. Write a short essay on transdermal drug delivery (TDD).

- **Key Factor: as** The lipophilicity of both the terpene enhancers and drug molecules influences effectiveness
- **Transdermal Drug Delivery (TDD) Challenge**: The main barrier to TDD is the stratum corneum (SC) of the skin.
- **Enhancement Methods**: Various strategies have been developed to boost drug penetration.
- **Penetration Enhancers (PEs)**:
  - Common solution: Use of natural terpenes.
  - **Example**: Limonene, known for safety and efficacy.
- **Mechanism of Terpenes**: Interact with SC intercellular lipids to enhance drug permeation.

Homework

Write a short essay on the use of nicotine patches as a form of transdermal drug delivery.

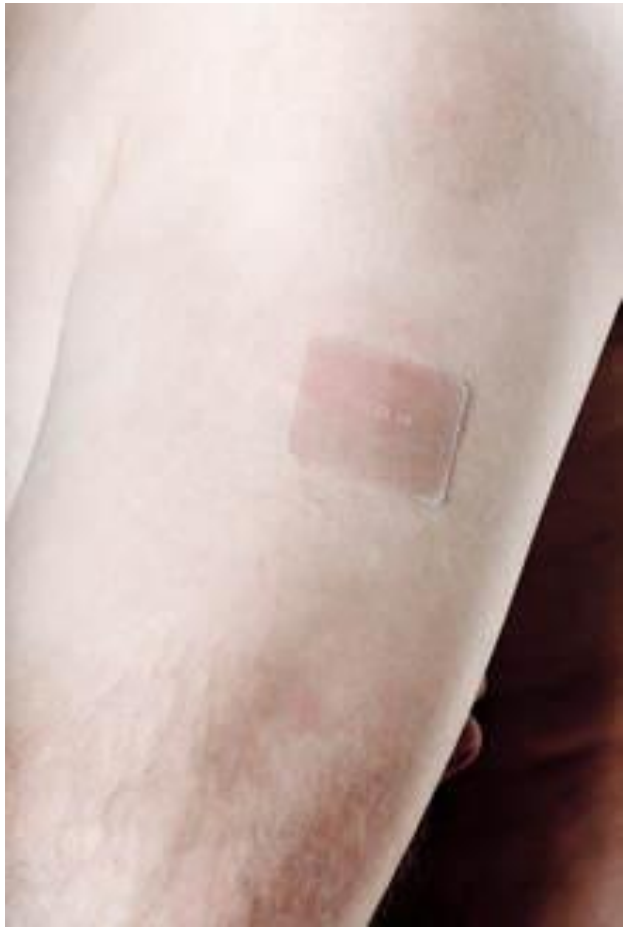


Image illustration the Nicotine patch

The **Gastrointestinal (G.I.)**

- The **Gastrointestinal (G.I.) Tract** plays a key role in the absorption of substances taken orally. Toxins and other compounds can pass through the intestinal lining by two main processes:

1. **Passive Diffusion**: Molecules move from an area of higher concentration to an area of lower concentration without the need for energy. This process is generally used by non-polar, lipid-soluble substances that can easily pass through the cell membrane.

2. **Active Transport**: This process requires energy and is used for molecules that need assistance to cross the intestinal wall. Carrier proteins in the membrane help transport these molecules against a concentration gradient.

- Together, these mechanisms allow various substances, including toxins, to pass through the gut wall and enter the bloodstream, where they can then be distributed throughout the body.

Absorption pathways in GI tract)

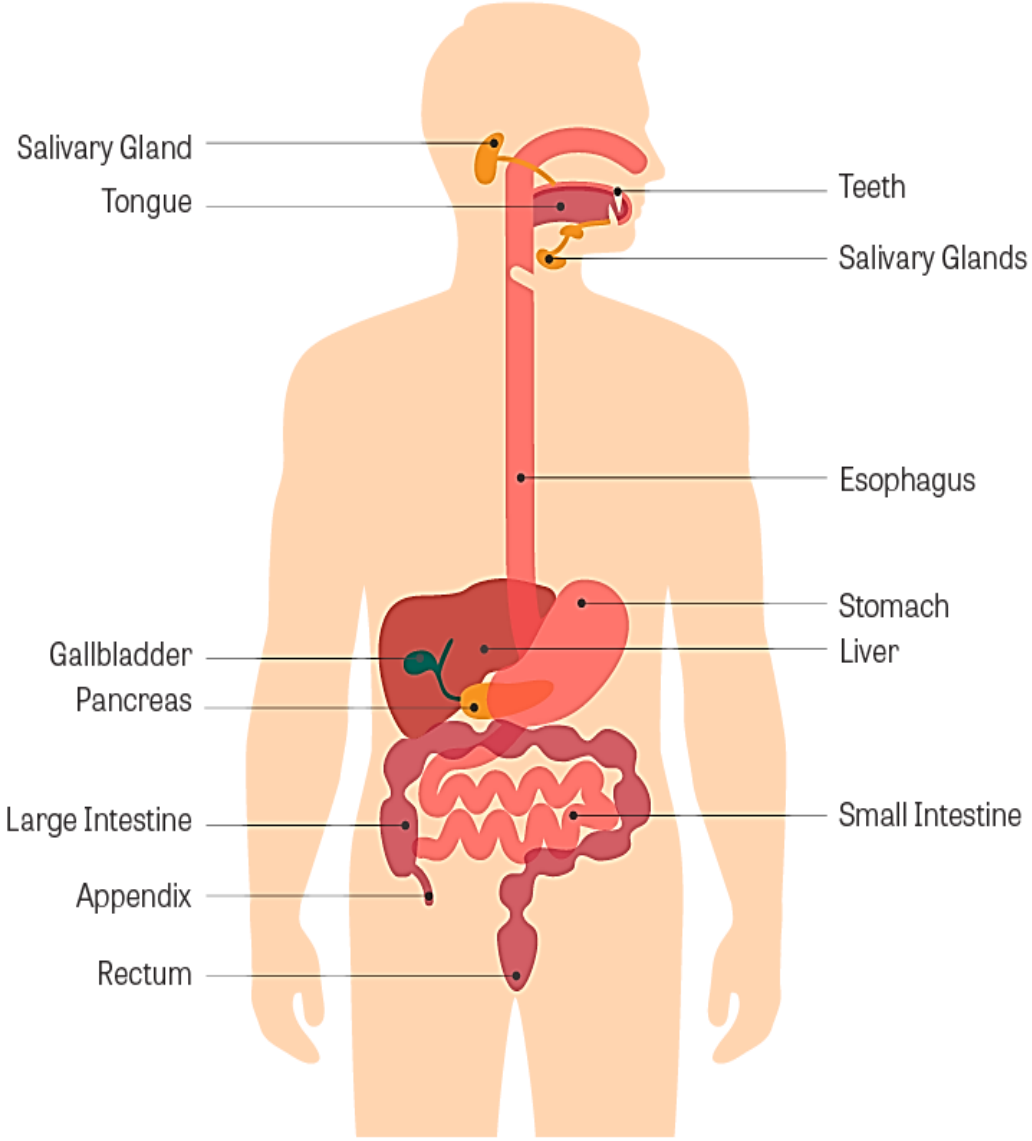


Image illustration the anatomy of gastrointestinal tract

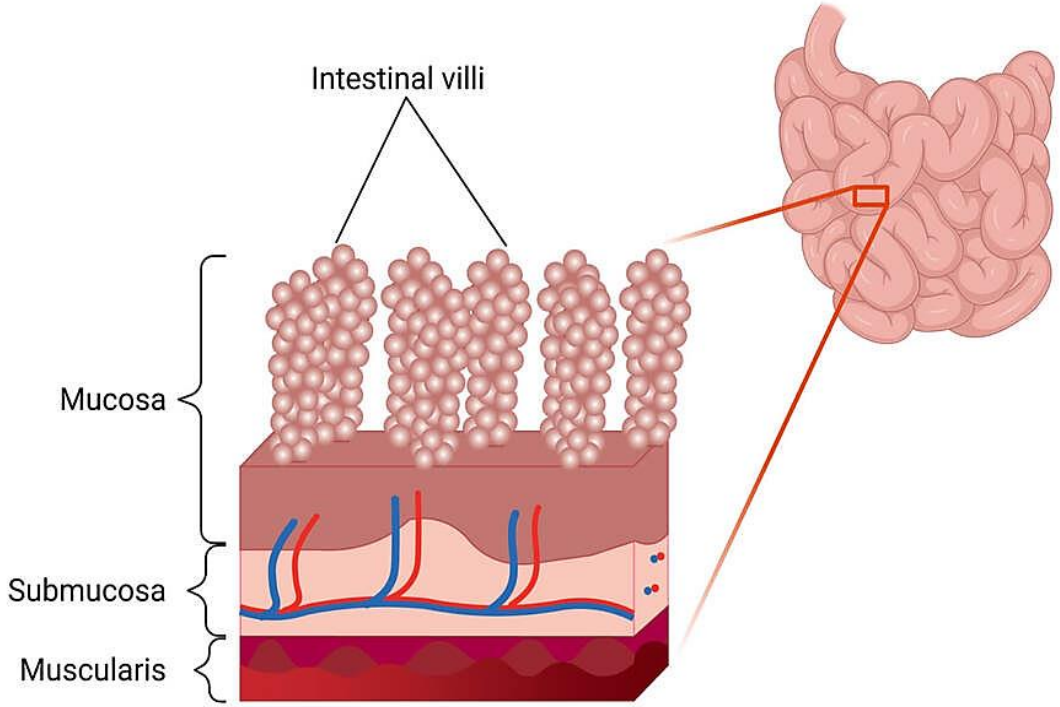
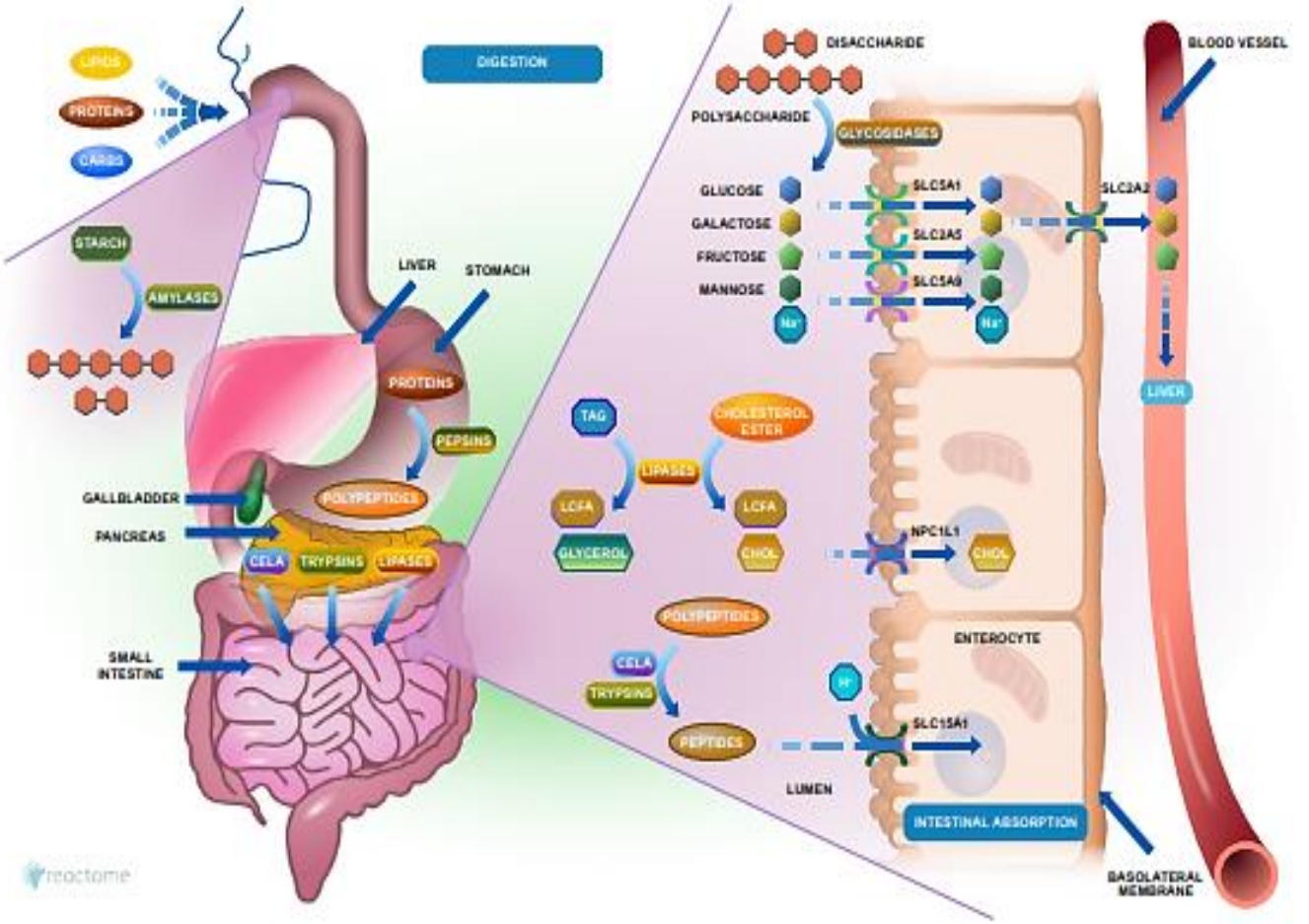
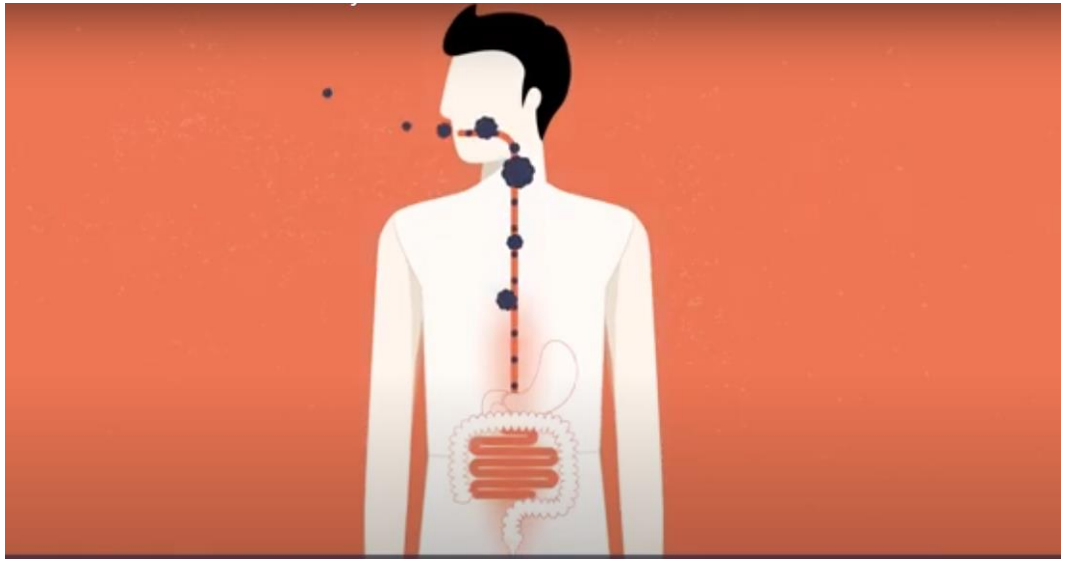
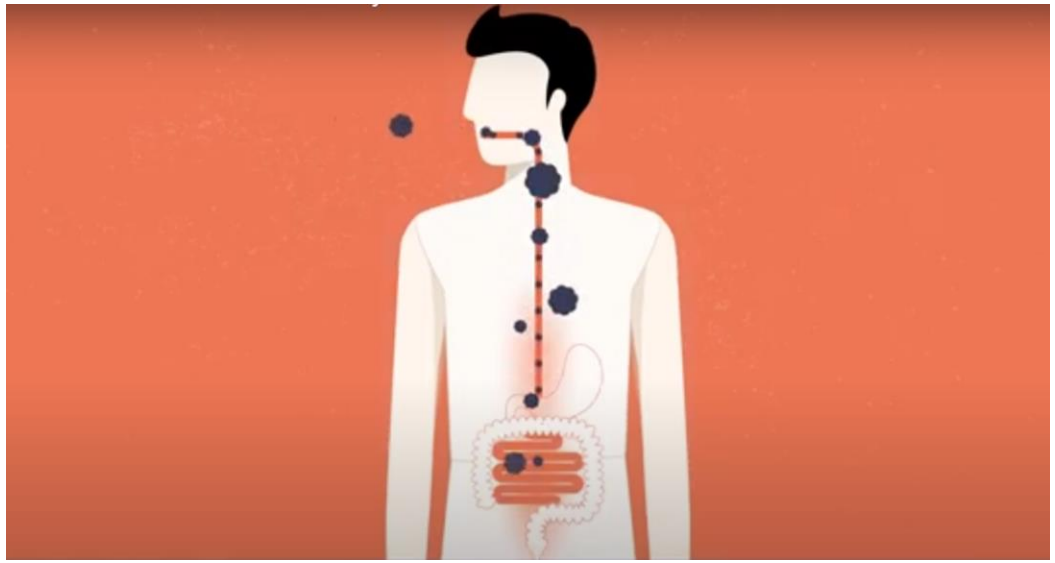


Image illustration the anatomy of structures in small intestine used for absorption

Absorption pathways in GI tract)







◦ **Image**: Illustration of absorption pathways (e.g., GI tract)

Training Questions

◦

1) The most important factor that determines whether a substance will be absorbed within the stomach is the:
a) Physical form as a solid or liquid
b) Molecular size
c) pH

2) The primary routes for absorption of environmental agents are:
a) Gastrointestinal tract, respiratory tract, and skin
b) Conjunctival exposures and skin wounds

3) The site of the gastrointestinal tract where most absorption takes place is:
a) Stomach
b) Small intestine
c) Colon and rectum

Training Questions **Answer.**

- 1. pH - **This is the correct answer.**
  The most important factor that determines absorption within the stomach is pH. Weak organic acids, which exist in a diffusible, nonionized and lipid-soluble form are readily absorbed in the high acidity of the stomach (pH 1-3). In contrast, weak bases will be highly ionized and therefore poorly absorbed.

Training Questions **Answer.**

- 2) Gastrointestinal tract, respiratory tract, and skin - **This is the correct answer.** Environmental agents may be found in contaminated food, water, or air. As such, they may be ingested, inhaled, or present on the skin.

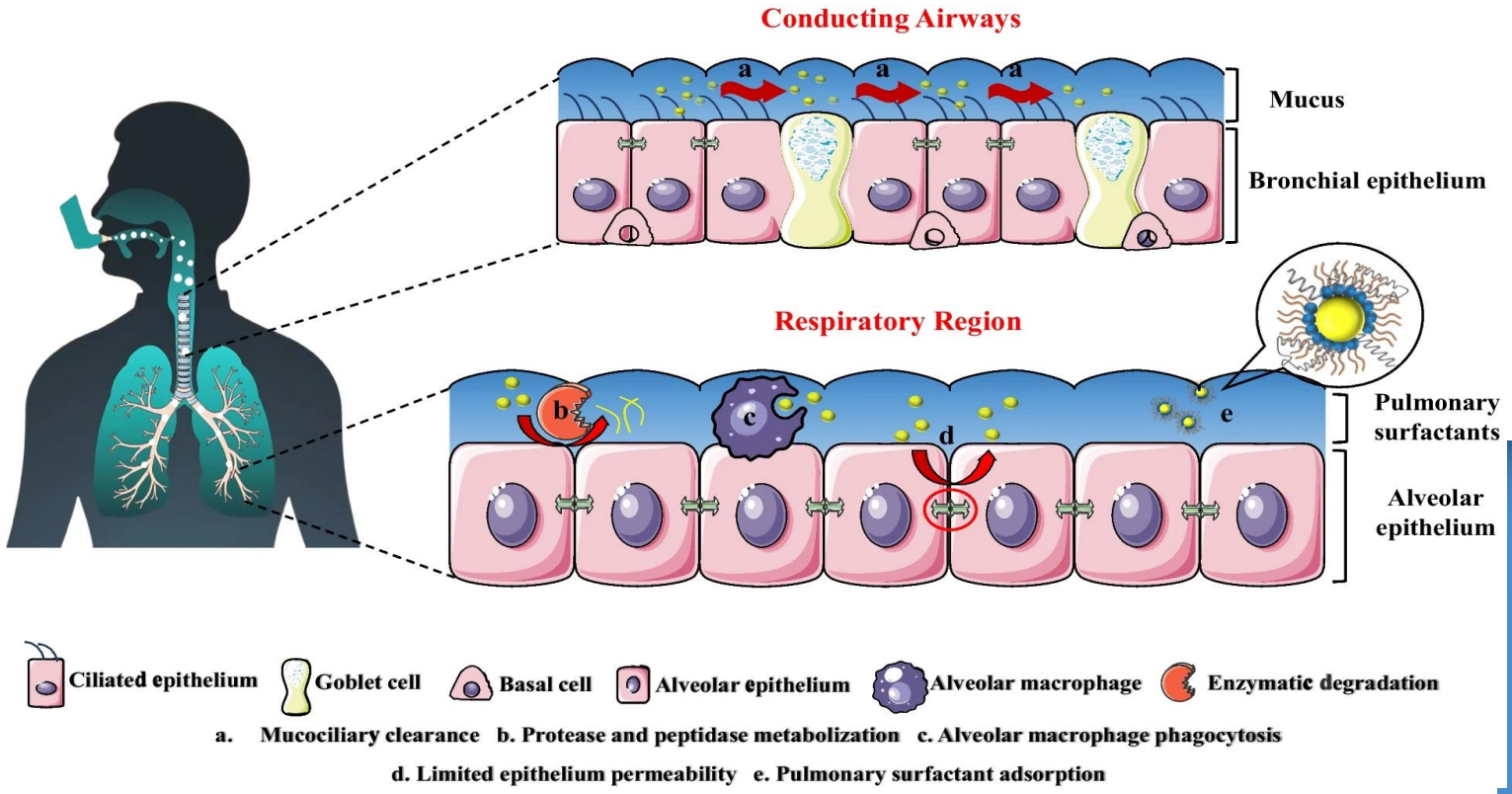
- 3) Small intestine - **This is the correct answer.** By far, the greatest absorption takes place in the intestine. This is due to the neutral pH and the large, thin, surface area that allows easy penetrable by passive diffusion. Weak bases, weak acids, lipid soluble substances and small molecules effectively enter the body from the intestine. In addition, special carrier-mediated and active transport systems exist.

Lungs:

The **lungs** serve as a critical site for **absorption** when it comes to gaseous or airborne toxins. The alveoli, tiny air sacs within the lungs, are designed for efficient gas exchange and possess a very thin membrane structure. This thin barrier and the rich **blood supply** surrounding the alveoli facilitate rapid absorption of substances into the bloodstream.

Toxins that are inhaled can easily pass through this membrane and quickly enter systemic circulation due to the vast surface area of the **alveoli** and their close interaction with **capillaries**.

- **Introduction to Toxicokinetic and Toxicodynamic absorption pathways of the Lung**



Schematic representation of challenges for the systemic absorption of inhaled proteins and peptides in the respiratory airways.

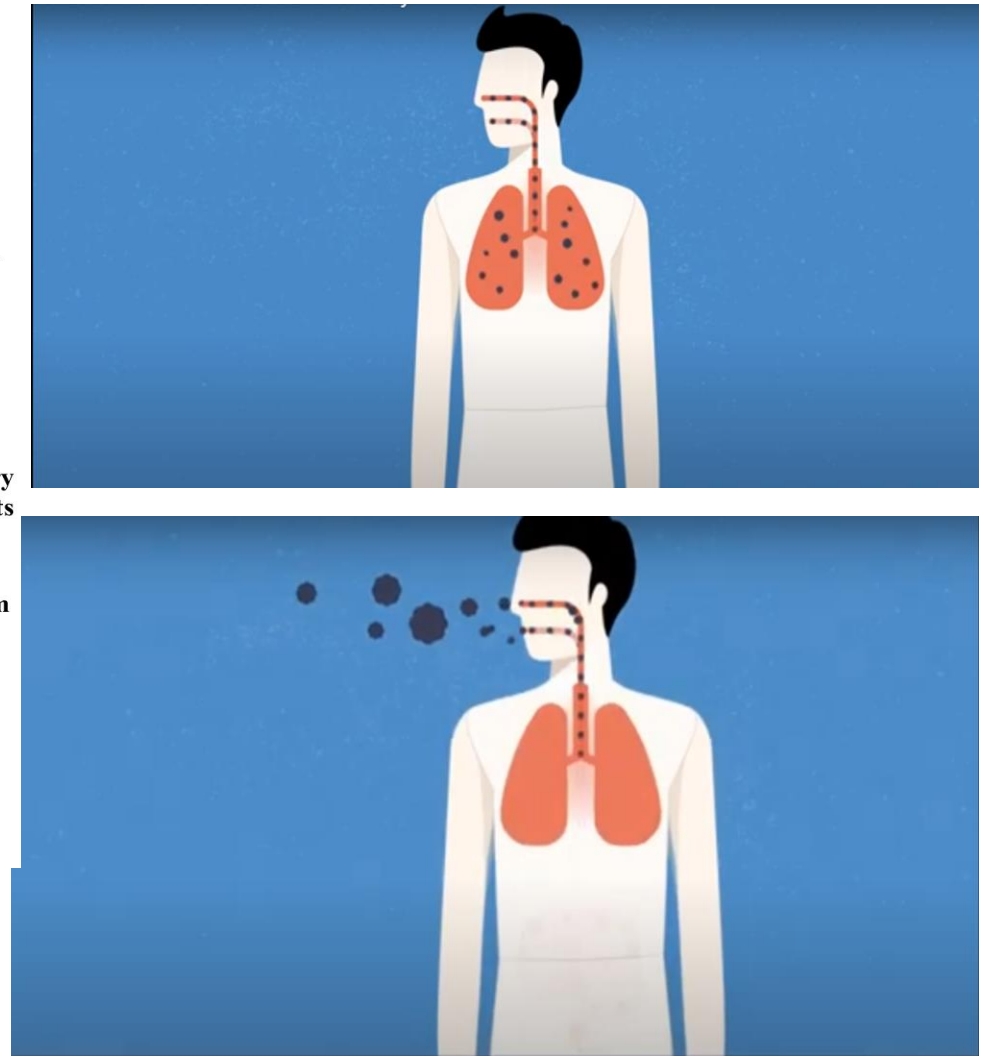
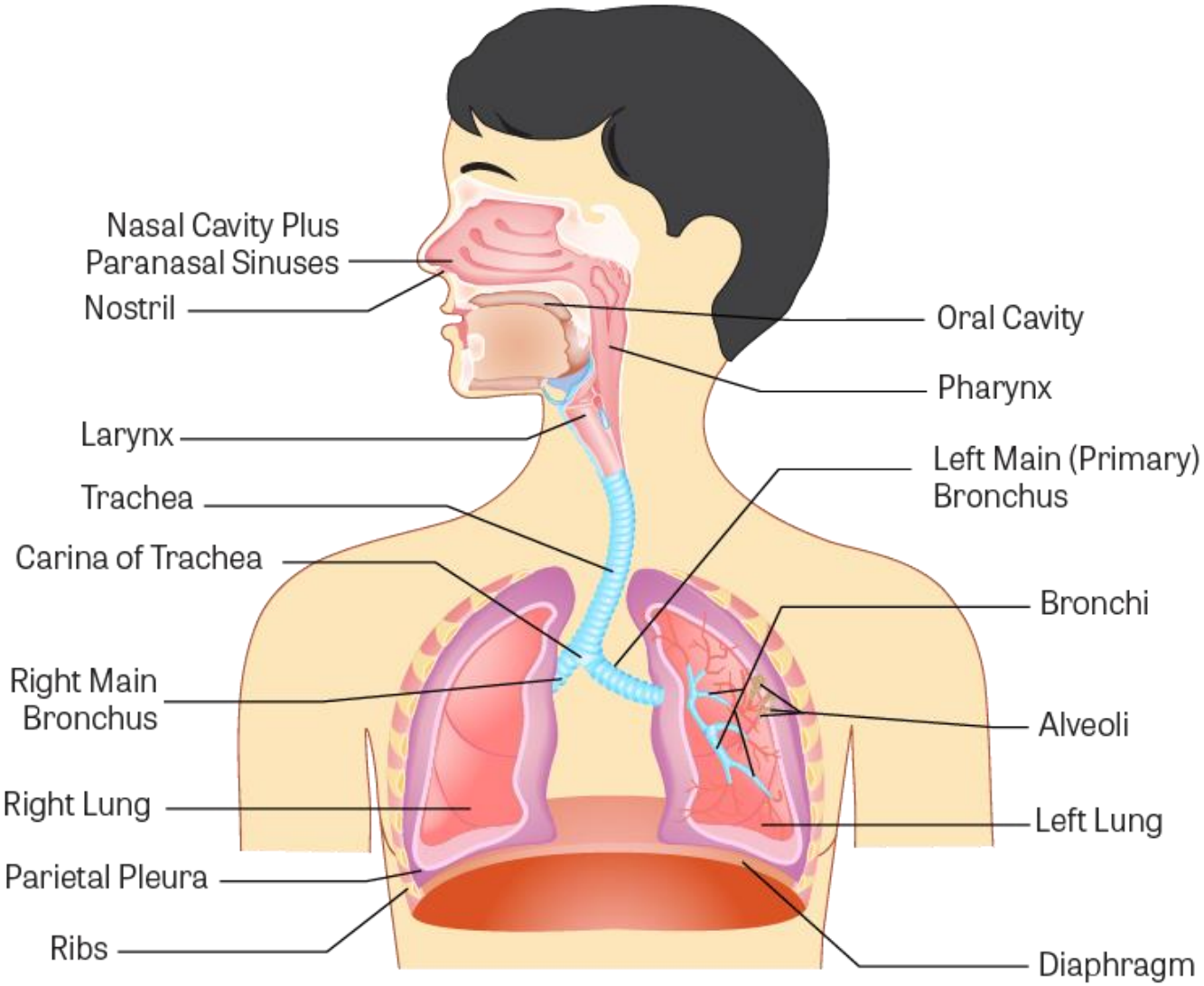
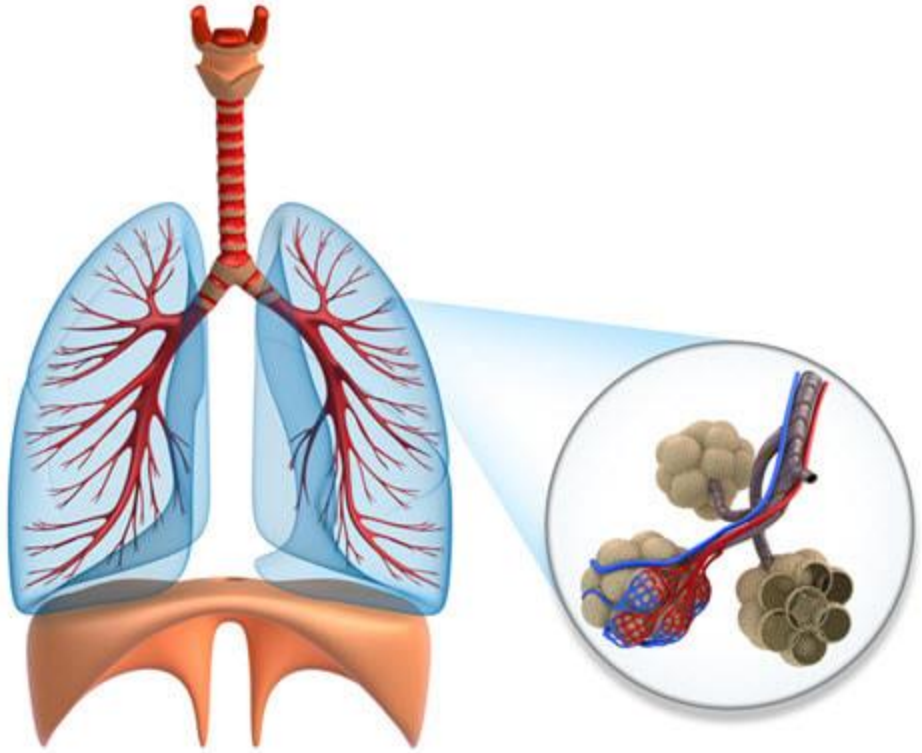


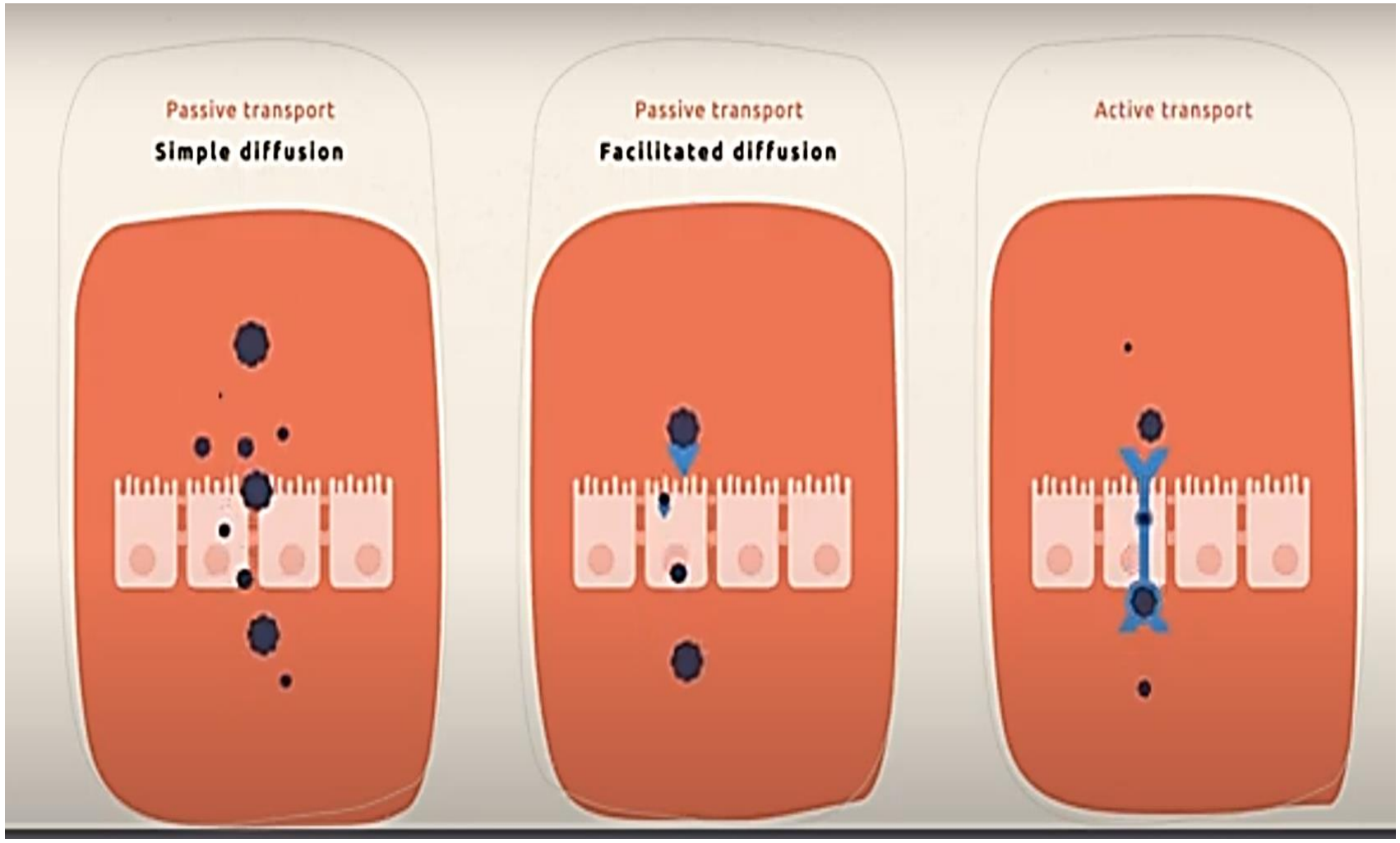
Image: Illustration of absorption pathways (e.g., Lung)





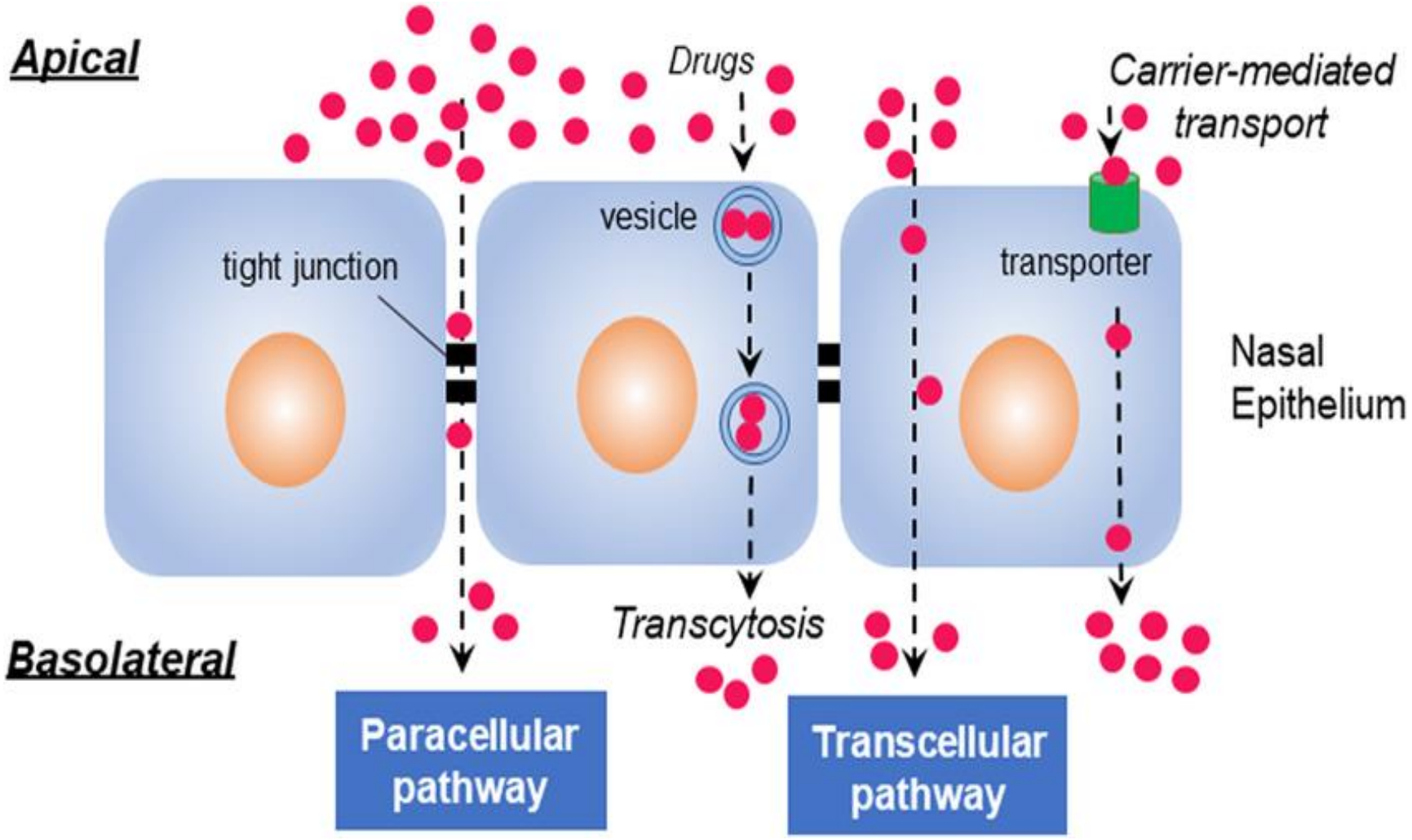
Anatomy of Respiratory Tract

The pass through epithelial cells by passive, diffusion and active transport



- Image Illustration the pass through epithelial cells by passive and facilitated diffusion. Or active transport

The pass through epithelial cells by passive



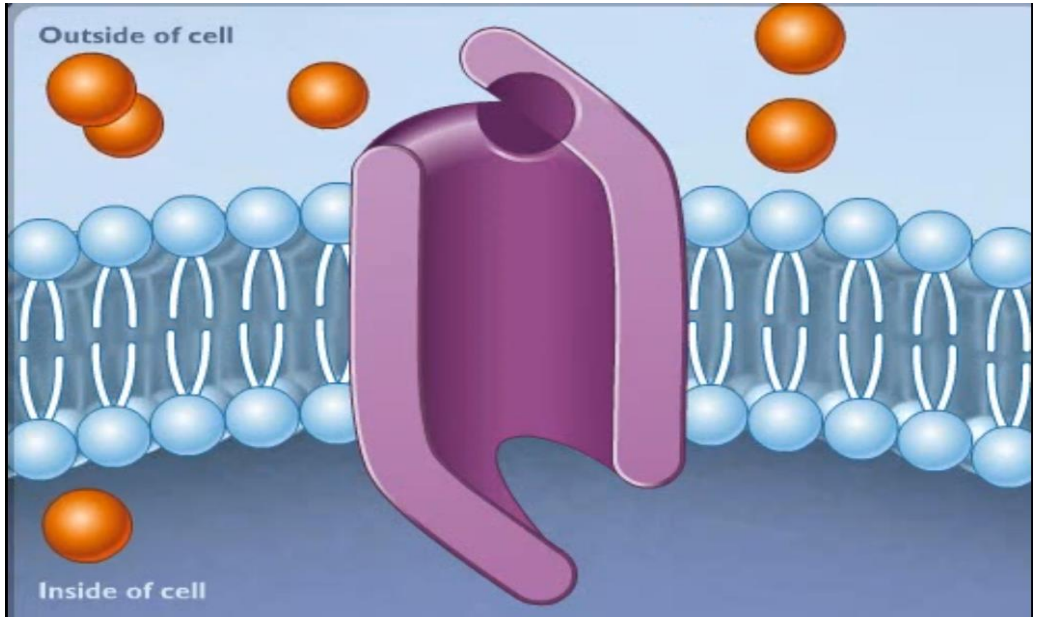
◦ Image Illustration the pass through epithelial cells by passive

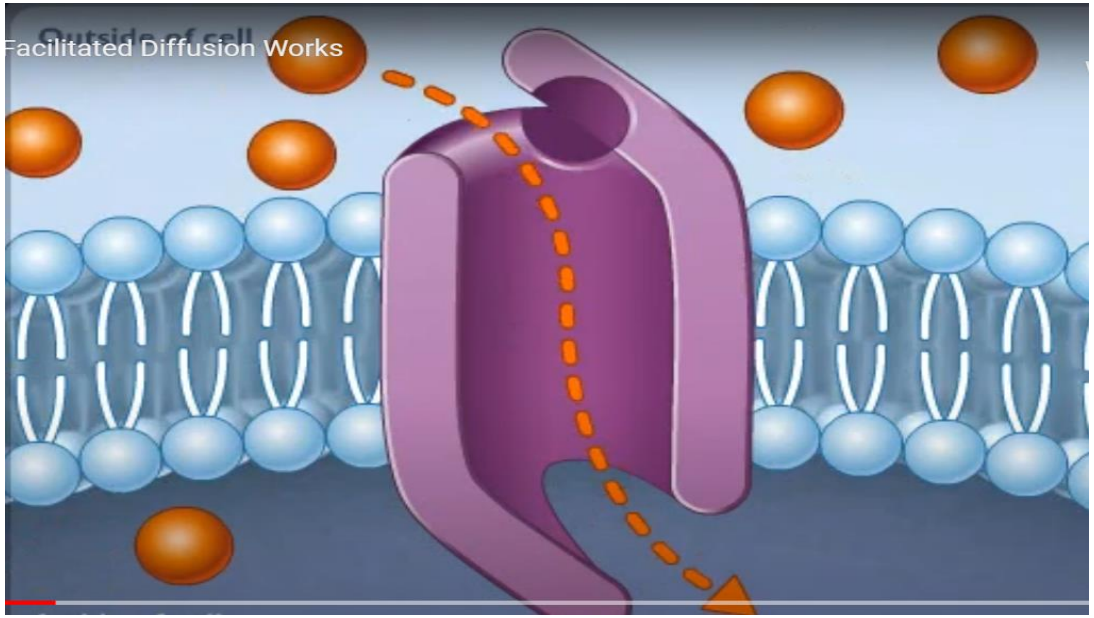
Passive diffusion through epithelial cells

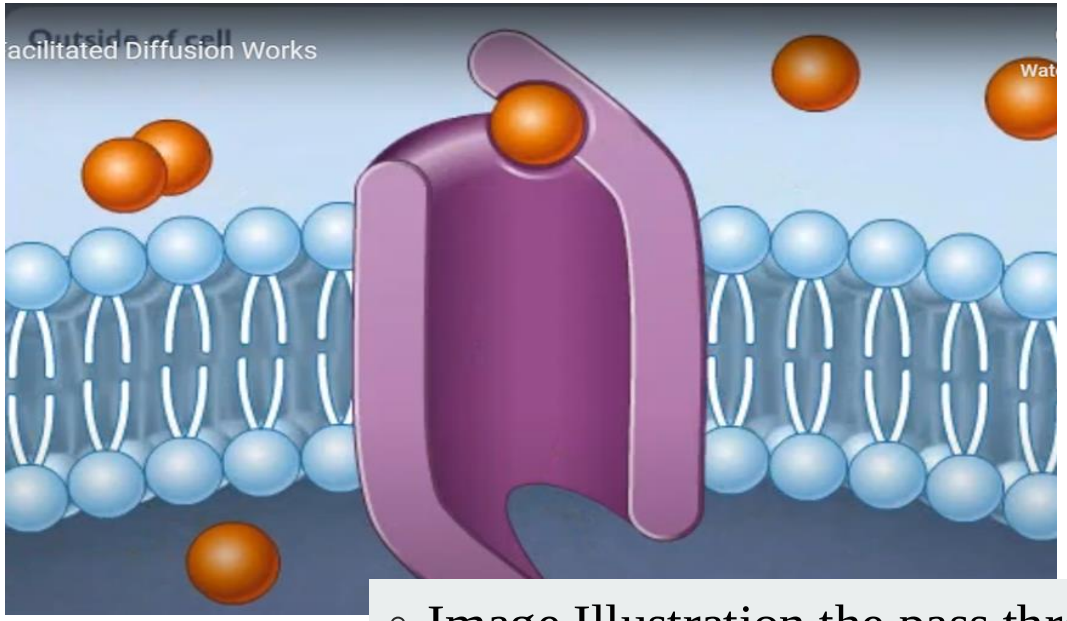
- Passive diffusion through epithelial cells is a process where substances move across cell membranes without the use of energy. This occurs due to the concentration gradient: substances naturally move from areas of higher concentration to areas of lower concentration.

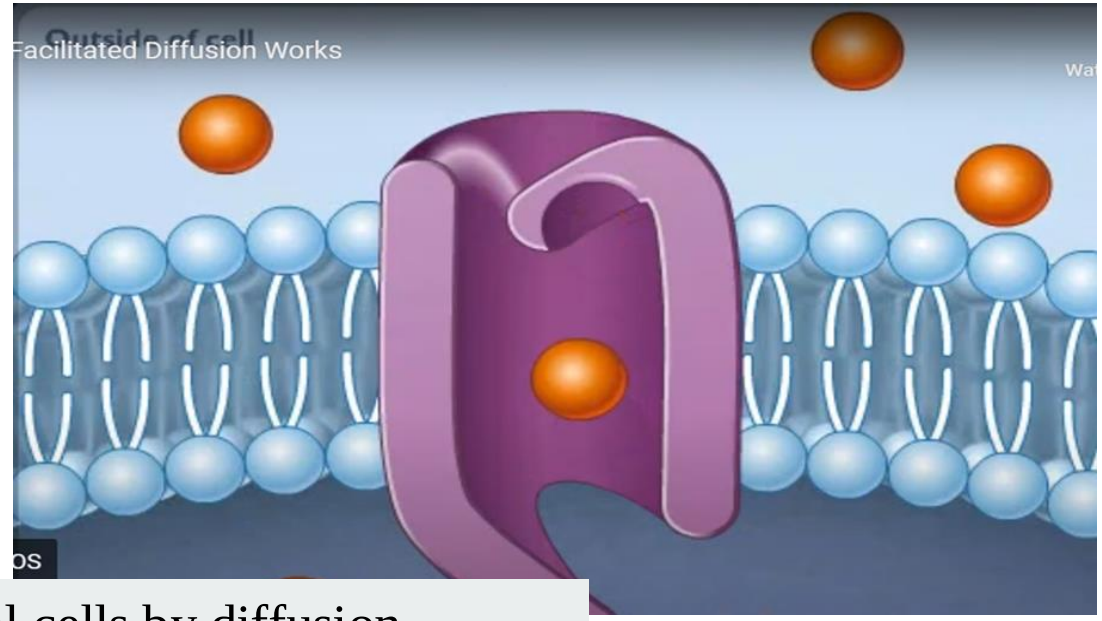
- Lipid-soluble molecules can easily pass through the lipid bilayer of epithelial cells, allowing them to be absorbed into the bloodstream or transported into tissues. This type of movement is critical for the absorption of many drugs and toxins in the body.

pass through epithelial cells facilitated by diffusion





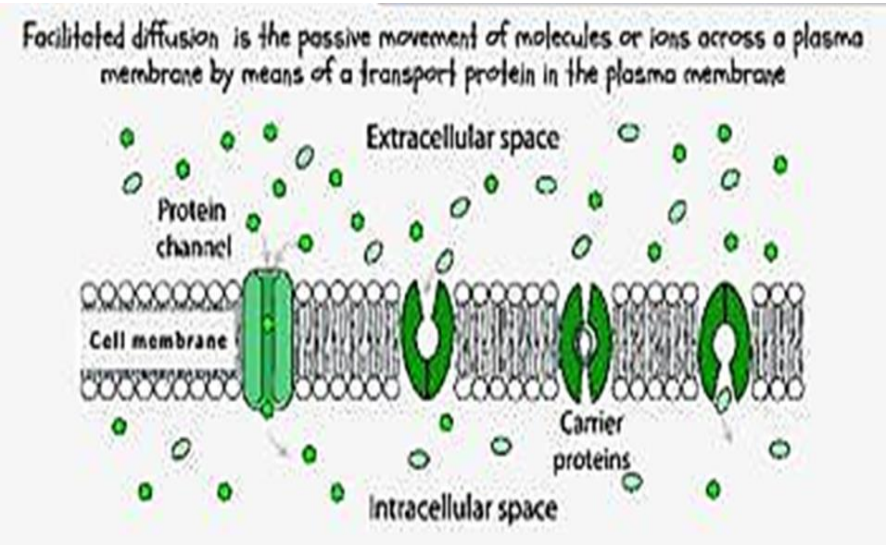


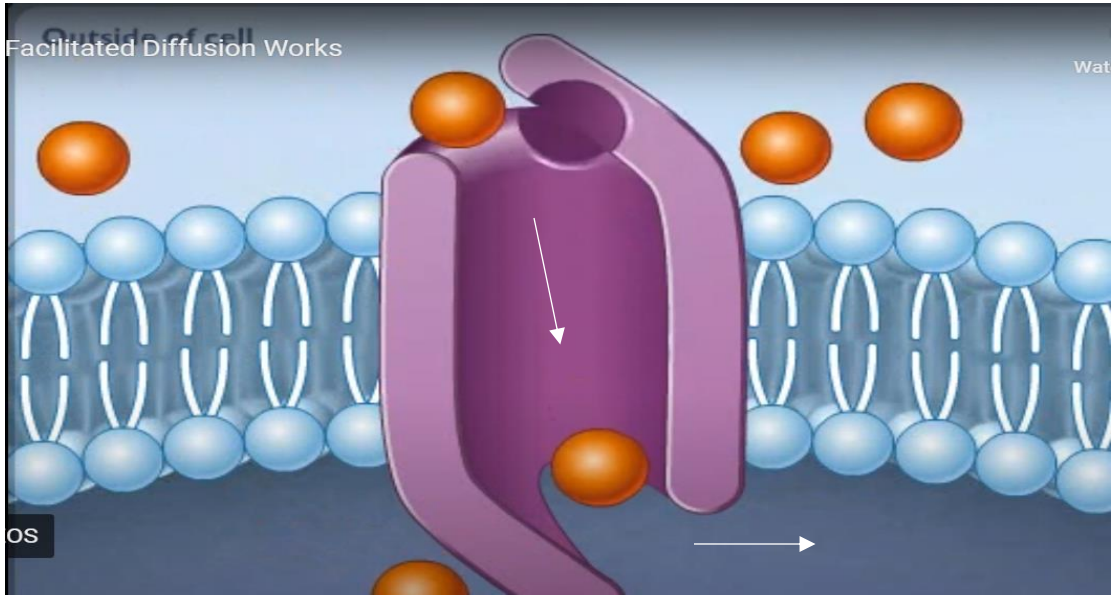


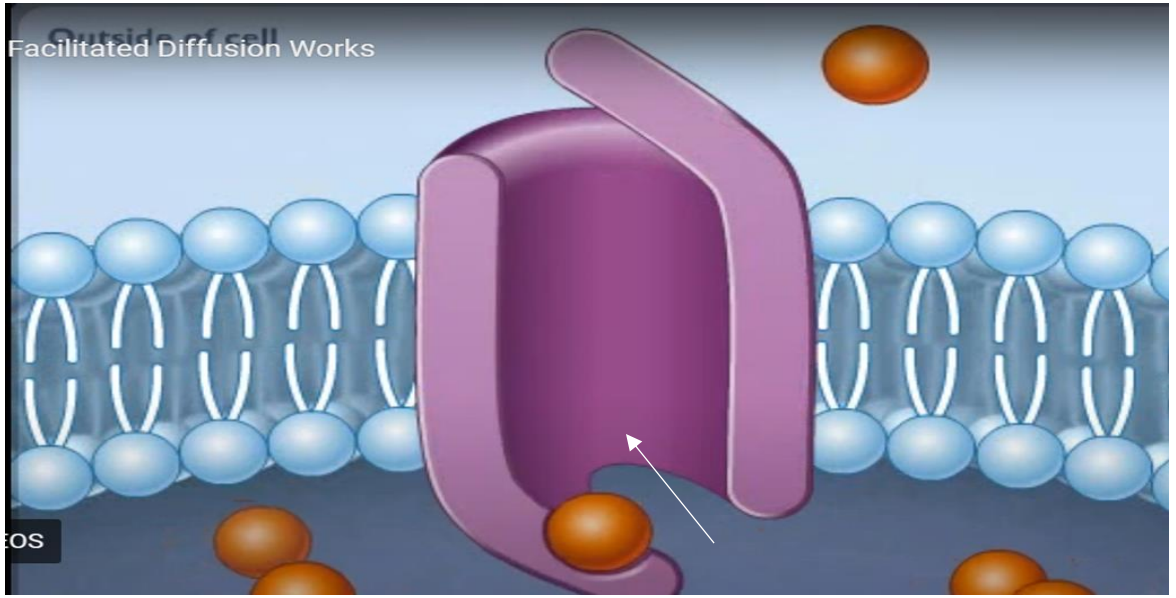
◦ Image Illustration the pass through epithelial cells by diffusion

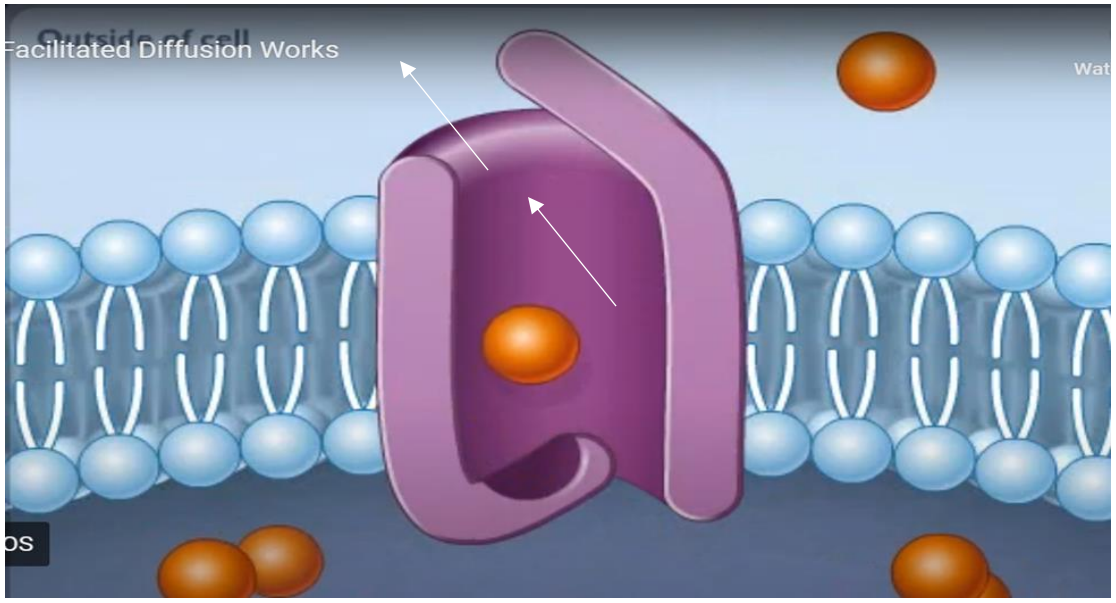
Facilitated diffusion

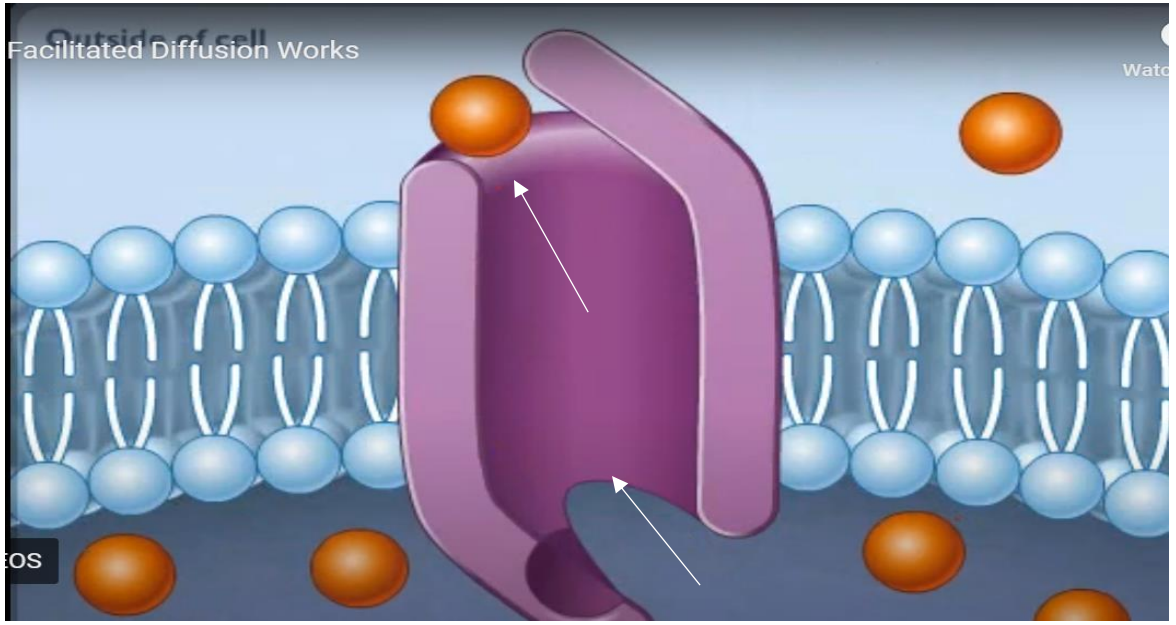
- Facilitated diffusion in cells is a passive process where molecules move across the cell membrane through protein channels or carriers. Unlike simple diffusion, this process helps specific, typically larger or polar substances pass through the lipid bilayer. The movement still occurs along the concentration gradient (from high to low concentration) and does not require energy. This mechanism is essential for transporting molecules like glucose and amino acids that cannot diffuse directly through the lipid membrane.











◦ Image Illustration the pass through epithelial cells by diffusion

Active Transport

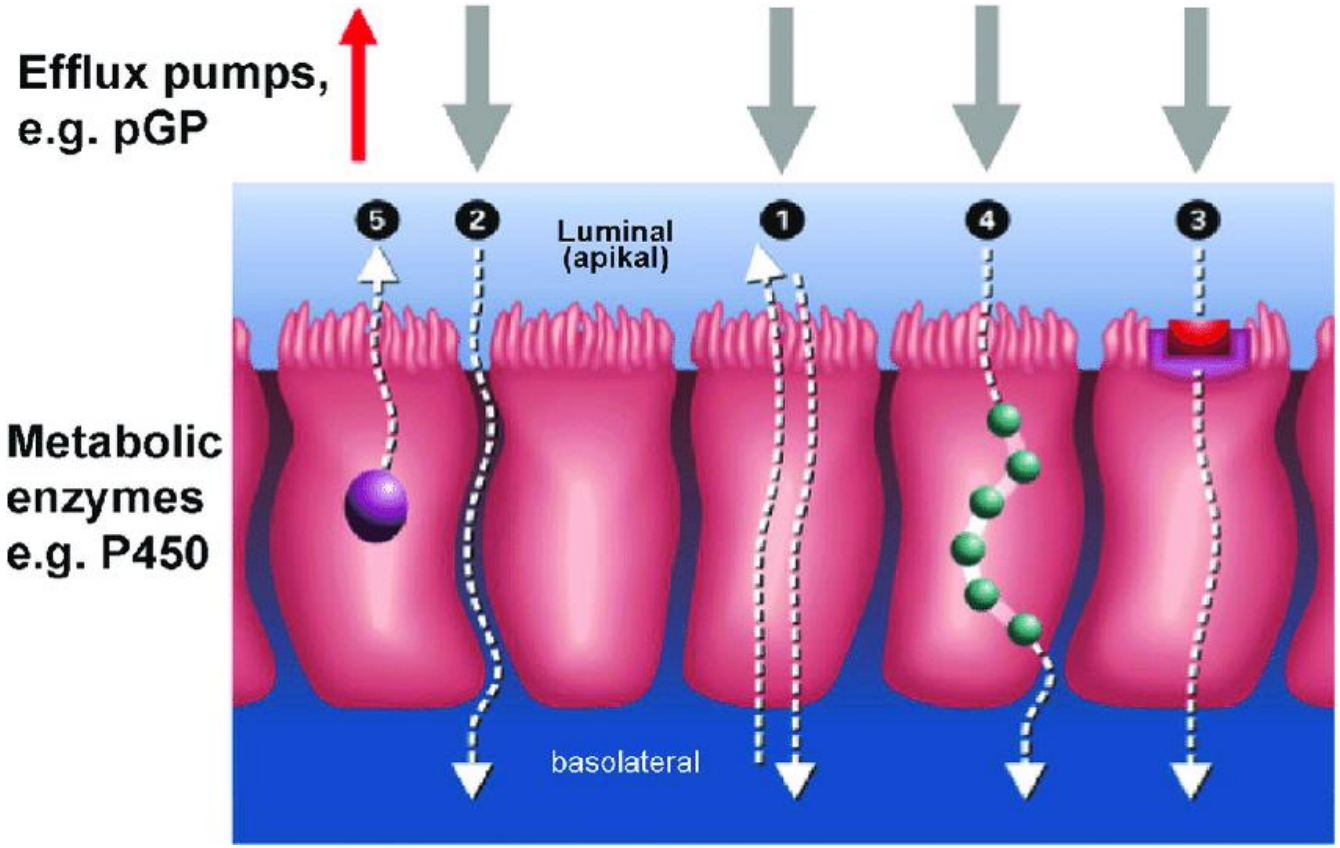


Image illustration the active transport is essential for various physiological processes, such as nutrient absorption in the intestines, electrolyte balance, and the maintenance of cell potential.

Active transport

- **Active transp**ort is a cellular process that moves molecules across a cell membrane from an area of lower concentration to an area of higher concentration, against their concentration gradient.

- This process requires energy, typically in the form of adenosine triphosphate (ATP), because it is working against the natural tendency of molecules to diffuse.

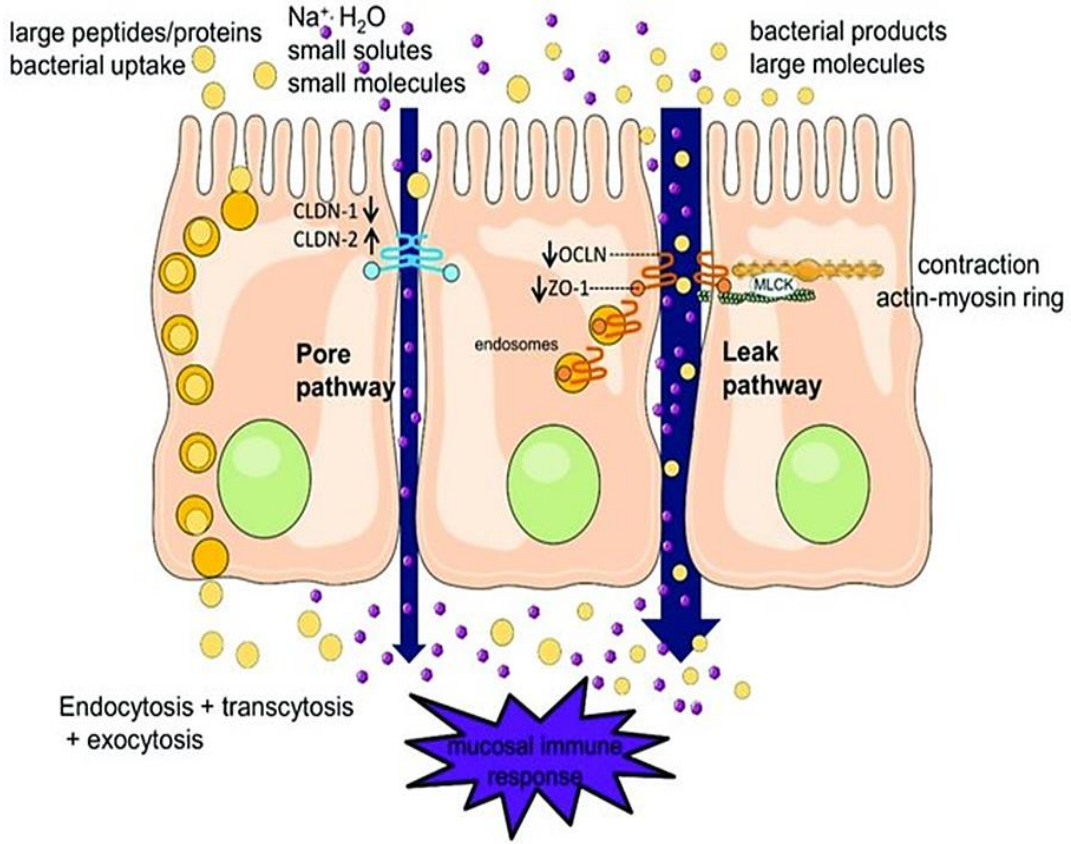


Image illustration the active transport is essential for various physiological processes, this process requires energy

What We've Covered

This lecture made the following main points:

- Absorption is the process by which toxicants gain entrance into the body.
- Ingested and inhaled materials are considered outside the body until they cross the cellular barriers of the gastrointestinal tract or respiratory system.
- The likelihood of absorption depends on the:
  - Route of exposure.
  - Concentration of the substance at the site of contact.
  - Chemical and physical properties of the substance.

◦

What We've Covered

This section made the following main points:

- Exposure routes include:
  - Primary routes:
    1. Gastrointestinal (GI) tract
       - Mouth and esophagus — poorly absorbed under normal conditions due to short exposure time (nicotine and nitroglycerin are notable exceptions).
       - Stomach — significant site for absorption of weak organic acids, but weak bases are poorly absorbed.
       - Intestine — greatest absorption of both weak bases and weak acids, particularly in the small intestine.
       - Colon and rectum — very little absorption, unless administered via suppository.

◦

What We've Covered

This section made the following main points:

- Exposure routes include:
  - Primary routes:
  - 2. Respiratory tract
    - Mucociliary escalator — movements of the cilia push mucus and anything contained within up and out into the throat to be swallowed or removed through the mouth.
    - Pulmonary region — most important site for absorption with about 50 times the surface area of the skin and very thin membranes.

◦

What We've Covered

This section made the following main points:

- Exposure routes include:
  - Primary routes:

3. Skin
    - Epidermis and stratum corneum — the only layer important in regulating the penetration of a skin contaminant.
    - Toxicants move across the stratum corneum by passive diffusion.
    - If a toxicant penetrates through the stratum corneum, it enters lower layers of the epidermis, dermis, and subcutaneous tissue, which are far less resistant to further diffusion.

Homework questions

- **Question 1:**
- **Explain the process of active transport in epithelial cells. Include the role of ATP and specific transport proteins in your answer.**
- **Question 2:**
- **Compare and contrast active transport and passive transport mechanisms in epithelial cells. What are the implications of these mechanisms for nutrient absorption in the intestines?**

Answers

- Key features of active transport include:
- Energy Requirement: Active transport requires energy to function, as it moves substances against their gradient.
- Transport Proteins: Specific proteins in the cell membrane, such as pumps and carriers, facilitate active transport. For example, the sodium-potassium pump actively transports sodium ions out of the cell and potassium ions into the cell, crucial for maintaining cellular function.
- Types of Active Transport:
- Primary Active Transport: Directly uses ATP to transport molecules.
- Secondary Active Transport (Cotransport):
- Uses the energy from the movement of one molecule down its concentration gradient to drive the transport of another molecule against its gradient.

Home work answer

- **Q2: Comparison of Active Transport and Passive Transport Mechanisms in Epithelial Cells:**

1.Energy Requirement:

1. **Active Transport:** Requires energy (ATP) to move substances against their concentration gradient.
2. **Passive Transport:** Does not require energy; substances move along their concentration gradient.

2.Direction of Movement:

1. **Active Transport:** Moves molecules from areas of lower concentration to areas of higher concentration.
2. **Passive Transport:** Moves molecules from areas of higher concentration to areas of lower concentration.

3.Types of Transport:

1. **Active Transport:** Involves transport proteins (e.g., pumps and carriers) to facilitate movement.
2. **Passive Transport:** Can occur via simple diffusion, facilitated diffusion (using carrier proteins), or osmosis (for water).

4.Specificity:

1. **Active Transport:** Highly specific, often transporting only certain ions or molecules.
2. **Passive Transport:** Can be less specific, allowing a wider range of molecules to pass through.

Home work answer

- **Q2: Implications for Nutrient Absorption in the Intestines:**
- **Active Transport:** Essential for the absorption of vital nutrients, such as glucose and amino acids, which are absorbed against their concentration gradients. This allows for efficient nutrient uptake even when intestinal concentrations are low.
- **Passive Transport:** Facilitates the absorption of small molecules and water, following their concentration gradients. This process helps balance the osmotic pressure and ensures that nutrients are absorbed effectively without additional energy expenditure.
- Overall, both mechanisms are crucial for efficient nutrient absorption, with active transport ensuring that essential nutrients are absorbed even when concentrations are low, while passive transport allows for the absorption of water and small molecules in a more energy-efficient manner.

Extra Home work Questions

- 1. Mechanism of Action:
- How does active transport play a role in the renal excretion of toxic substances from the bloodstream?
- 2. Specific Transporters:
- Which specific transport proteins are involved in the active transport of drugs used to eliminate toxins from the body, and how do they function?
- 3. Therapeutic Agents:
- Discuss how certain therapeutic agents utilize active transport mechanisms to enhance the elimination of heavy metals from the body
- 4. Ion Transport:
- In what ways does active transport of ions (such as sodium or potassium) affect the pharmacokinetics of antidotes used in toxic therapy?

Extra Home work Questions

- 5. Drug Interaction:
- How might the presence of competitive inhibitors affect the active transport of therapeutic agents aimed at removing toxins?
- 6. Toxicity and Transport Efficiency:
- How does the efficiency of active transport mechanisms impact the overall effectiveness of detoxification therapies in cases of acute poisoning?
- 7. Pathophysiological Conditions:
- What are the effects of renal or hepatic impairment on the active transport of therapeutic agents used in toxicology, and how can this influence treatment strategies?
- 8. Targeting Toxins:
- Describe the role of active transport in targeting specific toxins, such as methotrexate or digoxin, for elimination through therapy.

Thank you

References

1. **The Merck Manual of Diagnosis and Therapy** Publisher: Merck Edition: 20th Edition (2018)
   - An authoritative reference on medical diagnostics, including the diagnosis and treatment of poisoning and intoxication.
2. **A Textbook of Modern Toxicology**
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6. **Clinical toxicology, principles and mechanisms, 2 ed , Frank A. Barile,2010**

TOXICOTHERAPY

INTRODUCTION TO TOXICOKINETICS

2nd part Xenobiotic Absorption and Toxicokinetic Processes:

Dr. Ahmad Hamdy Ibrahim

Toxicotherapy PHAR 421

Semester one

Week number 4

27/10/2024

Objectives

- The students will able to

1. Understand Facilitated Diffusion:

- Explain the process of facilitated diffusion and its role in transporting chemicals into the bloodstream.

2. Identify Key Organs:

- Identify the organs, particularly the liver, that are involved in the metabolism of chemicals.

3. Explore Metabolic Processes:

- Describe the metabolic processes that occur in the liver and how they affect the chemical properties of substances.

4. Differentiate Metabolites:

- Differentiate between deactivated metabolites and potentially more toxic metabolites produced during liver metabolism.
- 5. Assess Biological Impact:
- Assess how the liver's biotransformation affects the overall toxicity and therapeutic efficacy of substances in the body.

6. Recognize Clinical Implications:

- Recognize the clinical implications of liver metabolism in drug therapy and toxicology.

Lecture Outcomes

- 1. Facilitated Diffusion:
- A. Definition and process Mechanisms of transport into the bloodstream
- B. Key Organs in Metabolism: Role of the liver in chemical metabolism and Other organs involved in metabolism
- 2. Metabolic Processes in the Liver:
- A. Biotransformation overview,
- B. Enzymatic reactions involved
- 3. Types of Metabolites:
- A. Deactivation of substances
- B. Formation of more toxic metabolites

4. Biological Impact of Liver Metabolism: A. Influence on toxicity, Therapeutic efficacy of substances

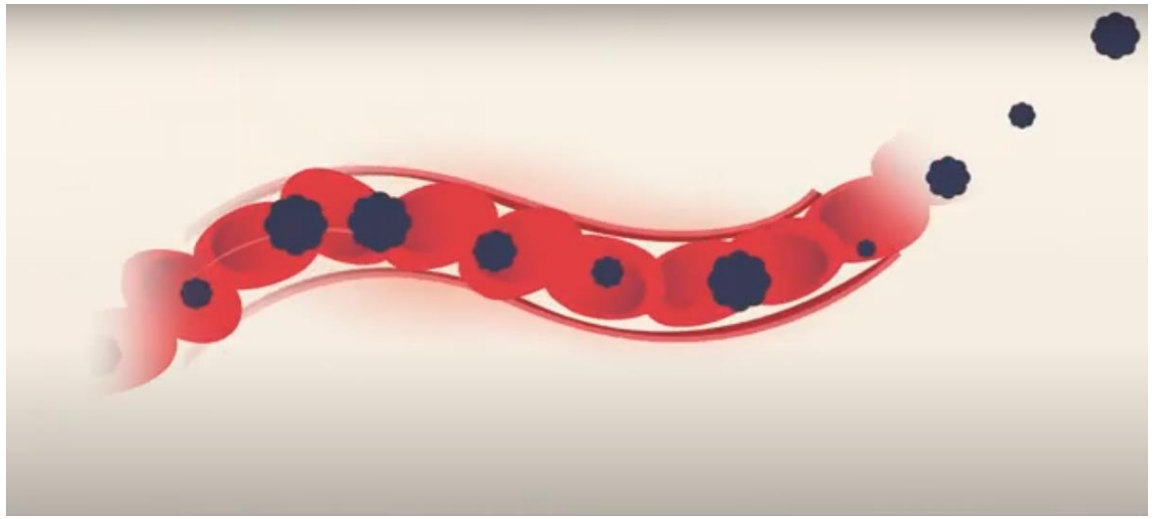
B. Clinical Implications: Impacts on drug therapy. CConsiderations in toxicology and treatment strategies

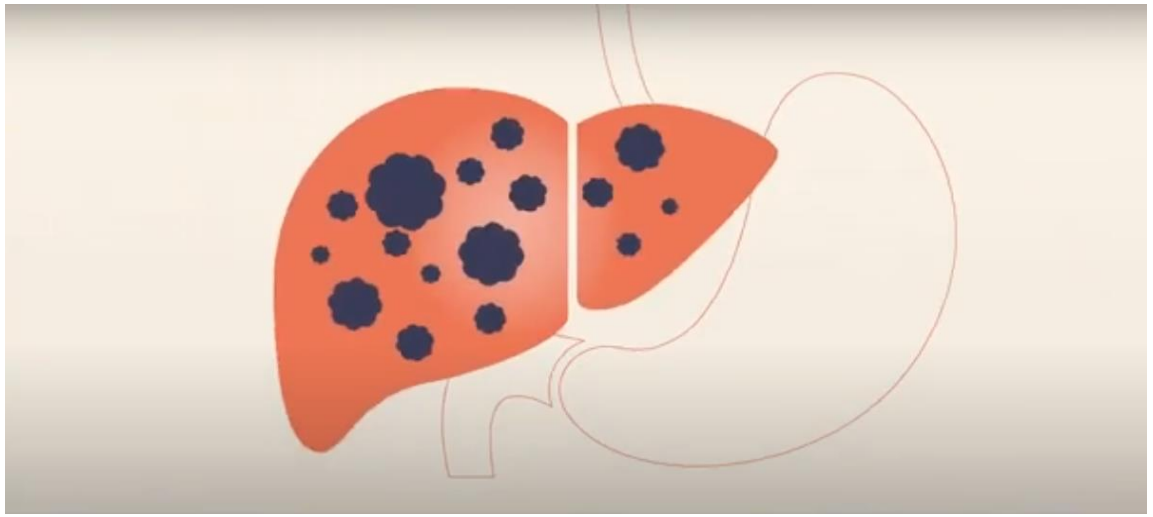
Chemicals enter the bloodstream

- Facilitated diffusion helps chemicals enter the bloodstream, where they are transported to organs like the liver. In the liver, a portion of these chemicals undergoes metabolism.

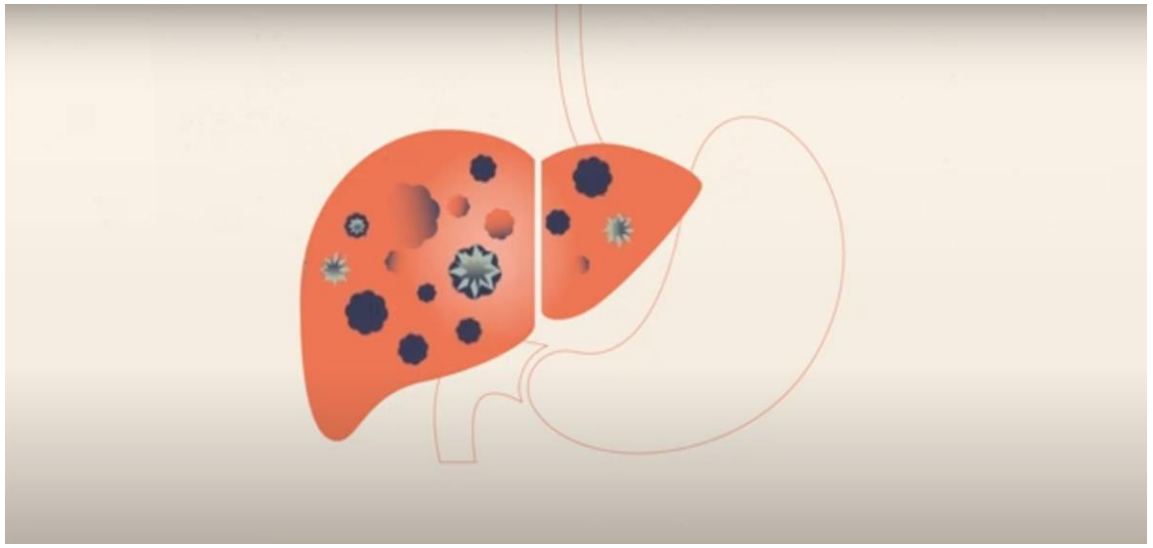
- This metabolic process can deactivate the substance, making it less harmful, or sometimes convert it into a more toxic metabolite. The liver’s role in biotransformation is crucial for modifying chemical properties and influencing how substances affect the body.

With bloodstream, chemicals are transported into the liver.





- Where a portion of a substance can be metabolized to deactivate or sometimes more toxic compound



Main Paths of Absorption

•**1. Gastrointestinal Tract**: Primary route for ingested substances (e.g., drugs, toxins).

•**2. Respiratory System**: Fast absorption of gases and airborne particles through the lungs.

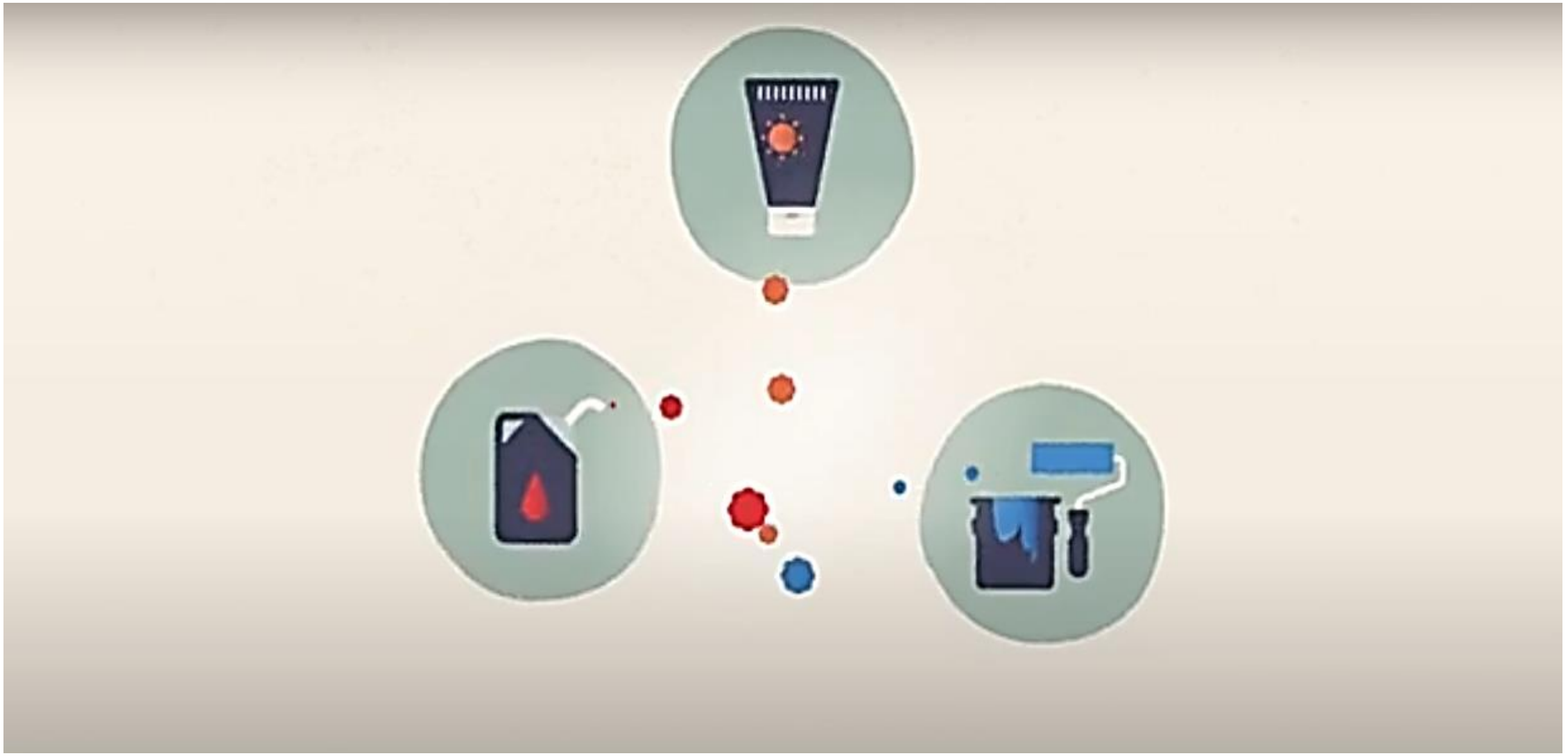
•**3. Skin (Dermal)**: Slower absorption, common for lipid-soluble substances.

The most lipid soluble toxic substances can penetrate the dermal

- Substances like sunscreen, gasoline, and home paint contain lipid-soluble compounds, which can penetrate the skin and potentially reach the bloodstream.

The skin acts as a barrier, but its outermost layer (the stratum corneum) allows substances that are lipid-soluble to diffuse through more easily. Once these substances pass this barrier, they can move into the deeper skin layers and reach capillaries, allowing absorption into the bloodstream.

This property is why precautions are recommended when handling petroleum products or paints and why effective sunblock formulations are designed to prevent harmful UV rays without unnecessary systemic absorption.



◦ Image illustration The most lipid soluble substances can penetrate the dermal and reach blood vessels. The Substances like sunscreen, gasoline, and home paint

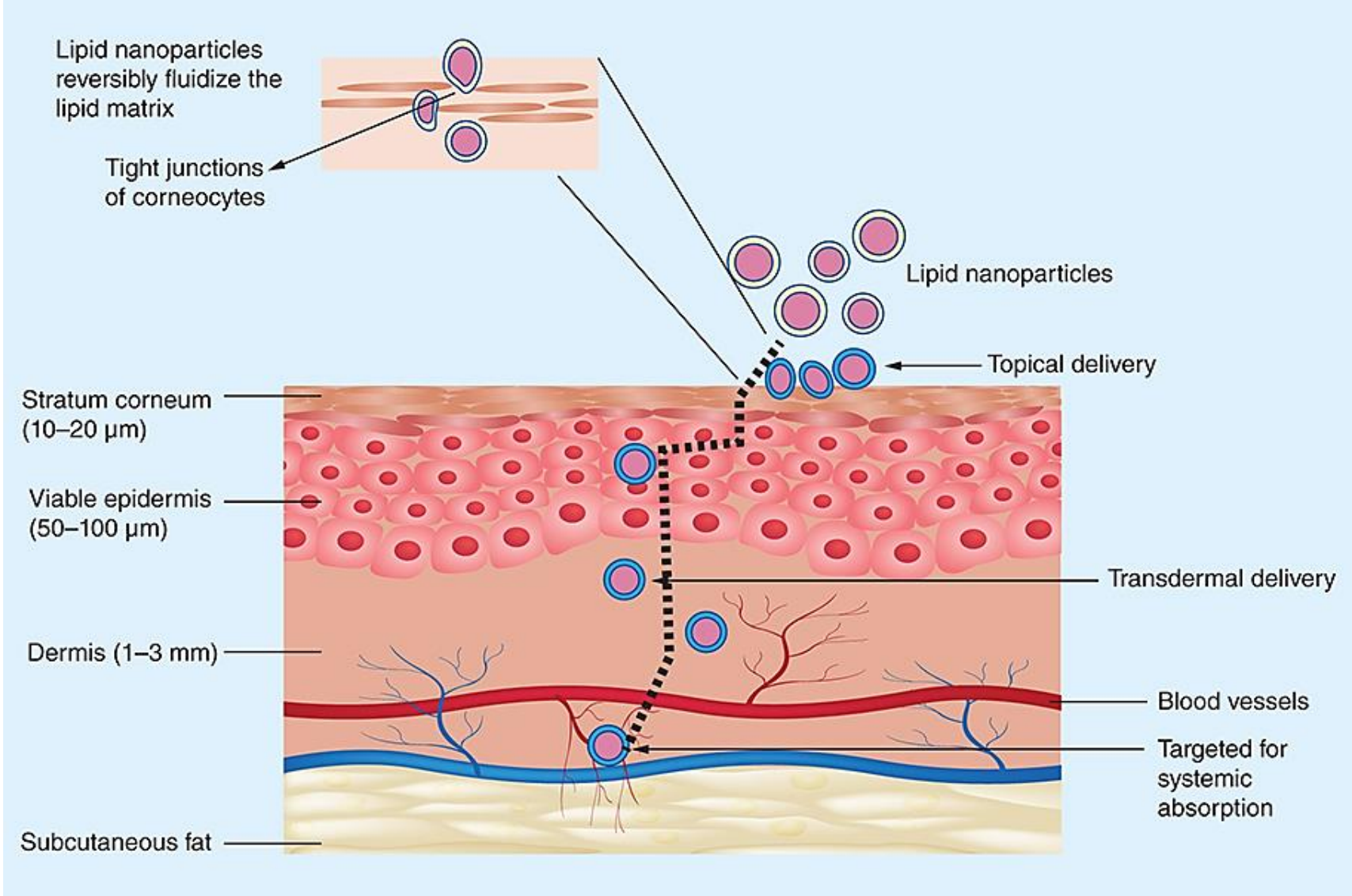
Mechanism explains why some medications and chemicals are delivered trans-dermally?

- Highly lipid-soluble substances can penetrate the skin more effectively because they can pass through the lipid-rich environment of the stratum corneum.

- Once they pass this outermost layer, they can diffuse through the deeper layers of the skin and reach blood vessels in the dermis, allowing them to enter the bloodstream and be distributed throughout the body.

- This mechanism explains why some medications and chemicals are delivered trans-dermally, such as through patches.

Lipid nanoparticles delivery applications



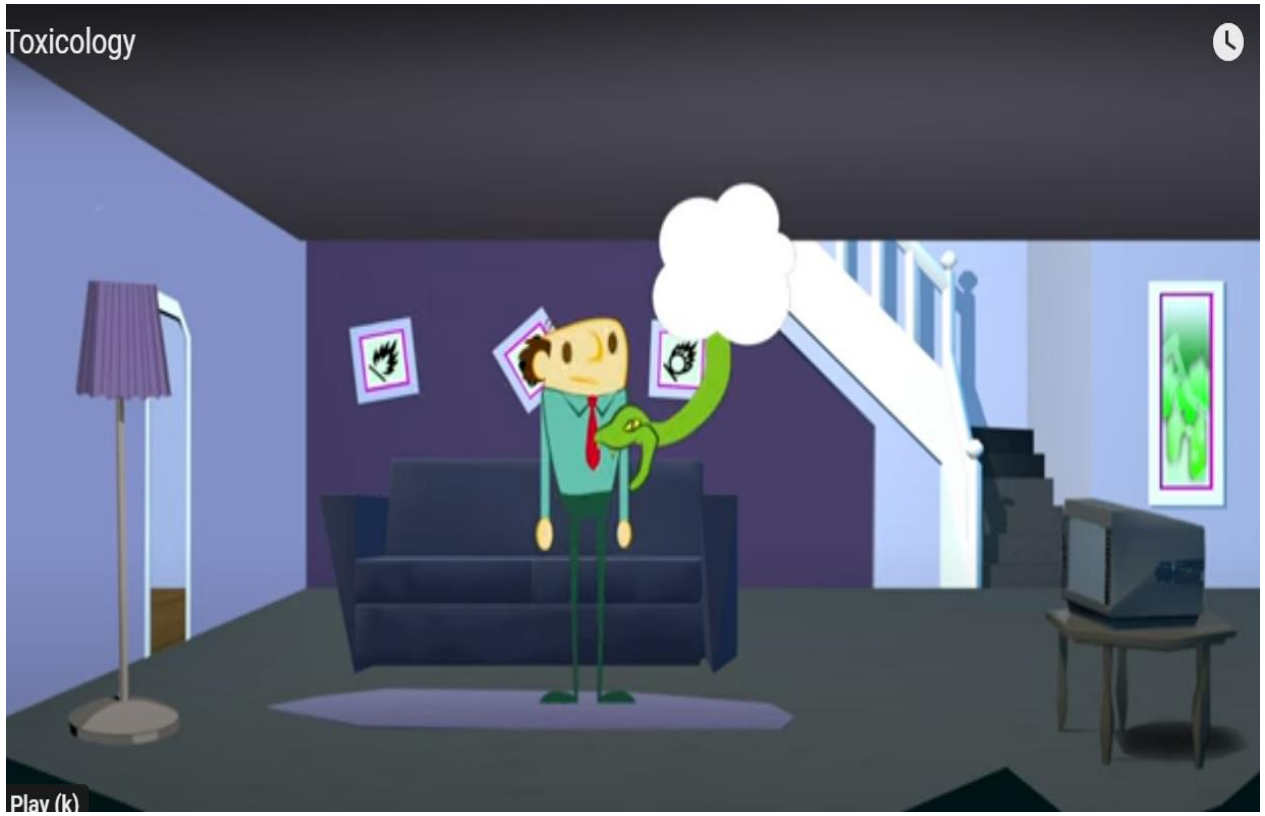
◦ Factors Influencing Absorption

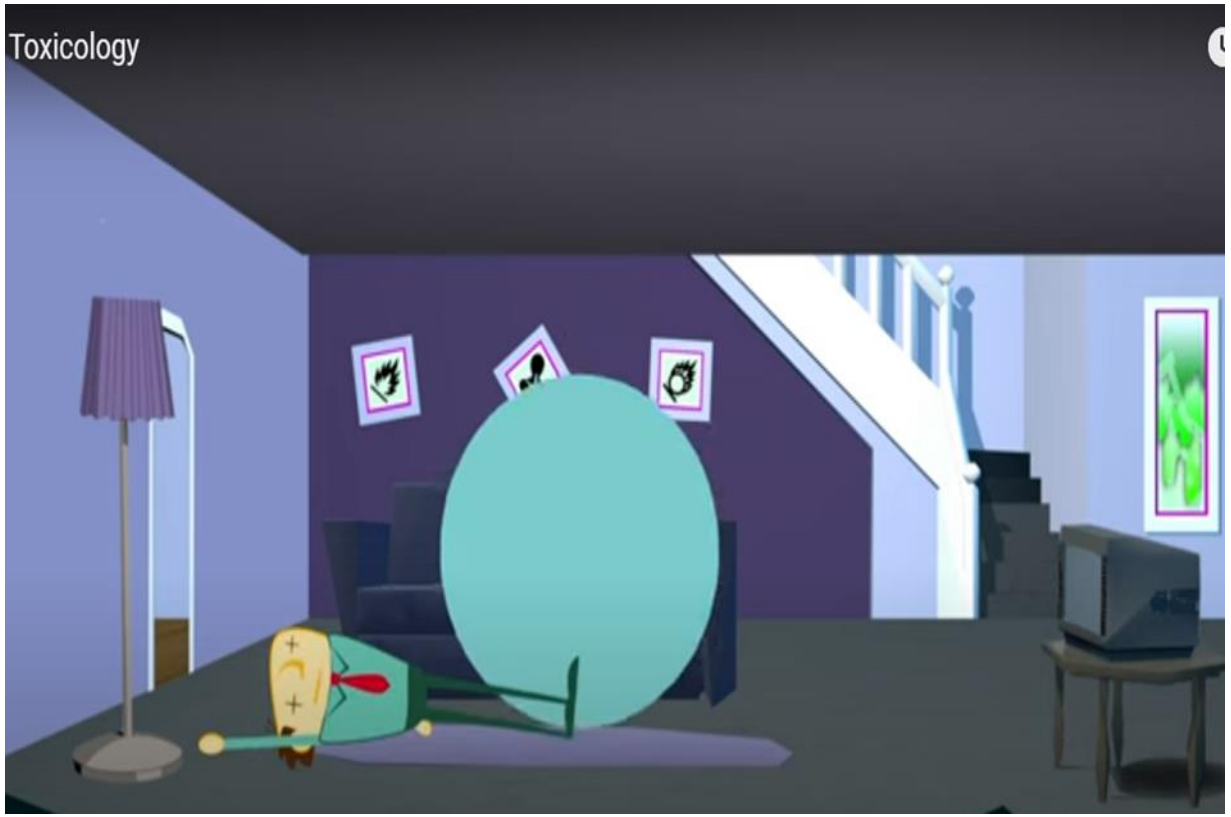
•**1. Chemical Properties**: Lipophilic compounds absorb more readily; hydrophilic may require transport.

•**2. Body Conditions**: pH, enzymes, and GI motility affect absorption efficiency.

•**Key Takeaway**: Absorption efficiency shapes a substance’s impact on health.

•**Conclusion**: Understanding xenobiotic absorption is critical in pharmacology and toxicology.





Question: After a snake bite, is the person going to die or not?

Thank you

References

1. **The Merck Manual of Diagnosis and Therapy** Publisher: Merck Edition: 20th Edition (2018)
   - An authoritative reference on medical diagnostics, including the diagnosis and treatment of poisoning and intoxication.
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TOXICOTHERAPY

INTRODUCTION TO TOXICOKINETICS

Xenobiotic Distribution and Biotransformation on the Toxicokinetic Processes:

Dr. Ahmad Hamdy Ibrahim

Toxicotherapy PHAR 421

Semester one

Week number 5

27/10/2024

Objectives

•**The students will be able to understand**

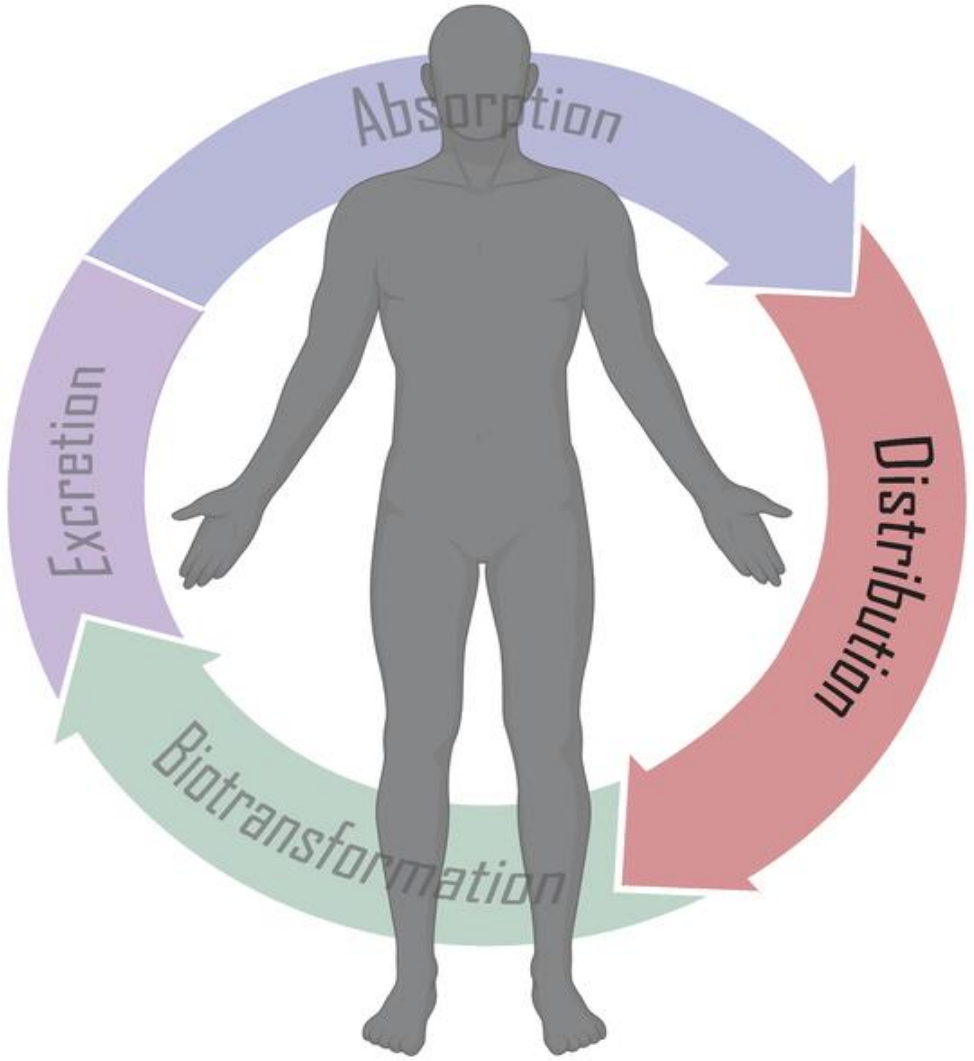
1. Xenobiotic Absorption:
•Understand the mechanisms and factors influencing xenobiotic absorption in the body.
2. Toxicokinetic Processes:
•Define and explain the four key processes of toxicokinetics: absorption, distribution, metabolism, and excretion.
3. Absorption:
•Describe the routes and processes of xenobiotic absorption into systemic circulation.
4. Distribution:
•Analyze how xenobiotics are distributed throughout the body and the factors affecting their distribution.
5. Metabolism:
•Examine the metabolic pathways of xenobiotics in the liver and their implications for toxicity.
6. Excretion:
•Identify the routes of excretion for xenobiotics and discuss their importance in detoxification.

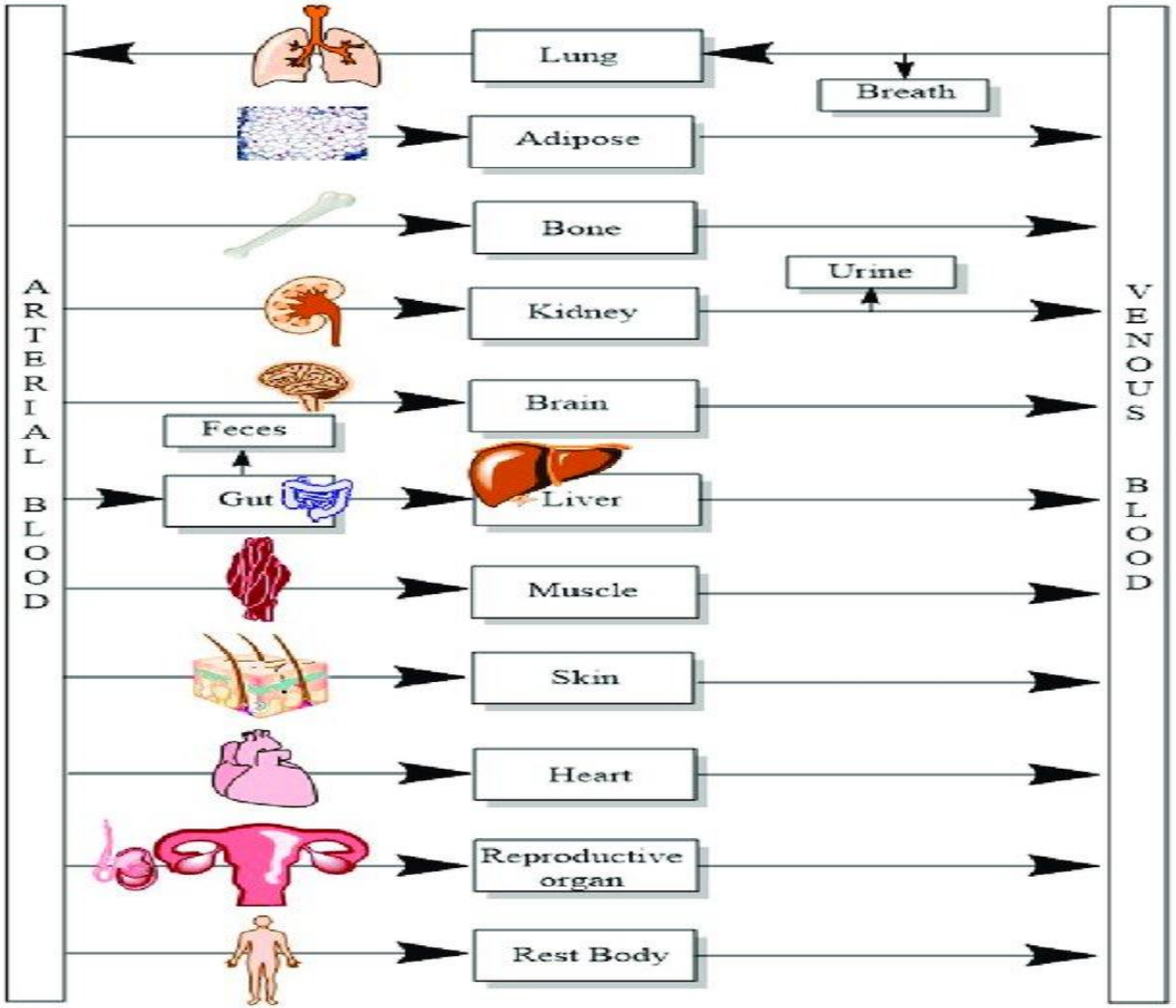
Outcomes from the lecture

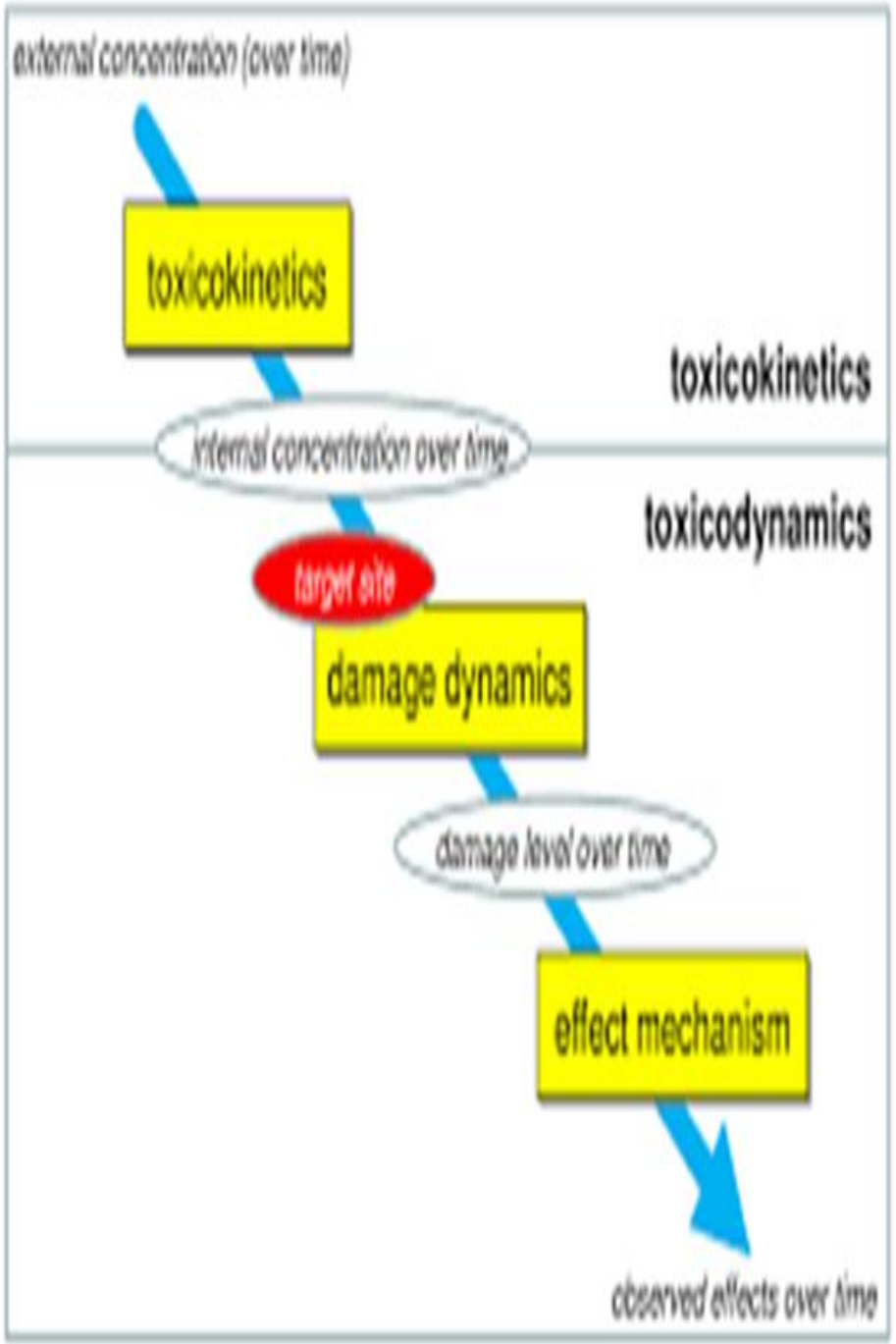
1. **Understanding of Toxicokinetics:**
    1. Students will be able to describe the processes of absorption, distribution, metabolism, and excretion of xenobiotics and their significance in toxicology.
2. **Application of Knowledge:**
    1. Students will be able to apply their knowledge of toxicokinetics to assess how various factors influence the bioavailability and toxicity of xenobiotics in the body.
3. **Critical Analysis of Metabolism:**
    1. Students will develop the ability to critically analyze how metabolic transformations in the liver can either detoxify xenobiotics or convert them into more harmful metabolites, impacting overall health.

: Xenobiotic Absorption

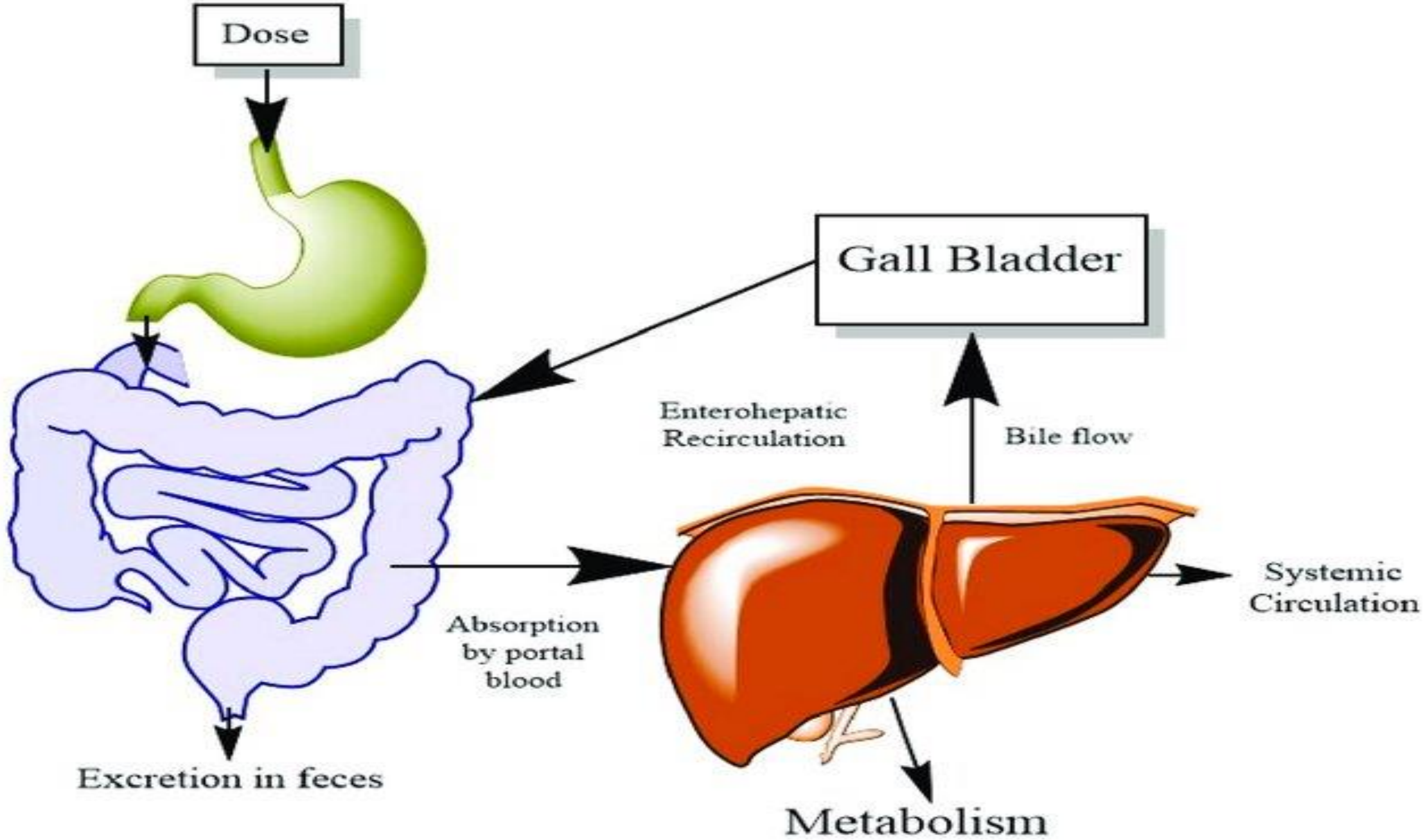
- **Toxicokinetic Processes:**
  - Absorption
  - Distribution
  - Metabolism
  - Excretion







Oral absorption of xenobiotic followed by enterohepatic recirculation (EHR). EHR occurs by biliary excretion followed by intestinal reabsorption of xenobiotic along with hepatic conjugation and intestinal deconjugation.


Dose
Gall Bladder
Enterohepatic
Recirculation
Bile flow
Absorption
by portal
blood
Systemic
Circulation
Excretion in feces
Metabolism

Volume of distribution

- The volume of distribution may provide useful estimates as to how extensive the toxicant is distributed in the body.
- For example, a very high apparent VD may indicate that the toxicant has distributed to a particular tissue or storage area such as adipose tissue.
- In addition, the body burden for a toxicant can be estimated from knowledge of the VD by using the formula:

$$V_D = \frac{\text{dose } (mg)}{\text{plasma conc } (mg/L)}$$

$$\text{body burden } (mg) = \text{plasma conc } (mg/L) \times V_D\ (L)$$

Once a chemical is in the blood stream:

It may be excreted.
It may be stored.
It may be biotransformed into different chemicals (metabolites).
Its metabolites may be excreted or stored.
The chemical or its metabolites may interact or bind with cellular components.
Most chemicals undergo some biotransformation. The degree with which various chemicals are biotransformed and the degree with which the parent chemical and its metabolites are stored or excreted vary with the nature of the exposure (dose level, frequency, and route of exposure)

. **Distribution of Xenobiotics**

- **Disposition Processes**
  - **Absorption**: Entry into the bloodstream.
  - **Distribution**: Movement to tissues and organs.
  - **Excretion**: Elimination from the body.
- **Volume of Distribution (Vd)**
  - Calculation: Vd = Dose / Plasma concentration.
  - Factors affecting Vd: Blood flow, molecular size, plasma protein binding.
- **Distribution Phases**
  - Initial phase: Blood flow.
  - Later phase: Tissue affinity (e.g., fat, bone).
- **Structural Aspects**
  - **Cell Membrane Structure**: Lipid bilayer, Lipophilic vs. Hydrophilic permeation.

Volume of Blood and Tissue Affinity

- Organs that receive larger **blood volumes** can potentially accumulate more of a given toxicant. Body regions that receive a large percentage of the total cardiac output include the liver (28%), kidneys (23%), heart muscle, and brain.

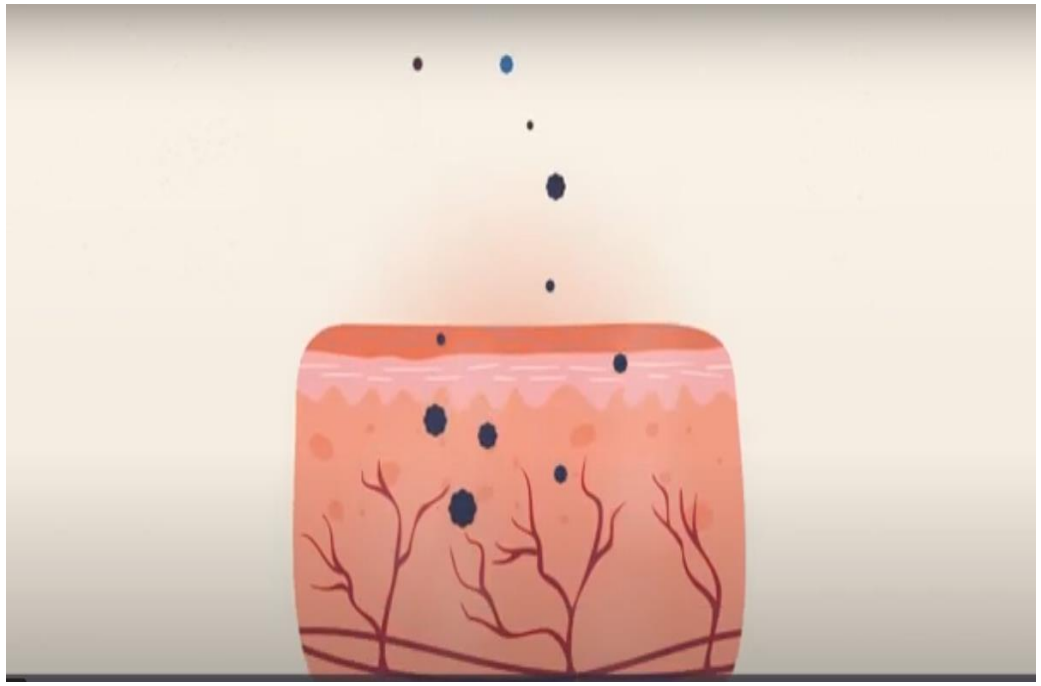
- Bone and adipose tissues have relatively low blood flow, even though they serve as primary storage sites for many toxicants.

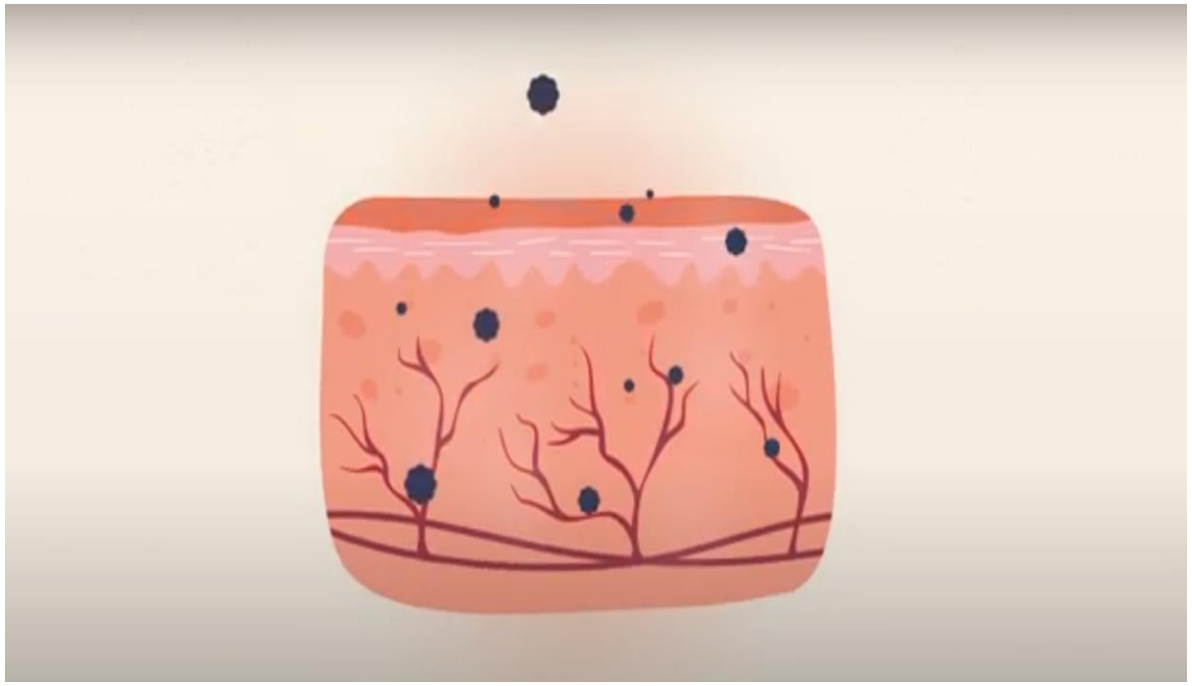
- This is especially true for toxicants that are fat-soluble and those that readily associate (or form complexes) with minerals commonly found in bone.

Tissue affinity

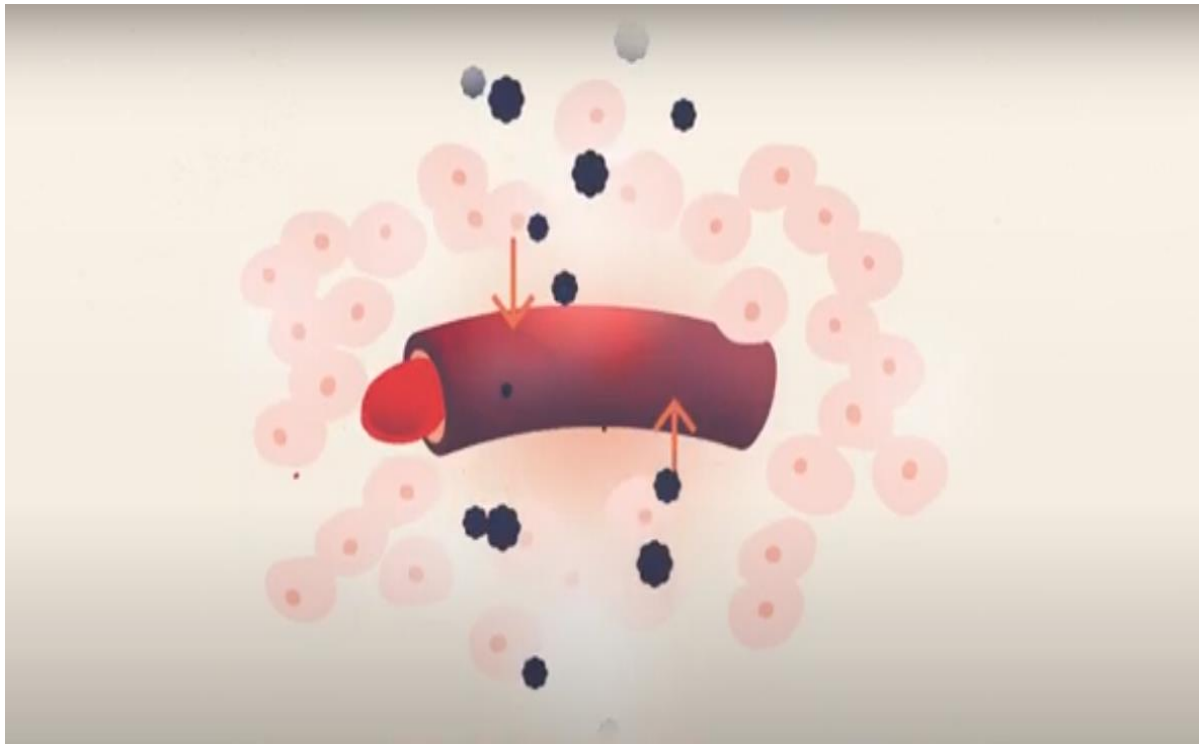
- **Tissue affinity** determines the degree of concentration of a toxicant. In fact, some tissues have a higher affinity for specific chemicals and accumulate a toxicant in great concentrations despite a rather low flow of blood.

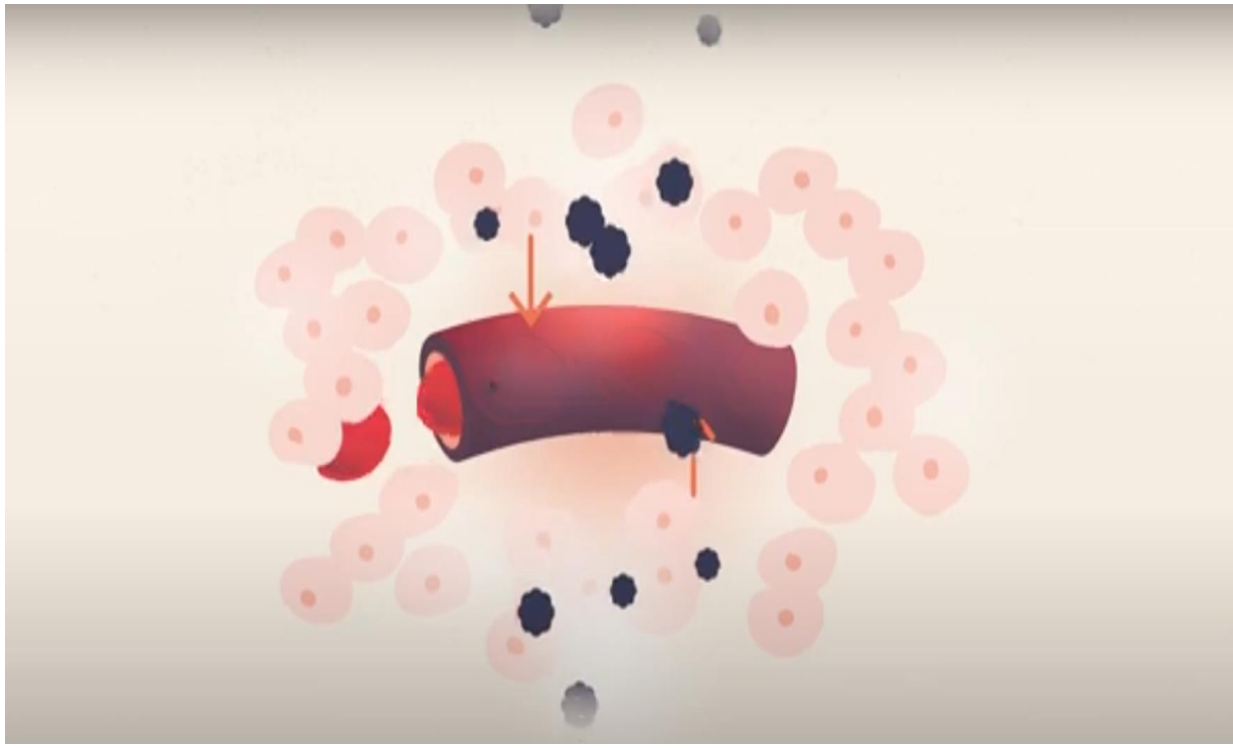
  For example, adipose tissue, which has a meager blood supply, concentrates lipid-soluble toxicants. Once deposited in these storage tissues, toxicants may remain for long periods, due to their solubility in the tissue and the relatively low blood flow.



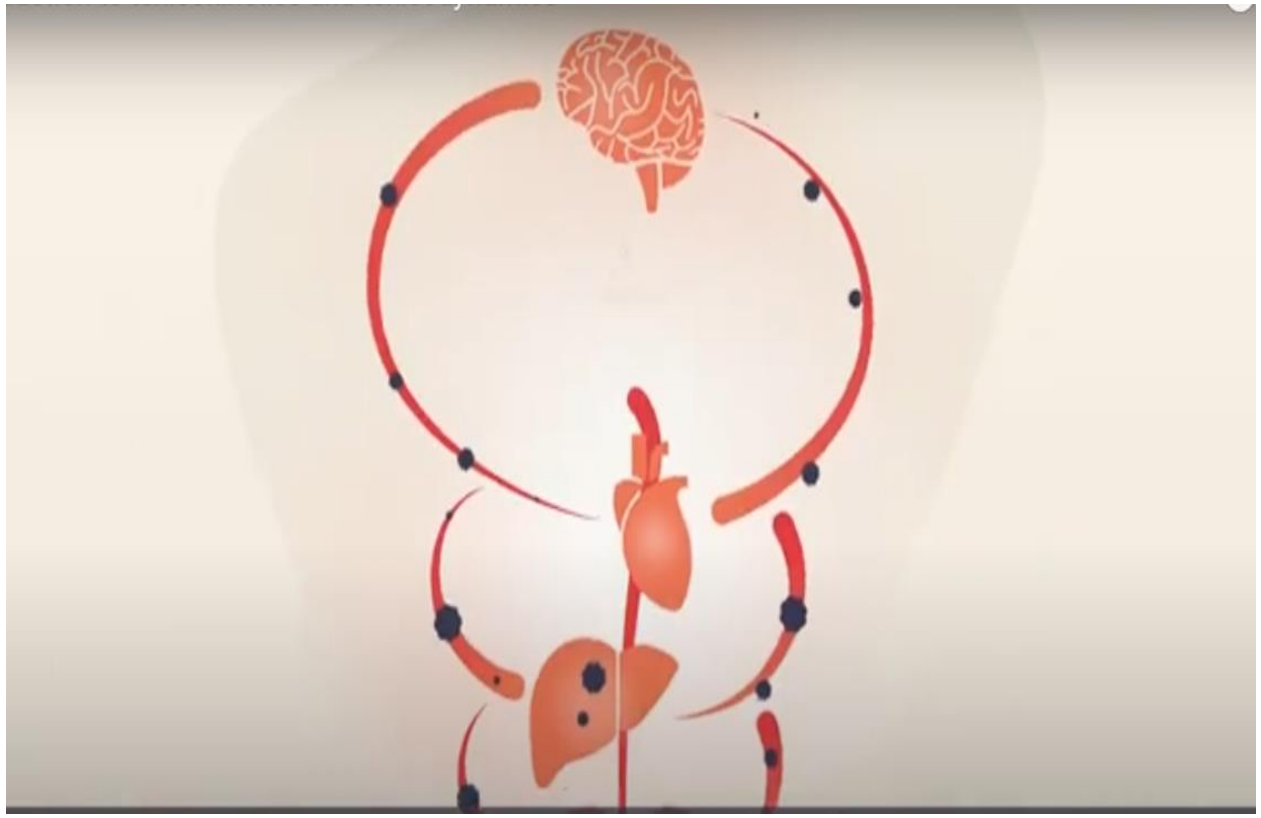


- Image : illustration the most lipid soluble substances can penetrate the epidermis and blood vessels.

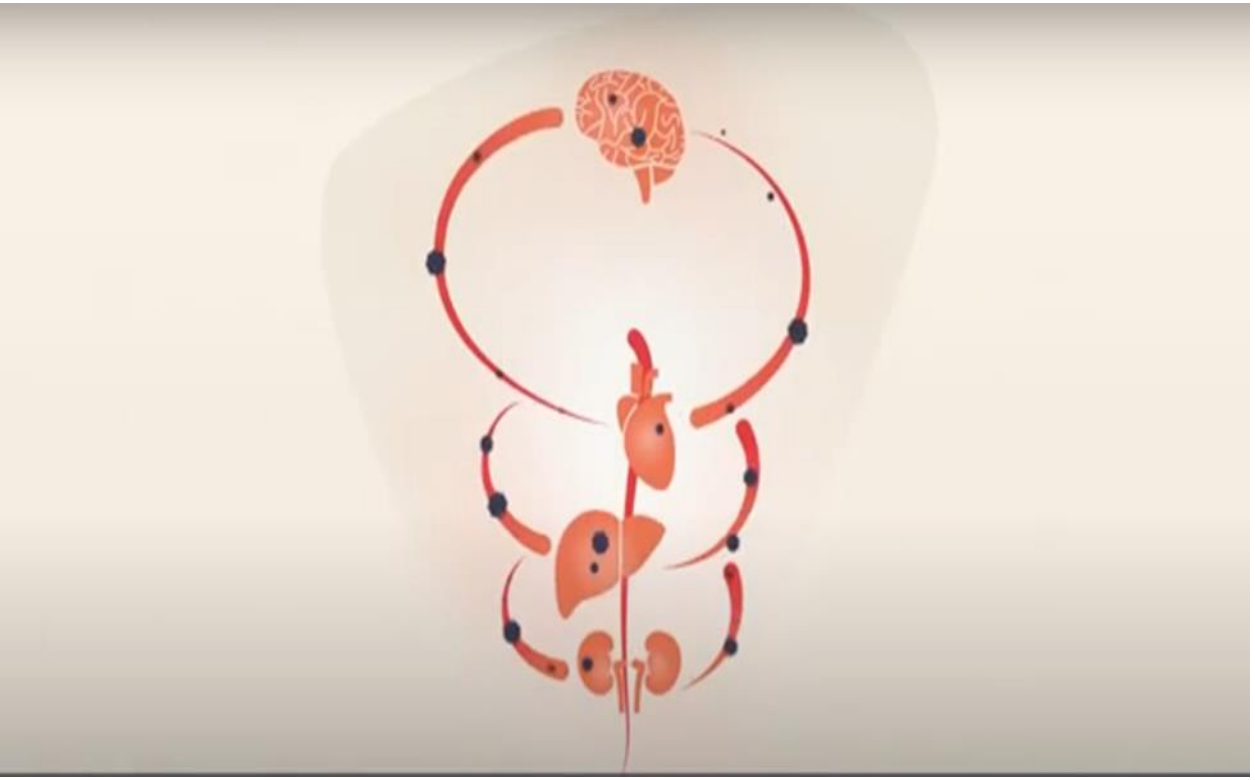


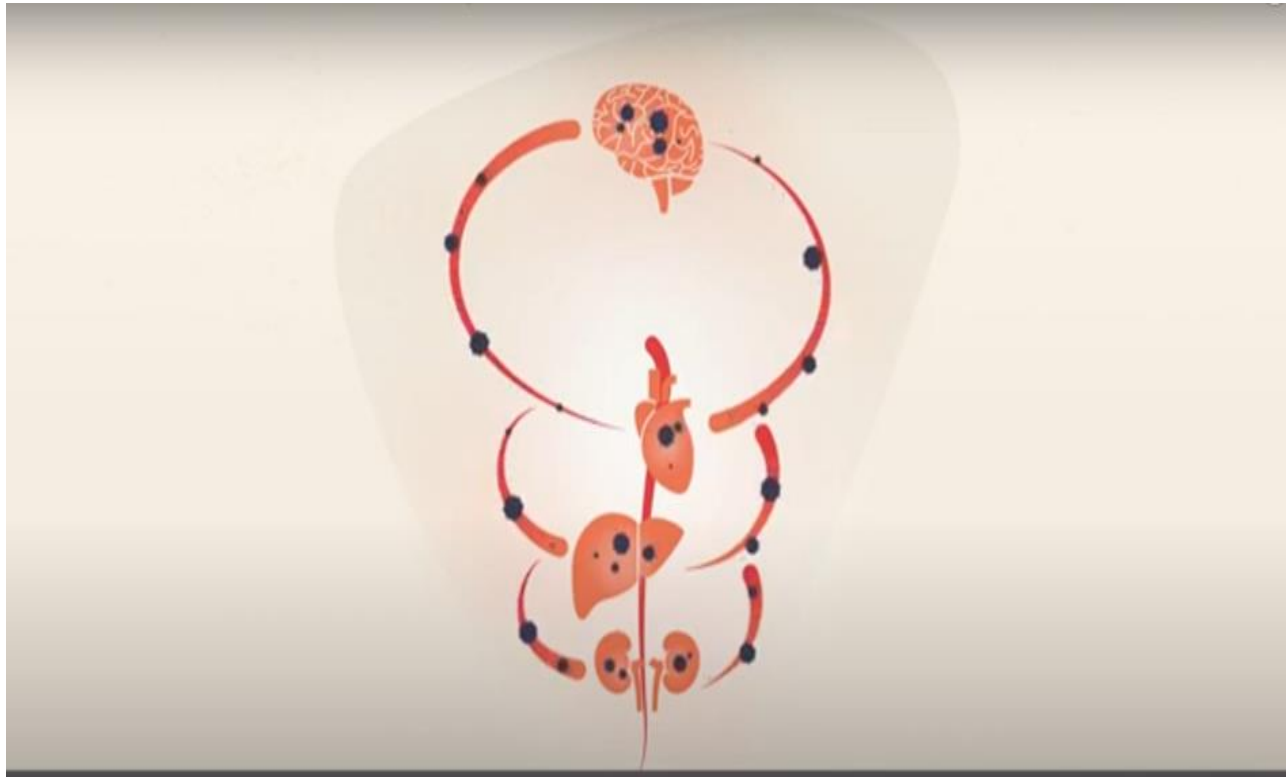


- Filtration in the capillaries help chemicals enter the fluid between the cells and intracellular



- Distribution depends on the rate of blood perfusion that is higher in the liver, heart, kidney and brain





- Distribution depends on the rate of blood perfusion that is higher in the liver, heart, kidney and brain

Knowledge Check Questions

- **1) When an ingested toxicant is absorbed, it passes through the cells lining the GI tract into the:**
  a) Intracellular fluid
  b) Gastric fluid
  c) Interstitial fluid

  2) The apparent volume of distribution represents the:
  a) Total volume of body fluids in which a toxicant is distributed
  b) Amount of blood plasma in which a toxicant is dissolved
  c) Amount of interstitial fluid that contains a toxicant

Solutions

- 1) Interstitial fluid - **This is the correct answer.**

- When a chemical is absorbed it passes through cell linings of the absorbing organ (in this case, the gastrointestinal tract) into the interstitial fluid (fluid surrounding cells) within that organ.

- 2) Total volume of body fluids in which a toxicant is distributed - **This is the correct answer.**
- The apparent volume of distribution (VD) represents the total volume of body fluids in which a toxicant is distributed. It consists of the interstitial fluid, intracellular fluid, and the blood plasma. Soon after absorption, a toxicant may be distributed to all three types of fluids, although the concentrations may be quite different. Rarely will a toxicant be distributed to only one type of fluid.

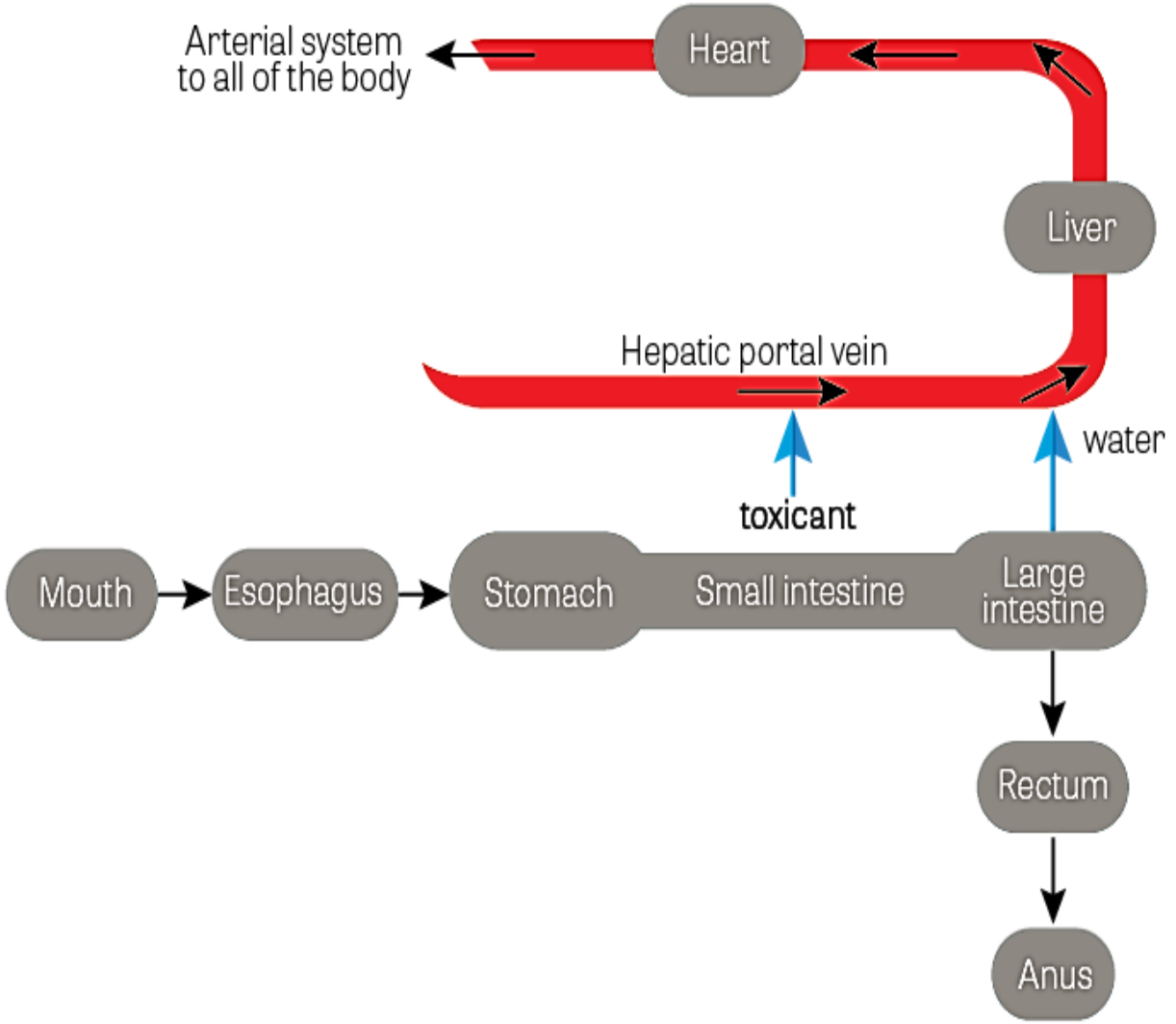
Movement of a toxicant through the portal system

Lung and Skin

Drugs and other substances that are absorbed through the lungs or skin enter the bloodstream to be carried throughout the body.

Thus, they avoid the liver (hepatic) first-pass effect that would have occurred if they had been absorbed from the gastrointestinal tract. These substances can have local effects in the lungs or skin in addition to having systemic effects, and some cells in the lungs and skin may metabolize the drug or other substance.

Examples of a "local first-pass effect" in the skin due to metabolism are when nitroglycerin and cortisol applied to the skin. Drugs administered intravenously or intramuscularly also enter the bloodstream to be carried throughout the body and avoid the liver (hepatic) first-pass effect.



Lymph

The delivery of drugs and bioactive compounds via the lymphatic system avoids first-pass metabolism by the liver and increases oral bioavailability.

It is also a way to deliver drugs for diseases that spread through the lymphatic system such as certain types of cancer and the human immunodeficiency virus (HIV).

For example, **liposomes** composed of **phosphatidylethanol** can enhance the oral bioavailability of poorly absorbed hydrophilic drugs such as **cefotaxime**.

Liposomes

- **Liposomes** are small sphere-shaped vesicles which consist of one or more bilayers created from cholesterol and phospholipids. They were first described in the mid-1960s. Liposomes offer several advantages for delivery of some drugs. They:

  Are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations.
- Can provide increased efficacy, stability, and therapeutic index for some drugs.
- Can reduce the toxicity of the encapsulated drug.

- Can help reduce the exposure of sensitive tissues to toxic drugs.
- Can be used with other molecules to offer site-specific "ligand-targeted liposome design" for delivery of a drug to a tumor or elsewhere in the body.

Blood

The blood levels of a drug or other substance depend on the site of absorption, whether being absorbed after subcutaneous injection or more quickly from intramuscular injection.

These blood levels also depend on the individual's rate of local and systemic biotransformation, and the rate of excretion. Uptake and release can occur in areas of the body away from the first site of absorption.

Some anesthetics can be taken up by the lungs and later released, impacting blood levels.

Lidocaine, given intravenously, is one example of this later release. Further, as noted, the metabolism of a substance can vary widely from person-to-person due to factors such as genetic differences, age, diet, and diseases that affect metabolism.

Some advantages of intramuscular injections:

- They are absorbed faster than subcutaneous injection, partly because muscle tissue has a larger blood supply than tissue just under the skin.
- They can hold a greater injected volume of drug (or vaccine) than a subcutaneous tissue injection can.
- They can be used instead of intravenous injection if a drug is irritating to veins or if a suitable vein cannot be located.
- They may be used instead of oral delivery if a drug is known to be degraded by stomach acids.

Training Questions

- **1) The main difference in distribution of a toxicant absorbed from the gastrointestinal tract from toxicants absorbed through the skin or from inhalation is:**

a) The toxicant is distributed to more organs
b) A greater amount of the toxicant that is absorbed will be distributed to distant parts of the body
c) The toxicant enters the systemic circulatory system after first passing through the liver

Answer

- 1) The toxicant enters the systemic circulatory system after first passing through the liver - **This is the correct answer.**

Toxicants that enter the vascular system of the gastrointestinal tract are carried directly to the liver by the portal system. Thus, toxicants are immediately subject to biotransformation or excretion by the liver. This is often referred to as the "first pass effect."

Structural Barriers to Distribution

- Organs or tissues differ in the amount of a chemical that they receive or to which they are exposed. This is primarily due to two factors:

- 1) **volume of blood** flowing through a specific tissue.
- 2) **presence of special barriers** to slow down a toxicant's entrance.

Structural Barriers to Distribution

- During distribution, the passage of toxicants from capillaries into various tissues or organs is not uniform.

- **Structural barriers** exist that restrict the entrance of toxicants into certain organs or tissues.

- The primary barriers are those of the brain, placenta, and testes.

Blood-Brain Barrier

- The **blood-brain barrier** protects the brain from most toxicants. Specialized cells called astrocytes possess many small branches, which form a barrier between the capillary endothelium and the neurons of the brain.

- Lipids in the astrocyte cell walls and very tight junctions between adjacent endothelial cells limit the passage of water-soluble molecules.

- The blood-brain barrier is not completely impenetrable and its penetrability can vary with health status/disease state, but it does slow down the rate at which toxicants cross into brain tissue while allowing essential nutrients, including oxygen, to pass through.

Placental Barrier

- The **placental barrier** protects the sensitive, developing fetus from most toxicants distributed in the maternal circulation. This barrier consists of several cell layers between the maternal and fetal circulatory vessels in the placenta.

- Lipids in the cell membranes limit the diffusion of water-soluble toxicants. However, nutrients, gases, and wastes of the developing fetus can pass through the placental barrier.

- As in the case of the blood-brain barrier, the placental barrier is not completely impenetrable but effectively slows down the diffusion of most toxicants from the mother into the fetus.

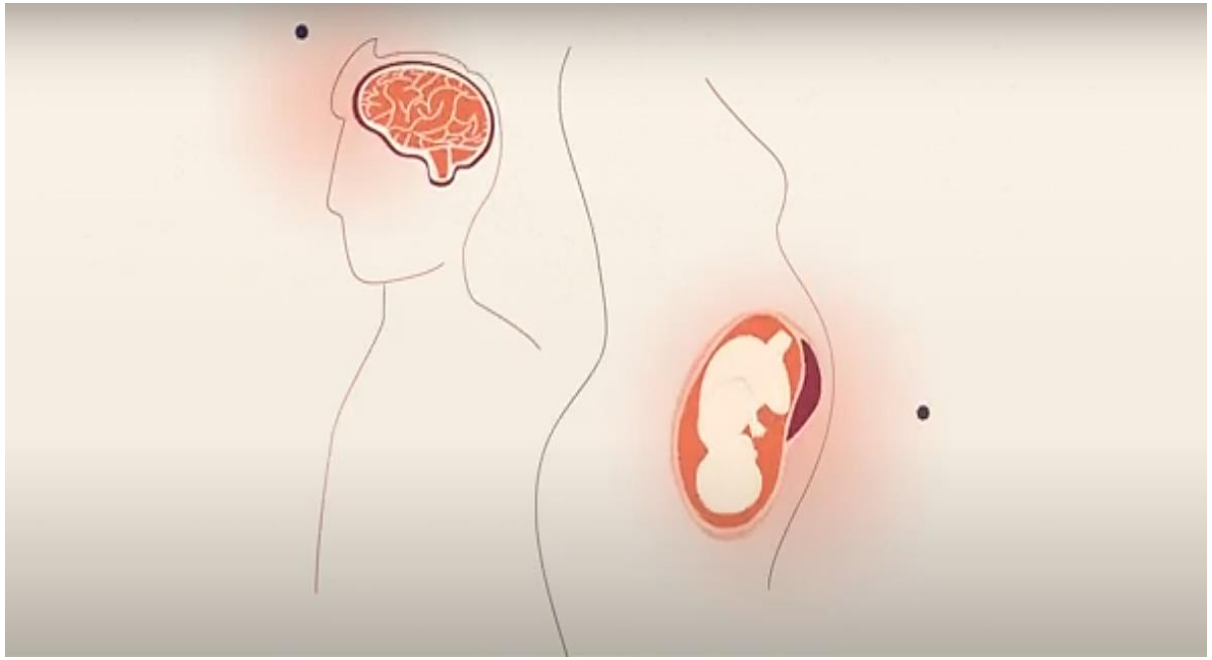
Release of lipid-soluble toxins

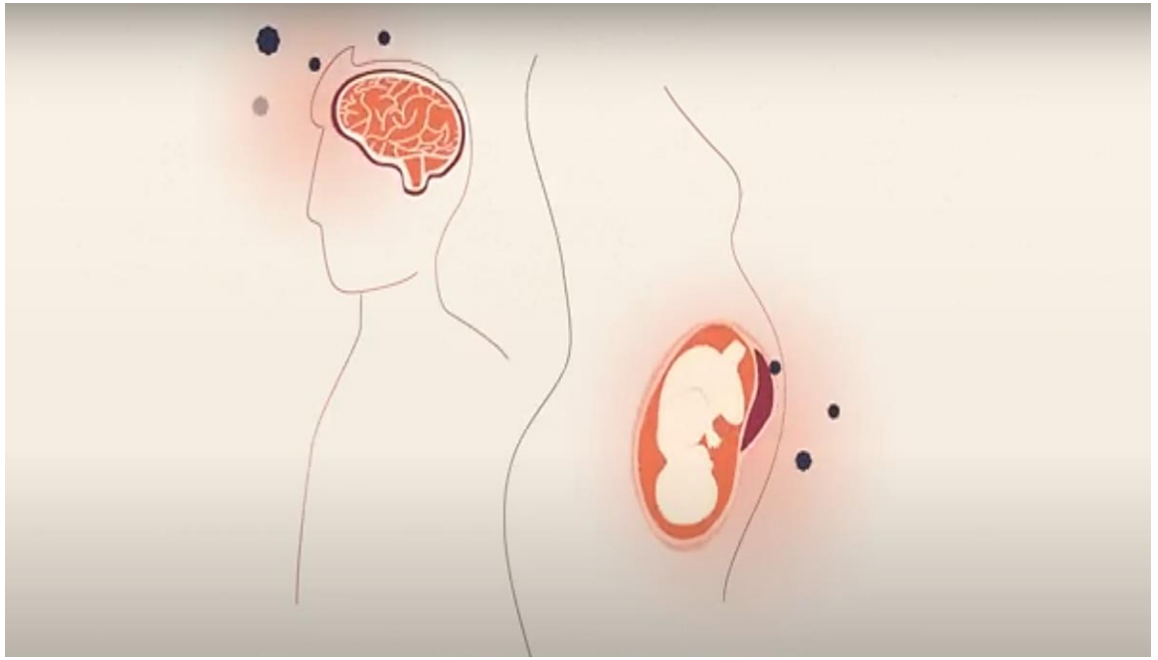
- During certain physiological conditions such as pregnancy and lactation, stored toxins, including heavy metals and fat-soluble substances, can be released back into the bloodstream.
- This happens because the body mobilizes fat stores to support the growing fetus or produce milk, leading to the release of lipid-soluble toxins. These released substances can cross the placental barrier and enter the fetal circulation or be excreted into breast milk,
- potentially exposing the baby to harmful toxins. This process highlights the importance of managing toxin exposure, especially for women of childbearing age.

During pregnancy and lactation released substances can cross the placental barrier

- Image illustration getting back into blood stream again in certain physiological conditions, for example during pregnancy and lactation

Phenomena of Blood and Placental Barrier





- Image illustration some tissue are more protected from entering of chemicals the phenomena of blood and placental barrier

Certain tissues, like the brain and the developing fetus, are better protected from chemical entry due to the blood-brain barrier and placental barrier. The blood-brain barrier is composed of tightly packed endothelial cells, which prevent most chemicals from entering the brain, protecting it from potentially harmful substances. Similarly, the placental barrier helps regulate which substances can pass from a mother's bloodstream to the fetus, acting as a protective filter to minimize exposure to harmful chemicals while still allowing essential nutrients to pass through.

Knowledge Check Questions

- **1) Organs may differ greatly in the concentration of a toxicant in them, due primarily to the:**

a) Rate of elimination of the toxicant by the kidneys
b) Distance of the organ from the heart since the toxicant disintegrates quickly in the blood plasma
c) Volume of blood flow and the presence of special barriers

Knowledge Check Questions

- **2) The placental barrier protects the fetus from toxicants in the maternal blood because:**

a) Substances in the maternal blood must move through several layers of cells in order to gain entrance to placental blood
b) The placenta does not contain circulating fetal blood that can absorb toxicants from the maternal blood
c) Toxicants in maternal blood are usually lipid soluble and must be water-soluble in order to penetrate through the placental cell layers

Answers

- 1) Volume of blood flow and the presence of special barriers - **This is the correct answer.**

Organs or tissues differ in the amount of a chemical that they receive or to which they are exposed. This is primarily due to two factors, the **volume of blood** flowing through a specific tissue and the **presence of special "barriers"** to slow down toxicant entrance. Organs that receive larger blood volumes can potentially accumulate more of a given toxicant.

- 2) Substances in the maternal blood must move through several layers of cells in order to gain entrance to placental blood - **This is the correct answer.**

The placental barrier protects the developing and sensitive fetus from most toxicants distributed in the maternal circulation. This barrier consists of several cell layers between the maternal and fetal circulatory vessels in the placenta. Lipids in the cell membranes limit the diffusion of water-soluble toxicants.

-

Storage Sites

- **Storage** of toxicants in body tissues sometimes occurs. Initially, when a toxicant enters the blood plasma, it may be bound to plasma proteins.

- Toxicants attached to proteins are considered a form of storage because they do not contribute to the chemical's toxic potential. Albumin is the most abundant plasma protein that binds toxicants.

- Normally, the toxicant is only bound to the albumin for a relatively short time. The primary sites for toxicant storage are adipose tissue, bone, liver, and kidneys.

Liver and Kidneys

- The **liver** is a storage site for some toxicants. It has a large blood flow and its hepatocytes (that is, liver cells) contain proteins that bind to some chemicals, including toxicants.

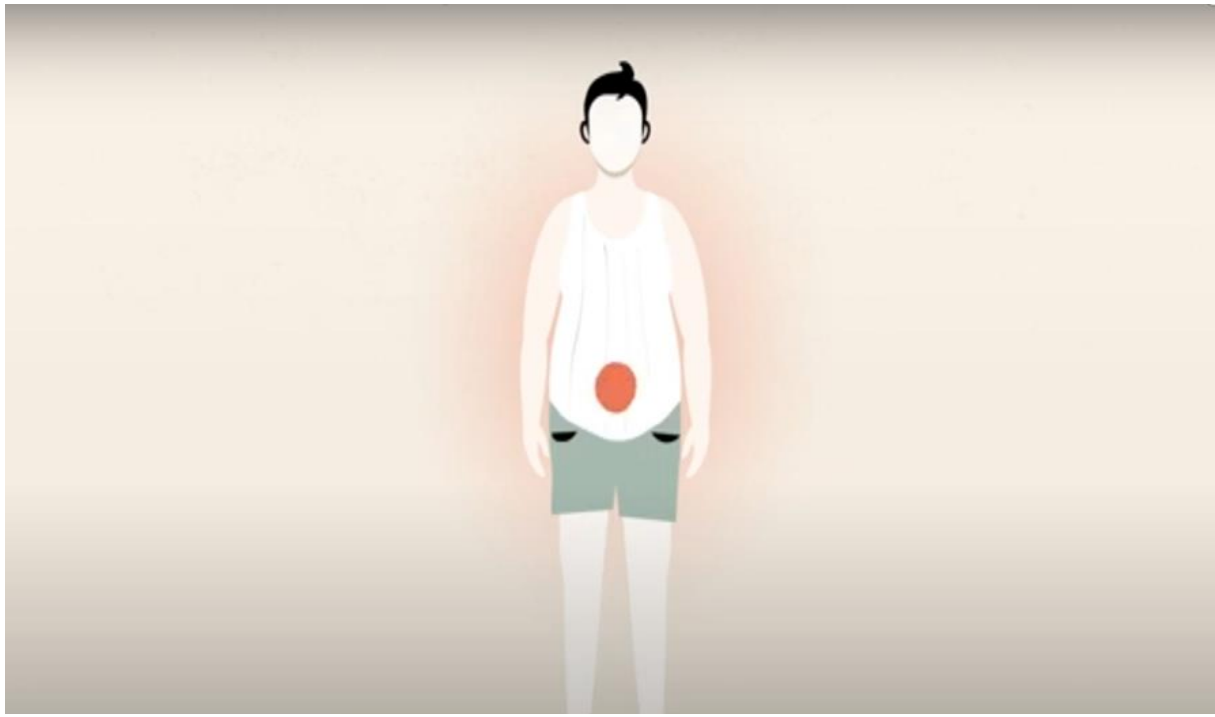
  As with the liver, the **kidneys** have a high blood flow, which preferentially exposes these organs to toxicants in high concentrations.

- Storage in the kidneys is associated primarily with the cells of the nephron (the functional unit for urine formation).

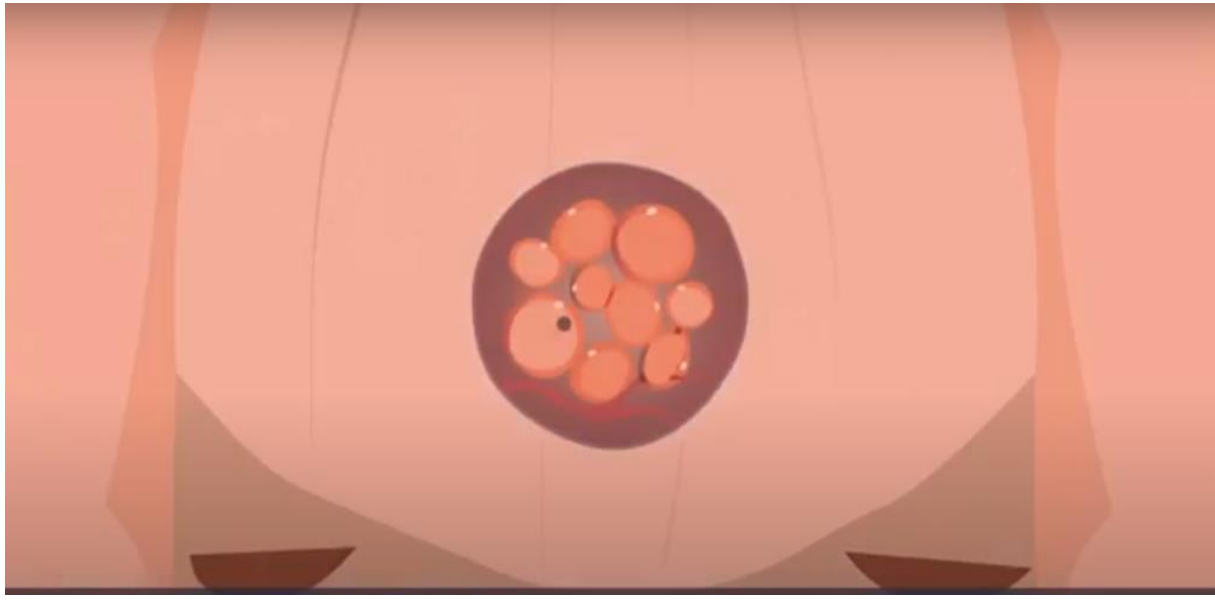
Adipose Tissue

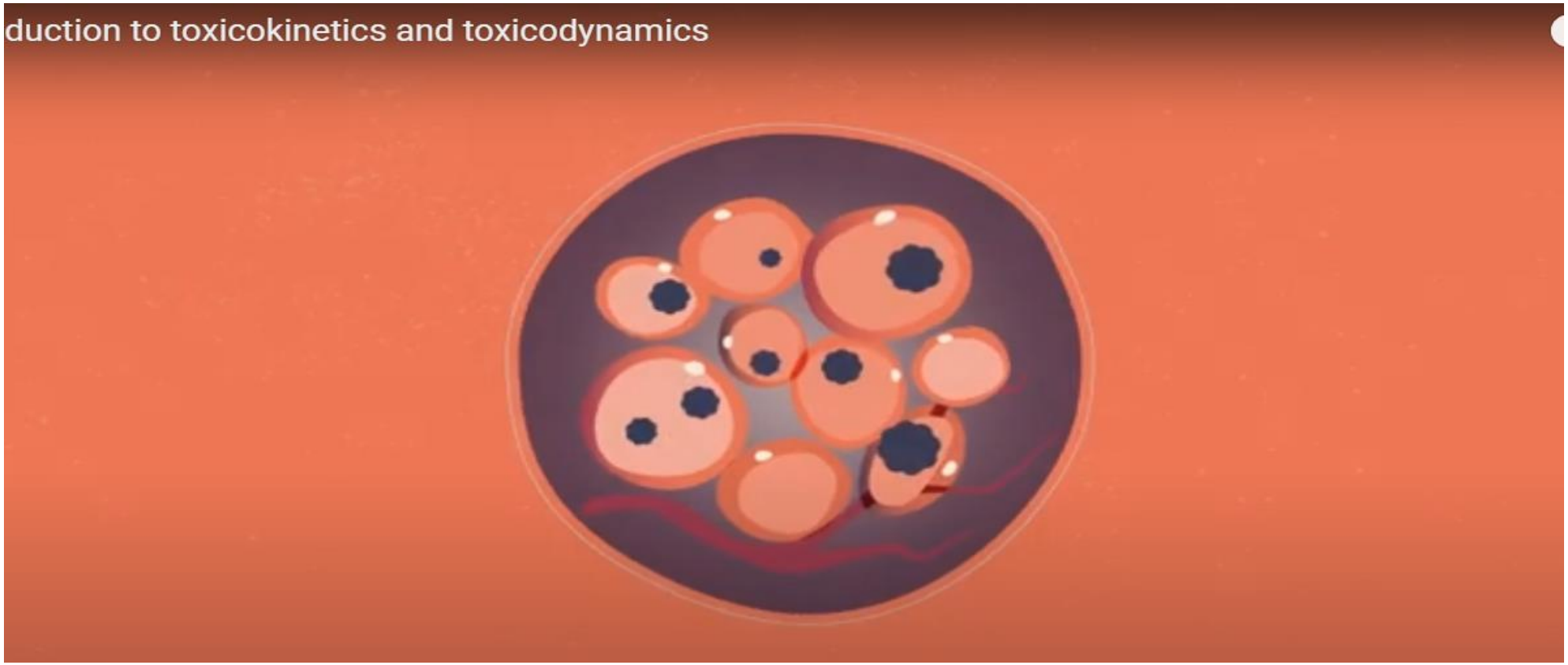
- Lipid-soluble toxicants are often stored in **adipose tissues**. Adipose tissue is located in several areas of the body but mainly in subcutaneous tissue. Lipid-soluble toxicants can be deposited along with triglycerides in adipose tissues.

- The lipids are in a continual exchange with blood and thus the toxicant may be mobilized into the blood for further distribution and elimination, or redeposited in other adipose tissue cells.



- Chemicals with high affinity for certain tissues, for example, bone or adipose tissue can accumulated store for long time





- Chemicals with a high affinity for specific tissues, such as bone or adipose (fat) tissue, can accumulate and be stored in these sites for extended periods. This occurs because these tissues possess properties that facilitate the uptake and retention of certain substances. For example, fat-soluble compounds tend to be sequestered in adipose tissue, while some metals and certain pharmaceuticals can be deposited in bones. This accumulation can lead to prolonged exposure and potential toxicity, as the stored chemicals may gradually be released back into circulation over time, potentially impacting health even after the initial exposure has ended.

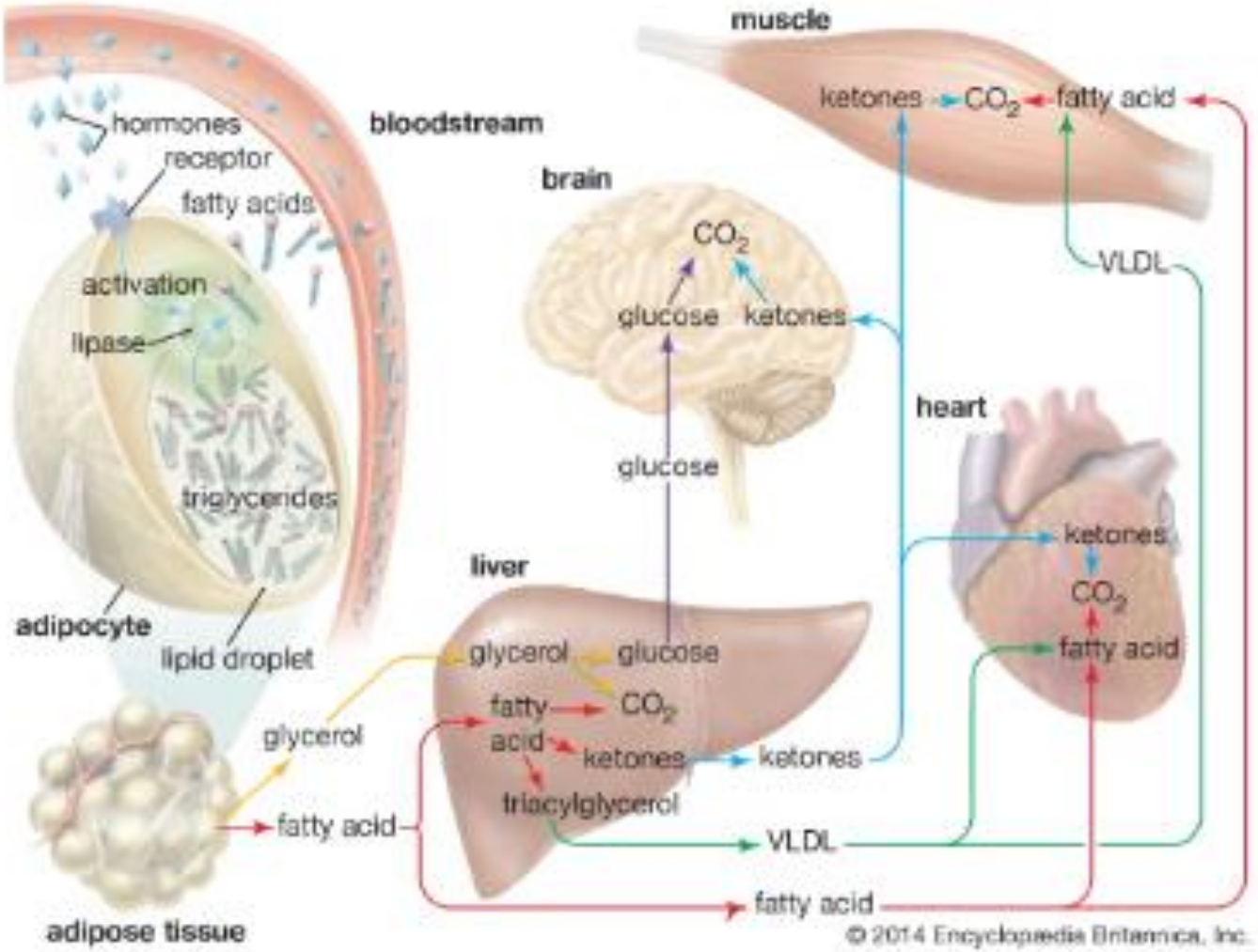


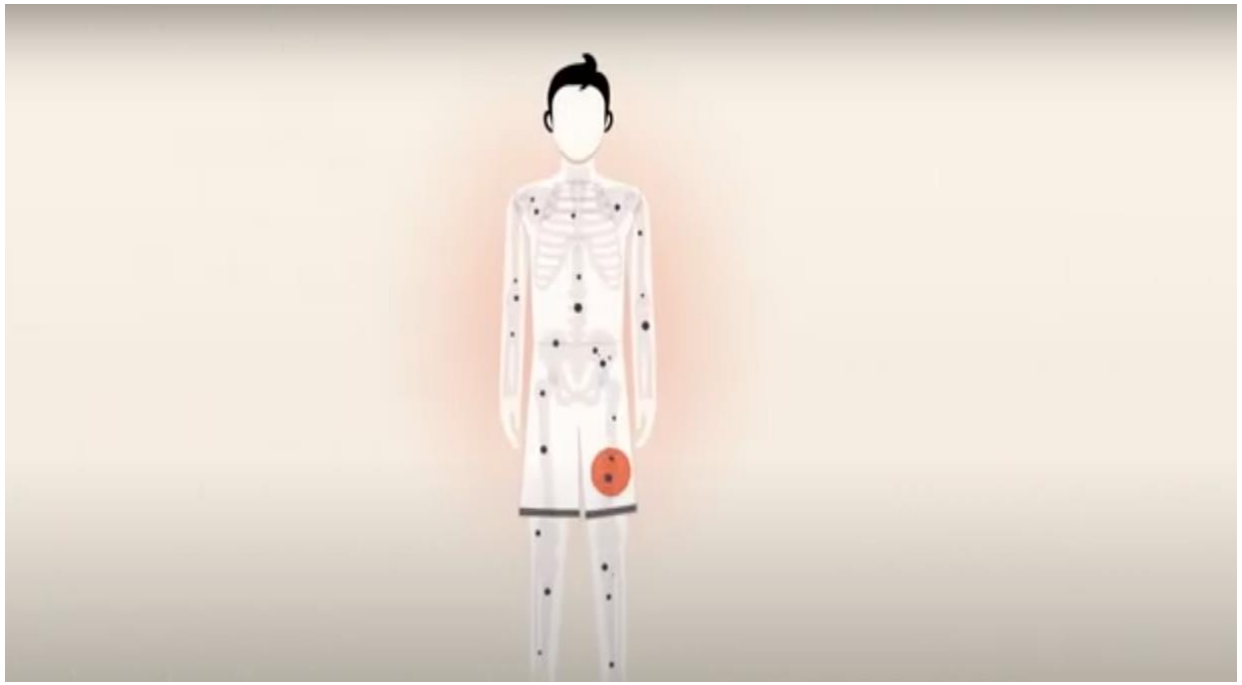
Image illustration hormone signaling; adipose tissue
When hormones signal the need for energy, fatty acids and glycerol are released from triglycerides stored in fat cells (adipocytes) and are delivered to organs and tissues in the body.

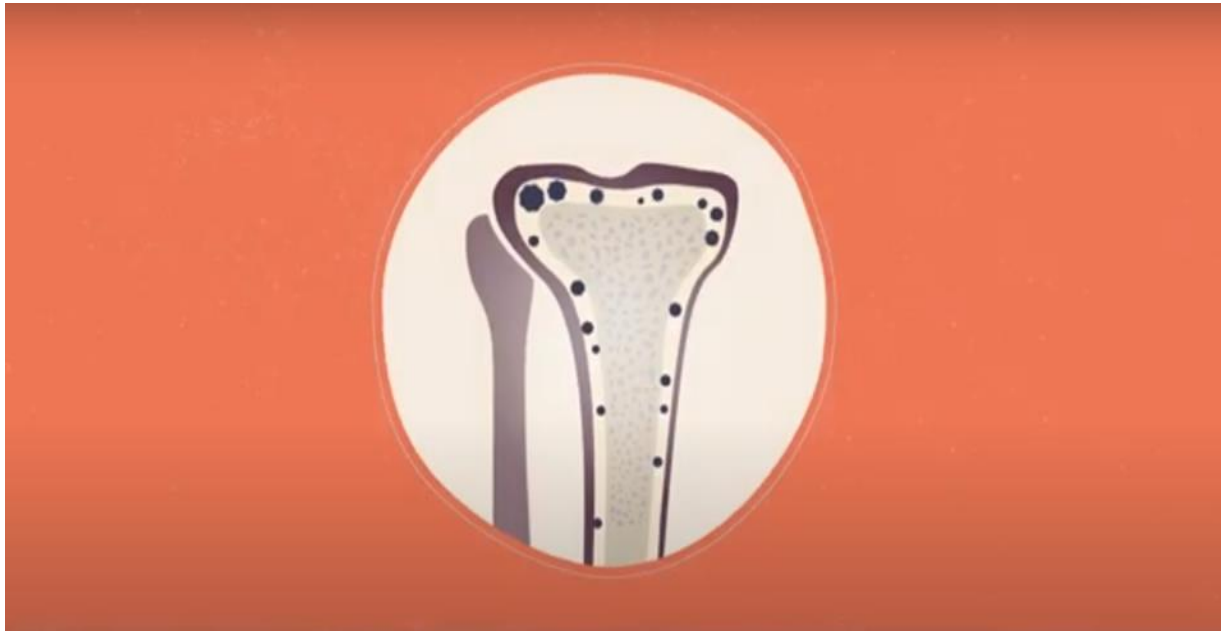
Bone

- **Bone** is another major site for storage. Bone is composed of proteins and the mineral salt hydroxyapatite. Bone contains a sparse blood supply but is a live organ.

- During the normal processes that form bone, calcium and hydroxyl ions are incorporated into the hydroxyapatite-calcium matrix.

- Several chemicals, primarily elements, follow the same kinetics as calcium and hydroxyl ions and therefore can be substituted for them in the bone matrix.





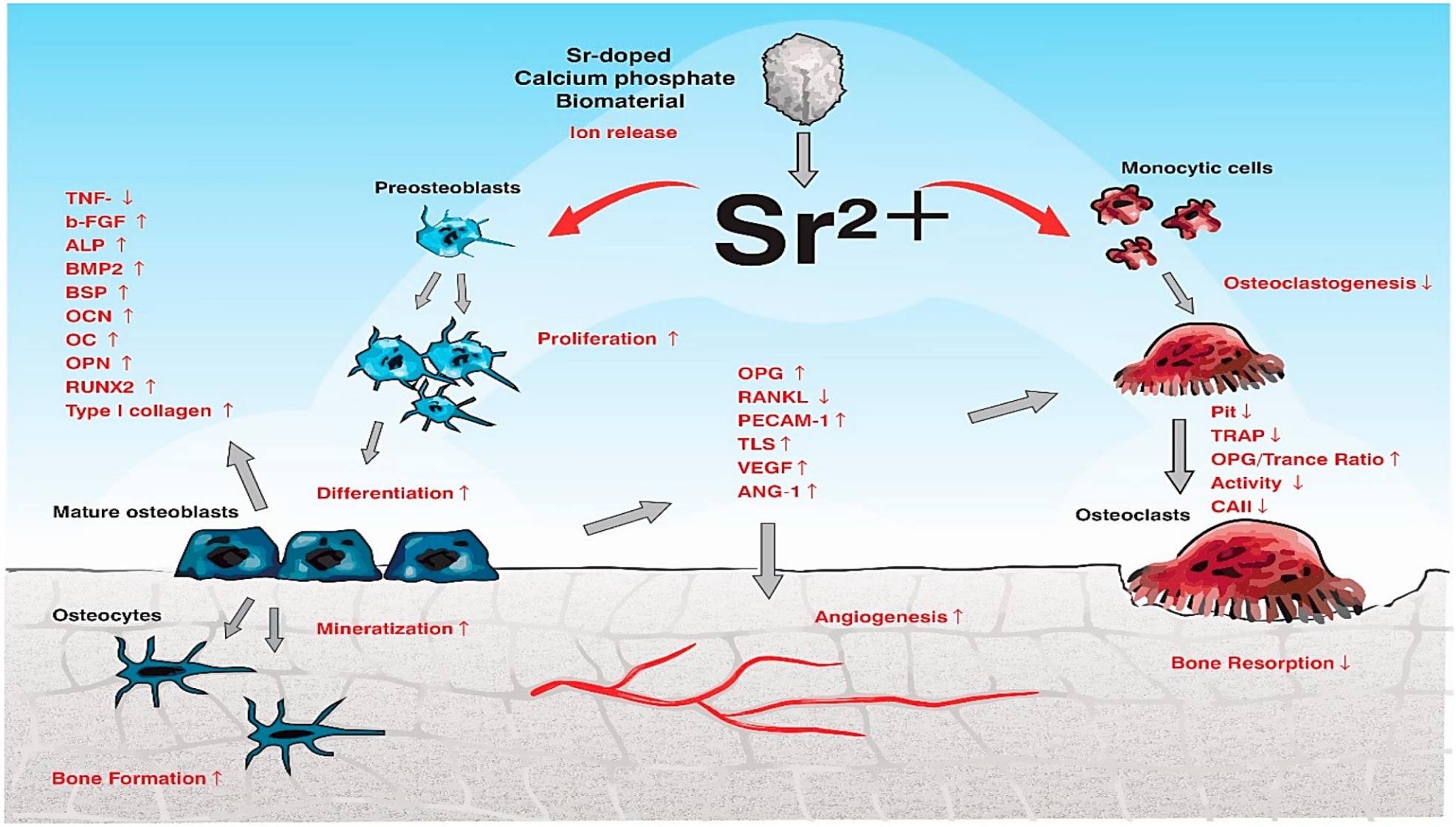
- Chemicals with high affinity for certain tissues, for example, bone or adipose tissue can accumulated store for long time

Bone

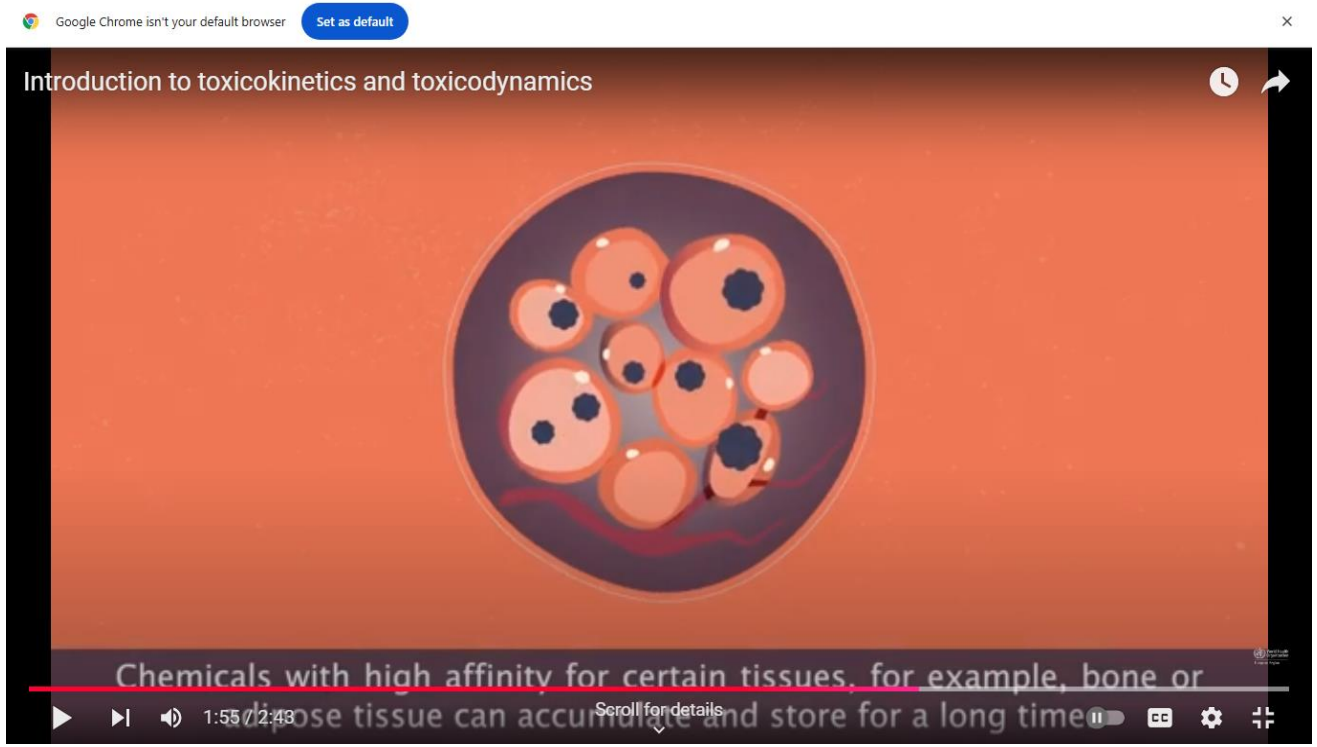
- For example, strontium (Sr) or lead (Pb) may be substituted for calcium (Ca), and fluoride (F-) may be substituted for hydroxyl (OH-) ions.

- Bone is continually being remodeled under normal conditions. Calcium and other minerals are continually being resorbed and replaced, on the average about every 10 years.

- Thus, any toxicants stored in the matrix will eventually be released to re-enter the circulatory system.



Schematic representation of the effects of doping calcium phosphate-based biomaterials with strontium ions on biological events, from strontium ion release into the biological medium to novel bone formation. Strontium also induces the release of angiogenic factors, enhancing tissue regeneration.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Introduction to toxicokinetics and toxicodynamics
Chemicals with high affinity for certain tissues, for example, bone or
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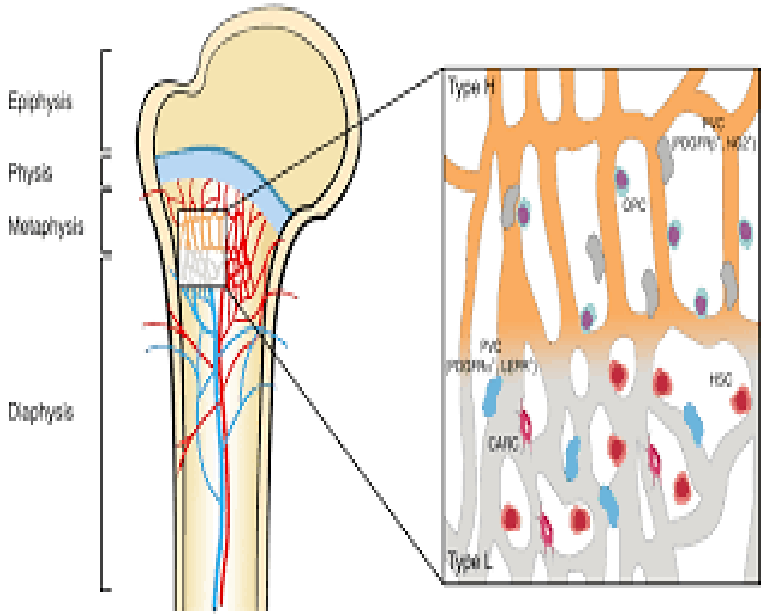
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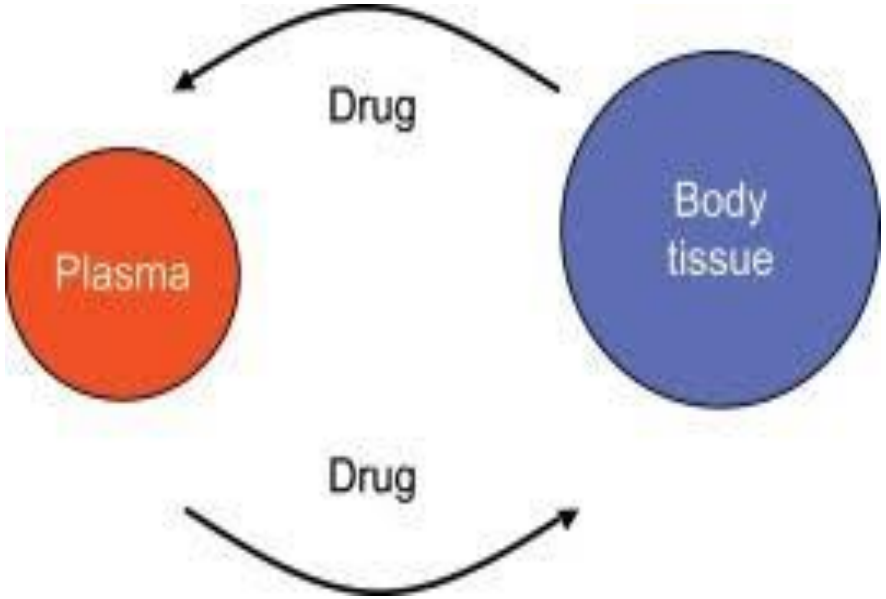
Drug
Plasma
Body tissue
Drug

Knowledge Check Questions

- **1) The areas of the body which most frequently store toxicants are:**

  a) Adrenal gland, thyroid gland, and pancreas

  b) Adipose tissue, bone, liver, and kidney

  c) Skeletal muscle, tendons, and leg joints

Answers

- 1) Adipose tissue, bone, liver, and kidney - **This is the correct answer.**

- The primary sites for toxicant storage are adipose tissue, bone, liver and kidneys. Lipid-soluble toxicants store in adipose tissues; chemicals that follow calcium or hydroxyl ion kinetics store in bone; and the liver and kidney cells are subjected to high concentrations of toxicants.

What We've Covered

This section made the following main points:

- Distribution is the process in which an absorbed chemical moves away from the site of absorption to other areas of the body.
- An absorbed chemical passes through cell linings of the absorbing organ (skin, lung, or gastrointestinal tract) into the interstitial fluid of that organ.
- The toxicant can leave the interstitial fluid by entering local tissue cells, blood capillaries and the blood circulatory system, or the lymphatic system.
- If the toxicant gains entrance into the blood plasma, it:
    - Travels bound or unbound along with the blood.
    - May be excreted, stored, or biotransformed, or may interact or bind with cellular components.

What We've Covered

This section made the following main points:

- The volume of distribution (VD) is the total volume (in liters) of body fluids in which a toxicant is distributed.
- The route of exposure is an important factor affecting the concentration of the toxicant or its metabolites at any specific location within the blood or lymph.
  - Toxicants entering from the GI tract or peritoneum are immediately subject to biotransformation or excretion by the liver and elimination by the lung (this is often called the "first-pass effect").
  - Toxicants absorbed through the lung or skin enter the blood and go directly to the heart and systemic circulation, thus being distributed to various organs before going to the liver (not subject to the first-pass effect).
  - Toxicants that enter the lymph will not go to the liver first, but will slowly enter systemic circulation.
  - The blood level of a toxicant depends on the site of absorption and the rate of biotransformation and excretion.

What We've Covered

This section made the following main points:

- Organs or tissues differ in the amount of a chemical they may receive, depending on:
  - Volume of blood — organs that receive larger blood volumes potentially accumulate more of a given toxicant.
  - Tissue affinity — some tissues have a higher affinity for specific chemicals, accumulating a toxicant in great concentrations despite a rather low flow of blood.
- Structural barriers to distribution include the blood-brain barrier and the placental barrier.
- Toxicants can also be stored:
  - When bound to plasma proteins in the blood
  - In adipose tissues
  - In bone
  - In the liver
  - In the kidneys

Introduction to Biotransformation

- **Biotransformation** is the process by which a substance changes from one chemical to another (transformed) by a chemical reaction within the body. **Metabolism** or **metabolic transformations** are terms frequently used for the biotransformation process. However, metabolism is sometimes not specific for the transformation process but may include other phases of toxicokinetics.

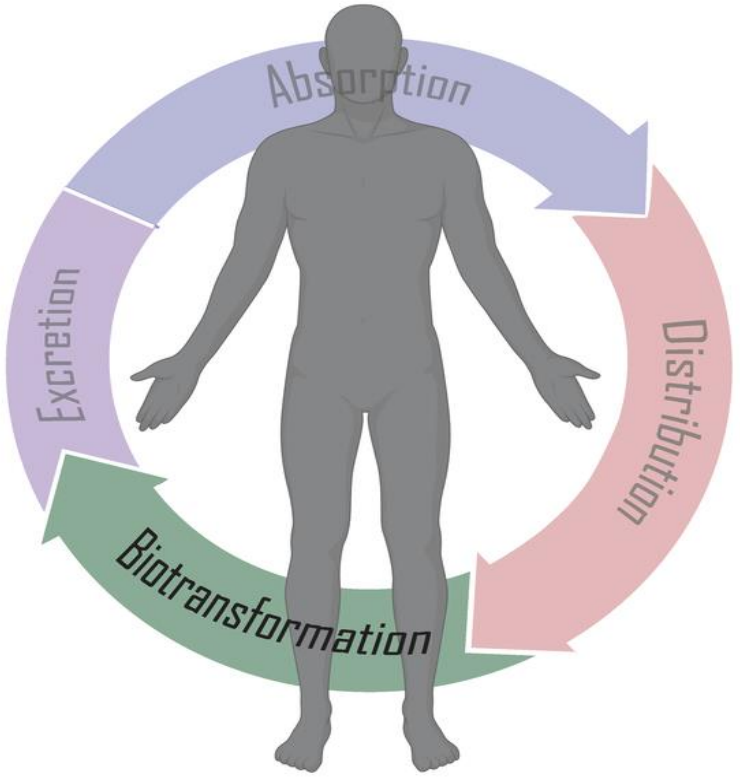

Image illustration Processes of toxicokinetics

Metabolism (Biotransformation)

- **Phases of Metabolism:**
  - **Phase I (Modification):** Oxidation, reduction.
  - **Phase II (Conjugation):** Increases solubility for excretion.
- **Enzymes Involved:** Cytochrome P450 enzymes.
- **Outcome:** Conversion into more or less toxic metabolites.

Importance of Biotransformation

- Biotransformation is vital to survival because it transforms absorbed nutrients (food, oxygen, etc.) into substances required for normal body functions. For some pharmaceuticals, it is a metabolite that is therapeutic and not the absorbed drug.

  For example, phenoxybenzamine, a drug given to relieve hypertension caused by pheochromocytoma, a kind of tumor, is biotransformed into a metabolite, which is the active agent.

  Biotransformation also serves as an important defense mechanism since toxic xenobiotics and body wastes are converted into less harmful substances and substances that can be excreted from the body.

Importance of Biotransformation

- Toxicants that are lipophilic, non-polar, and of low molecular weight are readily absorbed through the cell membranes of the skin, GI tract, and lung.

- These same chemical and physical properties control the distribution of a chemical throughout the body and its penetration into tissue cells.

- Lipophilic toxicants are hard for the body to eliminate and can accumulate to hazardous levels. However, most lipophilic toxicants can be transformed into hydrophilic metabolites that are less likely to pass through membranes of critical cells.

- Hydrophilic chemicals are easier for the body to eliminate than lipophilic substances. Biotransformation is thus a key body defense mechanism. Fortunately, the human body has a well-developed capacity to biotransform most xenobiotics as well as body wastes.

Hemoglobin

Hemoglobin, the oxygen-carrying iron-protein complex in red blood cells, is an example of a body waste that must be eliminated. The normal destruction of aged red blood cells releases hemoglobin.

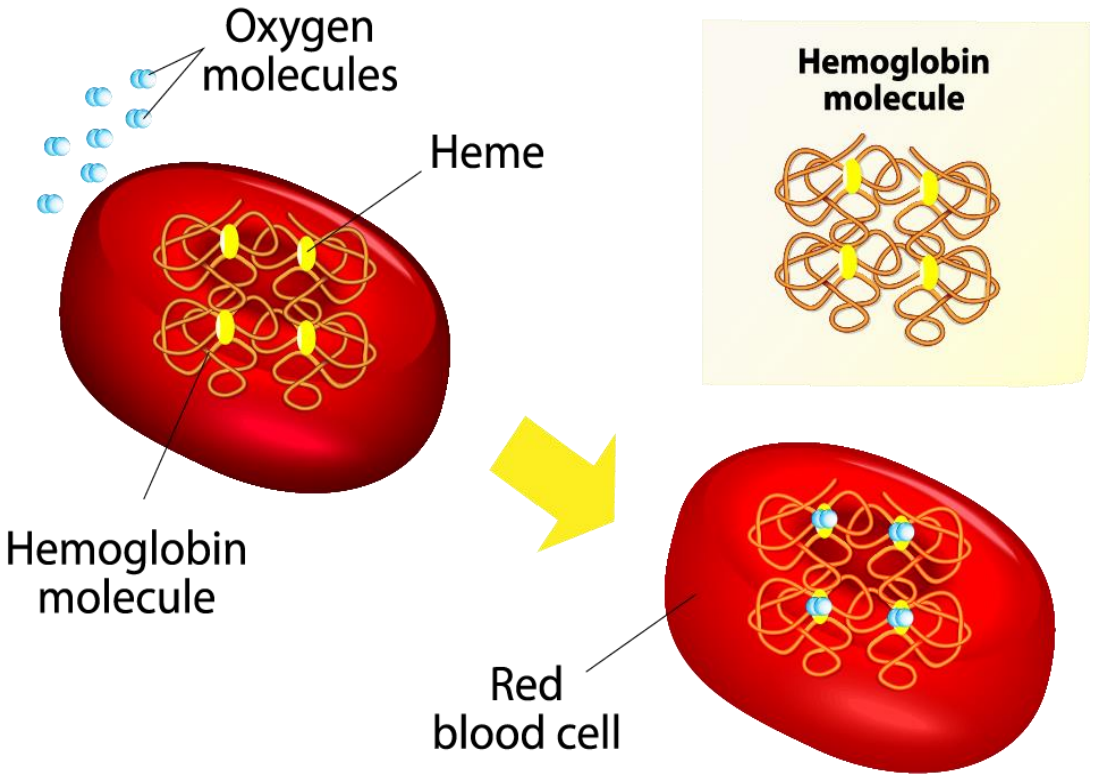

Image illustration Human hemoglobin

Bilirubin

- Bilirubin is one of several hemoglobin metabolites. If the body cannot eliminate bilirubin via the liver because of disease, medicine, or infection, bilirubin builds up in the body and the whites of the eyes and the skin may look yellow.

- Bilirubin is toxic to the brain of newborns and, if present in **high concentrations**, may cause irreversible brain injury.

- Biotransformation of the lipophilic bilirubin molecule in the liver results in the production of water-soluble (hydrophilic) metabolites excreted into bile and eliminated via the feces.

Potential Complications

- The biotransformation process is not perfect. **Detoxification** occurs when biotransformation results in metabolites of lower toxicity. In many cases, however, the metabolites are more toxic than the parent substance, a process called **bioactivation**.

- Occasionally, biotransformation can produce an unusually reactive metabolite that may interact with cellular macromolecules like DNA. This can lead to very serious health effects such as cancer or birth defects.

- An example is the biotransformation of vinyl chloride into vinyl chloride epoxide, which covalently binds to DNA and RNA, a step leading to cancer of the liver.

Mechanism of **Xenobiotics** heavy metal toxicity in human.

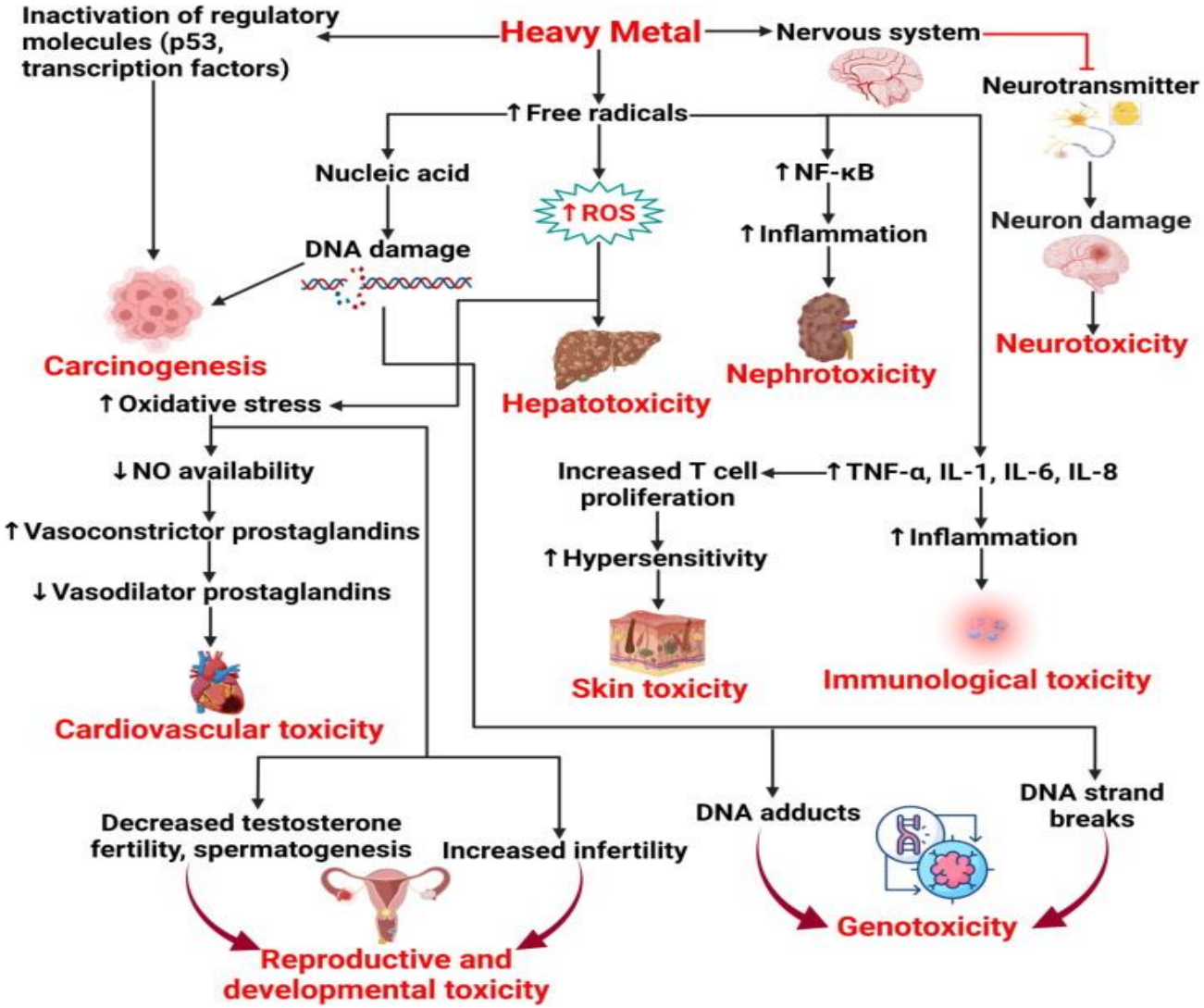

Image illustration the mechanism of heavy metal toxicity in human.

Heavy metal toxicity in humans primarily involves the disruption of cellular processes by binding to proteins and enzymes, interfering with their functions. This leads to oxidative stress, DNA damage, enzyme inhibition, and disruption of cellular signaling, which can cause organ damage and systemic health issues.

Generate reactive oxygen species (ROS)

- The mechanism of xenobiotic heavy metal toxicity in humans involves the metals binding to vital cellular components such as proteins and enzymes, altering their structure and inhibiting their function.

- These metals generate reactive oxygen species (ROS), leading to oxidative stress and cellular damage, including lipid peroxidation, DNA damage, and protein malfunction.

- Additionally, heavy metals can disrupt essential metal ion homeostasis, impair mitochondrial function, and interfere with cellular signaling pathways, contributing to tissue damage and toxicity.

Knowledge Check Questions

- **1) The term "biotransformation" refers to:**

a) An increase in electrical charge in tissues produced by a biological transformer
b) Chemical reactions in the body that create a new chemical from another chemical
c) The transformation of one type of cell in a tissue to another type of cell

2) Detoxification is a biotransformation process in which:

a) Metabolites of lower toxicity are produced
b) Metabolites of higher toxicity are produced

3) Bioactivation is a biotransformation process in which:

a) Metabolites of lower toxicity are produced
b) Metabolites of higher toxicity are produced

Solutions

- 1) Chemical reactions in the body that create a new chemical from another chemical - **This is the correct answer.**

Biotransformation is the process whereby a substance is changed from one chemical to another (transformed) by a chemical reaction within the body.

2) Metabolites of lower toxicity are produced - **This is the correct answer.**

When biotransformation results in metabolites of lower toxicity, the process is known as detoxification.

3) Metabolites of higher toxicity are produced - **This is the correct answer.**

When biotransformation results in metabolites of higher toxicity, this is known as bioactivation.

Metabolism of Xenobiotics

- **Biotransformation Processes**
  - **Phase I Reactions**: Oxidation, Reduction, Hydrolysis (e.g., Cytochrome P450 enzymes).
  - **Phase II Reactions**: Conjugation (e.g., Glucuronidation, Sulfation).
- **First Pass Metabolism**
  - Metabolism in the liver before reaching systemic circulation.
- **Factors Affecting Metabolism**
  - Genetic variations, Age, Liver function, Enzyme activity.
- **Case Examples**
  - Acetaminophen metabolism and toxicity.
  - Benzene metabolism leading to DNA damage.

Metabolism of xenobiotics

- Metabolism of xenobiotics refers to the biochemical processes that modify foreign substances entering the body, such as drugs, toxins, and environmental chemicals. These processes primarily occur in the liver and involve two main phases:

- Phase I Reactions: These involve the introduction or unmasking of functional groups (e.g., hydroxyl, amino) through processes like oxidation, reduction, or hydrolysis. Enzymes such as cytochrome P450 play a crucial role in these reactions, which can convert lipophilic compounds into more polar derivatives, making them easier to excrete.

- Phase II Reactions: These involve conjugation, where the metabolite from Phase I is linked to another substance (e.g., glucuronic acid, sulfate, glutathione) to form a more water-soluble compound. This enhances the compound's elimination from the body.

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TOXICOTHERAPY

INTRODUCTION TO TOXICOKINETICS

Xenobiotic Extraction and Toxicokinetic Processes:

Dr. Ahmad Hamdy Ibrahim

Toxicotherapy PHAR 421

Semester one

Week number 6

27/10/2024

Objectives

The students will be able to

1. Understand the importance of elimination in reducing the potential toxicity of xenobiotics.
2. Distinguish between the processes of excretion and elimination in the context of toxicology.
3. Identify key pathways and mechanisms by which xenobiotics and their metabolites are removed from the body.
4. Analyze factors that influence the rate of elimination and how they impact the concentration and toxicity of substances.
5. Explain the implications of slow versus rapid elimination on the potential for cellular damage and overall toxicity.

Introduction to Excretion

- Elimination from the body is very important in determining the potential toxicity of a xenobiotic. When the body rapidly eliminates a toxic xenobiotic (or its metabolites), it is less likely that they will be able to concentrate in and damage critical cells.

- The terms excretion and elimination are frequently used to describe the same process in which a substance leaves the body.

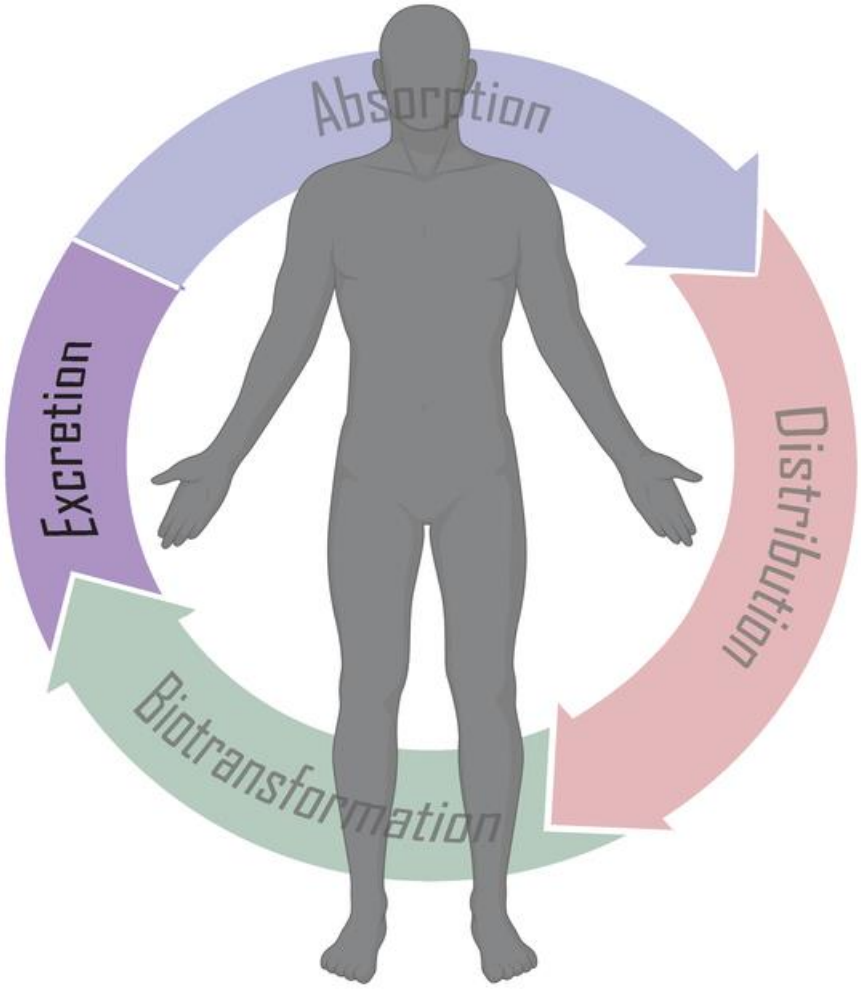


Image illustration Processes of toxicokinetics

Introduction to Elimination

- **Elimination** is sometimes used in a broader sense and includes the removal of the absorbed xenobiotic through metabolic pathways as well as through excretion.

- **Excretion**, as used here, pertains to the elimination of the xenobiotic and its metabolites by specific excretory organs.

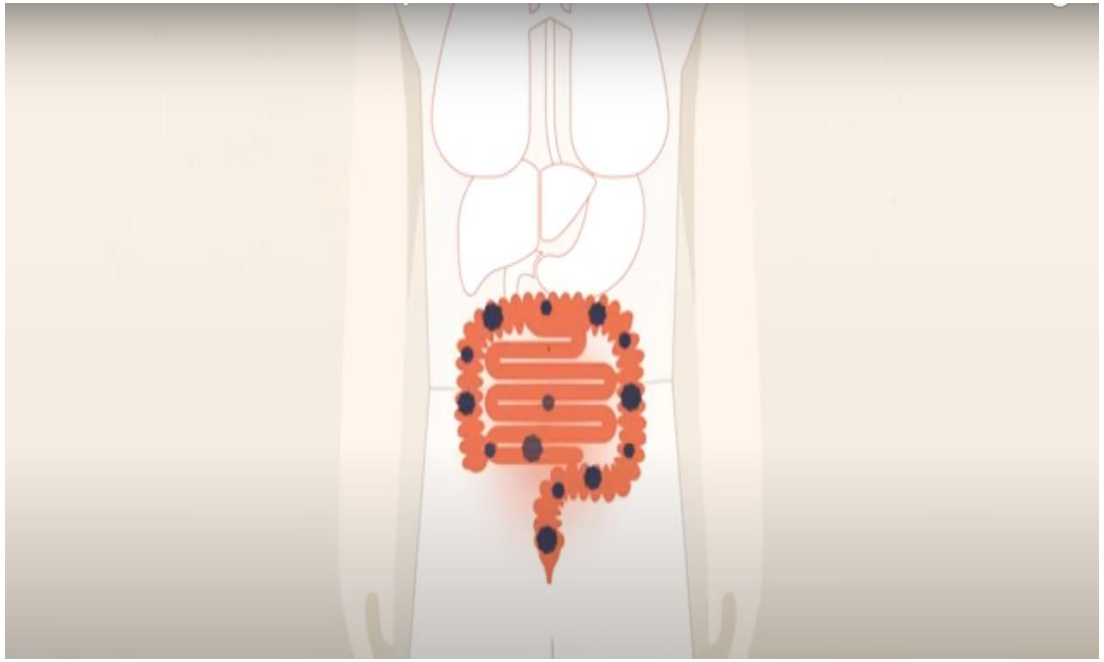
- Except for the lung, polar (hydrophilic) substances are more likely than lipid-soluble toxicants to be eliminated from the body. Chemicals must again pass through membranes in order to leave the body, and the same chemical and physical properties that governed passage across other membranes apply to excretory organs as well.

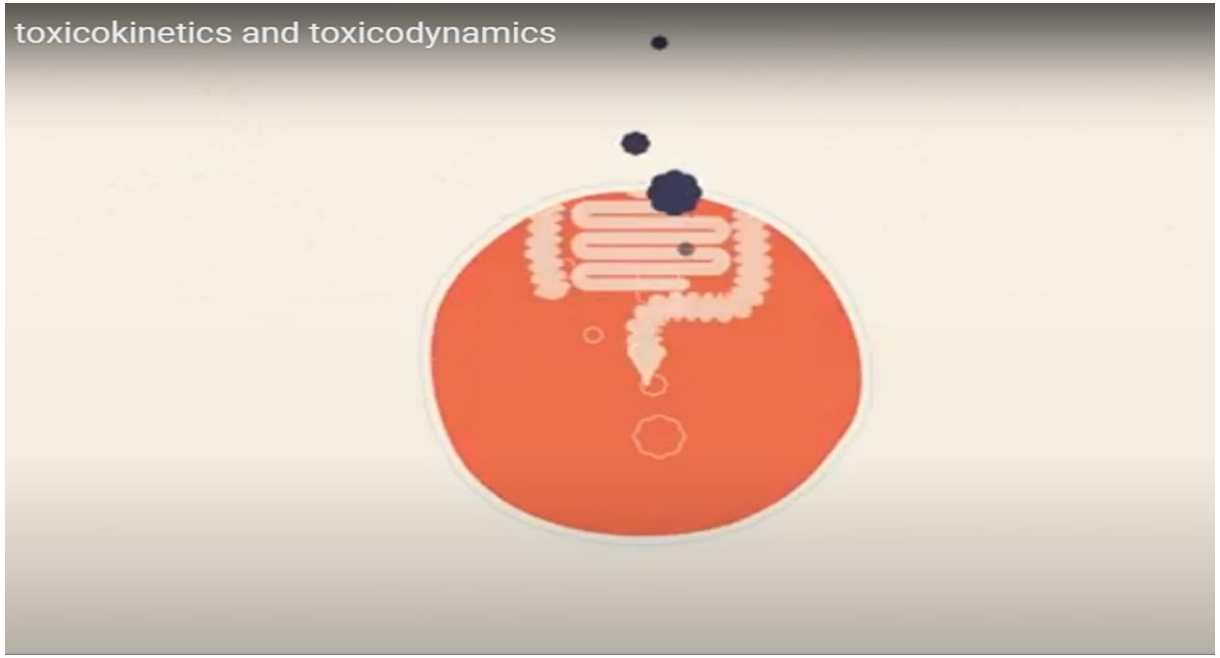
Primary Routes of Excretion

- The body uses several routes to eliminate toxicants or their metabolites. The main routes of excretion are via urine, feces, and exhaled air. Thus, the primary organ systems involved in excretion are the:
- Urinary system
- Gastrointestinal system
- Respiratory system

Extraction

- Extraction: Note absorbed Chemical continue through the digestive tract and eliminate with faces





- Image illustration The digestive tract eliminate the toxic with fasces

Extraction refers to the process where chemicals not absorbed into the bloodstream continue to move through the digestive tract. These unabsorbed substances are eventually excreted from the body as waste through feces. This pathway helps the body eliminate non-absorbed or excess compounds, preventing potential toxicity.

Knowledge Check Questions

- **1) The three major routes of excretion are:**
  a) Gastrointestinal tract, sweat, and saliva
  b) Mother's milk, tears, and semen
  c) Urinary excretion, fecal excretion, and exhaled air
-

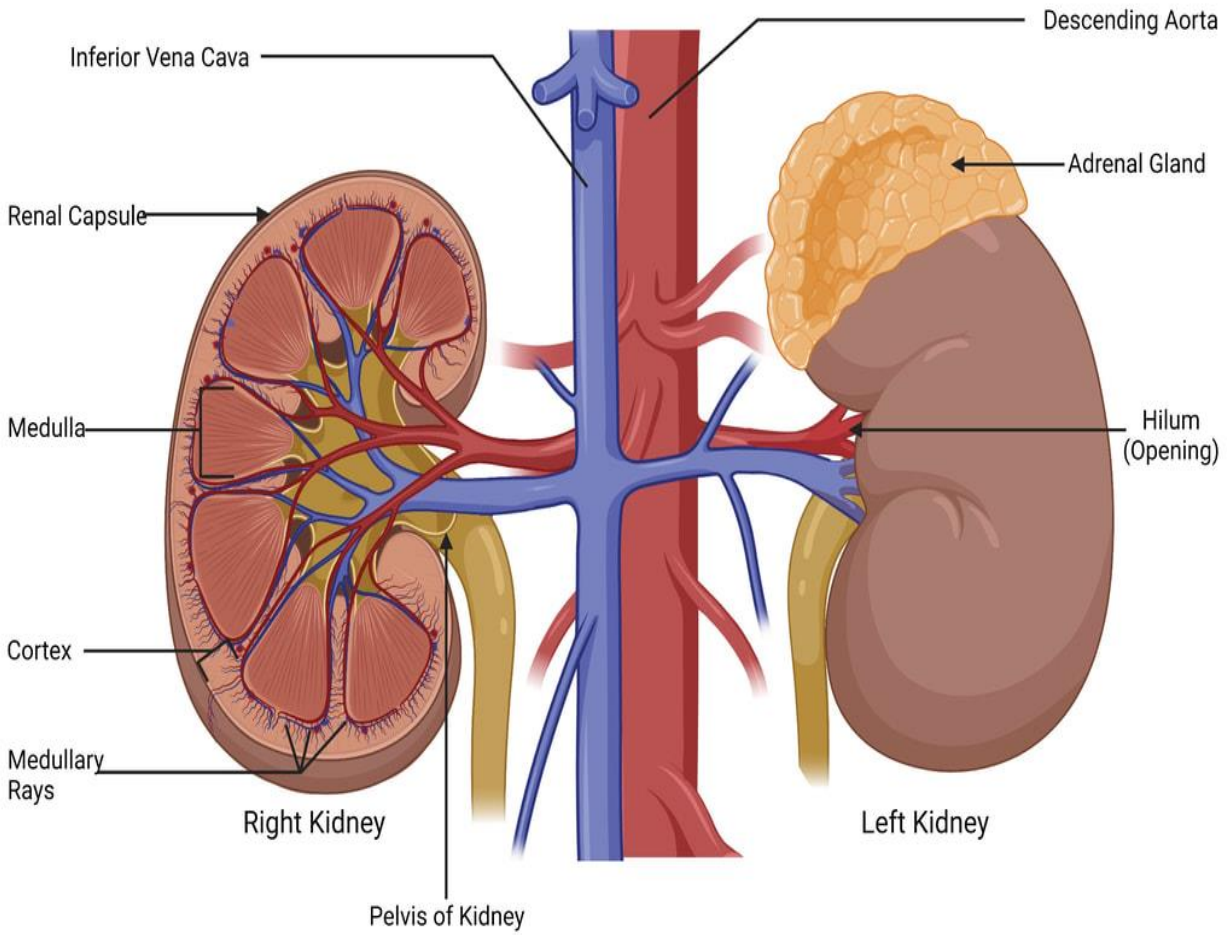
Solutions

- 1) Urinary excretion, fecal excretion, and exhaled air - **This is the correct answer.**

The main routes of excretion are via urine, feces, and exhaled air.

Urinary Excretion

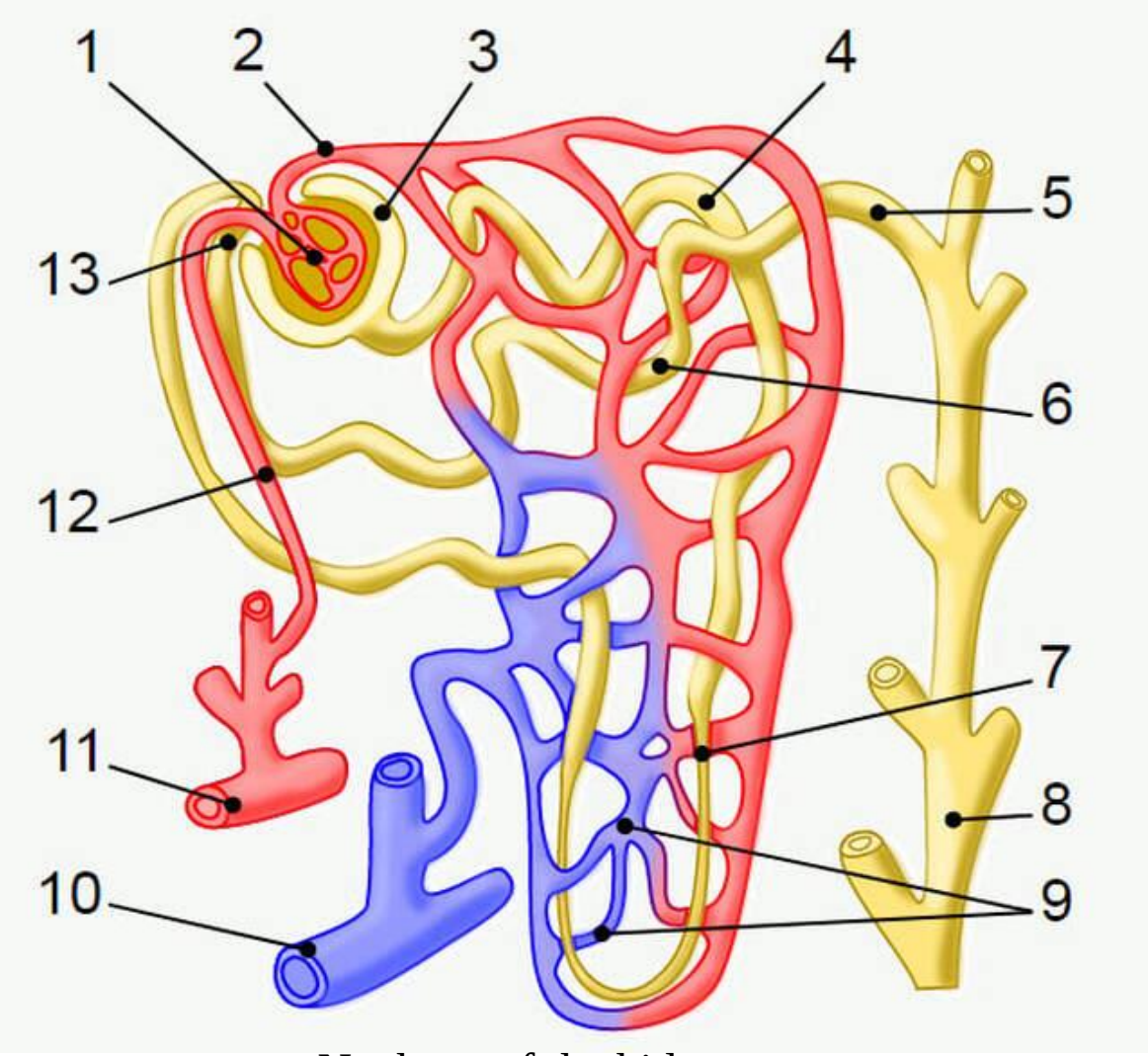
- The primary route in which the body eliminates substances is through the kidneys. The main function of the kidney is the excretion of body wastes and harmful chemicals into the urine. The functional unit of the kidney responsible for excretion is the nephron. Each kidney contains about one million nephrons. The nephron has three primary regions that function in the renal excretion process: the glomerulus, proximal tubule, and the distal tubule



1. Kidney Structure

Three processes are involved in urinary excretion:

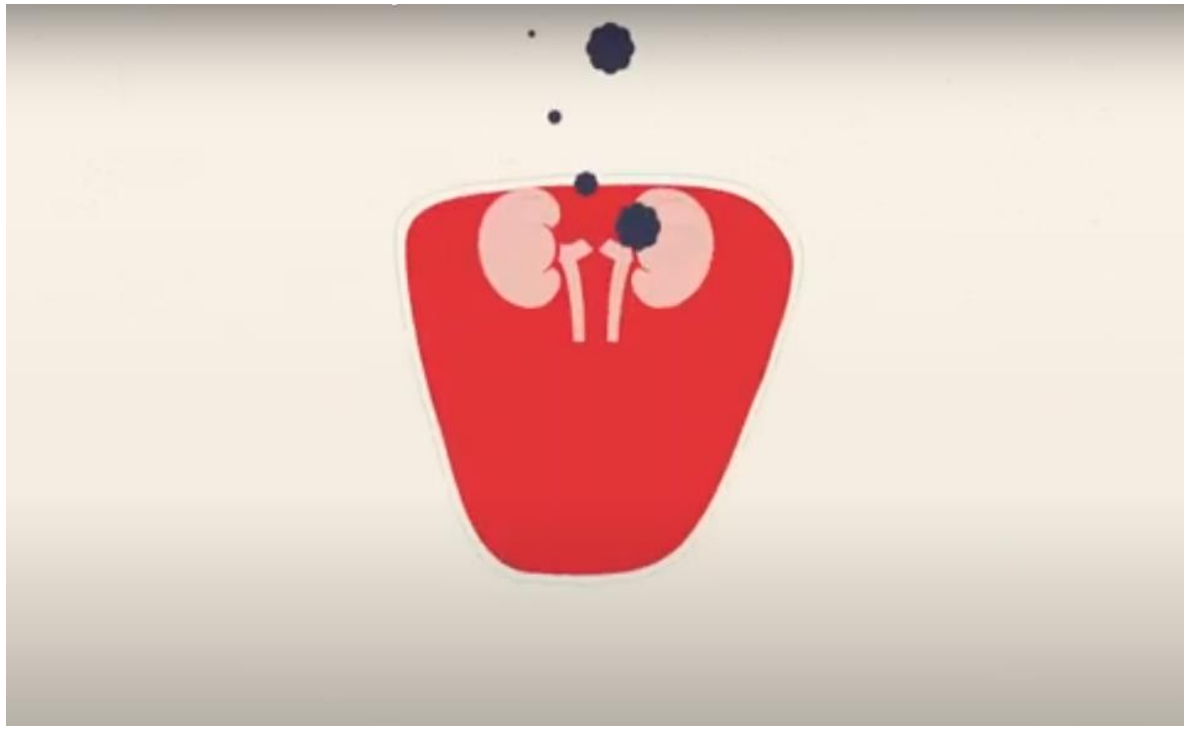
1. Filtration
2. Secretion
3. Reabsorption

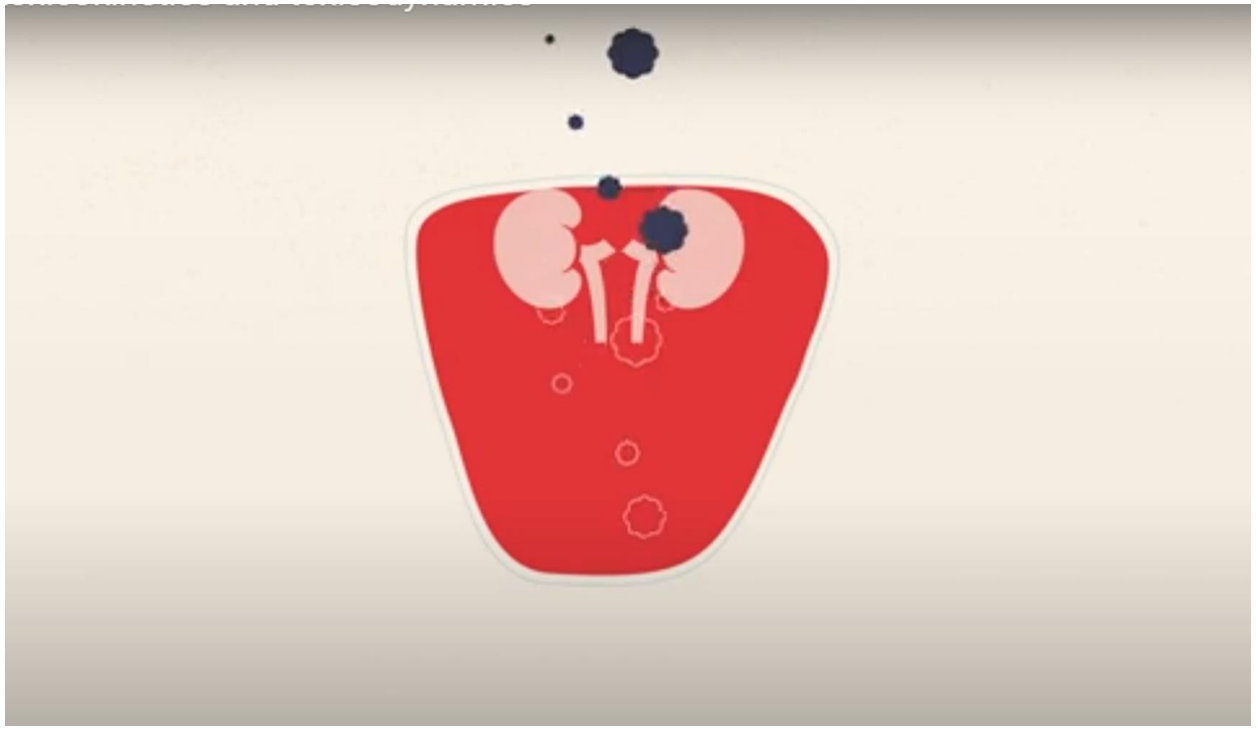


Nephron of the kidney

Legend:

1. Glomerulus
2. Efferent arteriole
3. Bowman's capsule
4. Proximal convoluted tubule
5. Cortical collecting duct
6. Distal convoluted tubule
7. Loop of Henle
8. Papillary duct
9. Peritubular capillaries
10. Arcuate vein
11. Arcuate artery
12. Afferent arteriole
13. Juxtaglomerular apparatus





- Chemicals are extracted through the kidneys with urine

Fecal Excretion

1. Elimination of toxicants in the feces occurs from two processes:Excretion in bile, which then enters the intestine ("biliary excretion").
2. Direct excretion into the lumen of the gastrointestinal tract ("intestinal excretion").

Biliary Excretion

- The **biliary route** is an important mechanism for fecal excretion of xenobiotics and is even more important for the excretion of their metabolites. This route generally involves active secretion rather than passive diffusion.

- Specific transport systems appear to exist for certain types of substances, for example, organic bases, organic acids, and neutral substances. Some heavy metals are excreted in the bile, for example, arsenic, lead, and mercury.

- However, the most likely substances to be excreted via the bile are comparatively large, ionized molecules, such as those having a large molecular weight (conjugates greater than 300).

Biliary Excretion

- Once a substance has been excreted by the liver into the bile, and then into the intestinal tract, it can be eliminated from the body in the feces, or it may be reabsorbed.

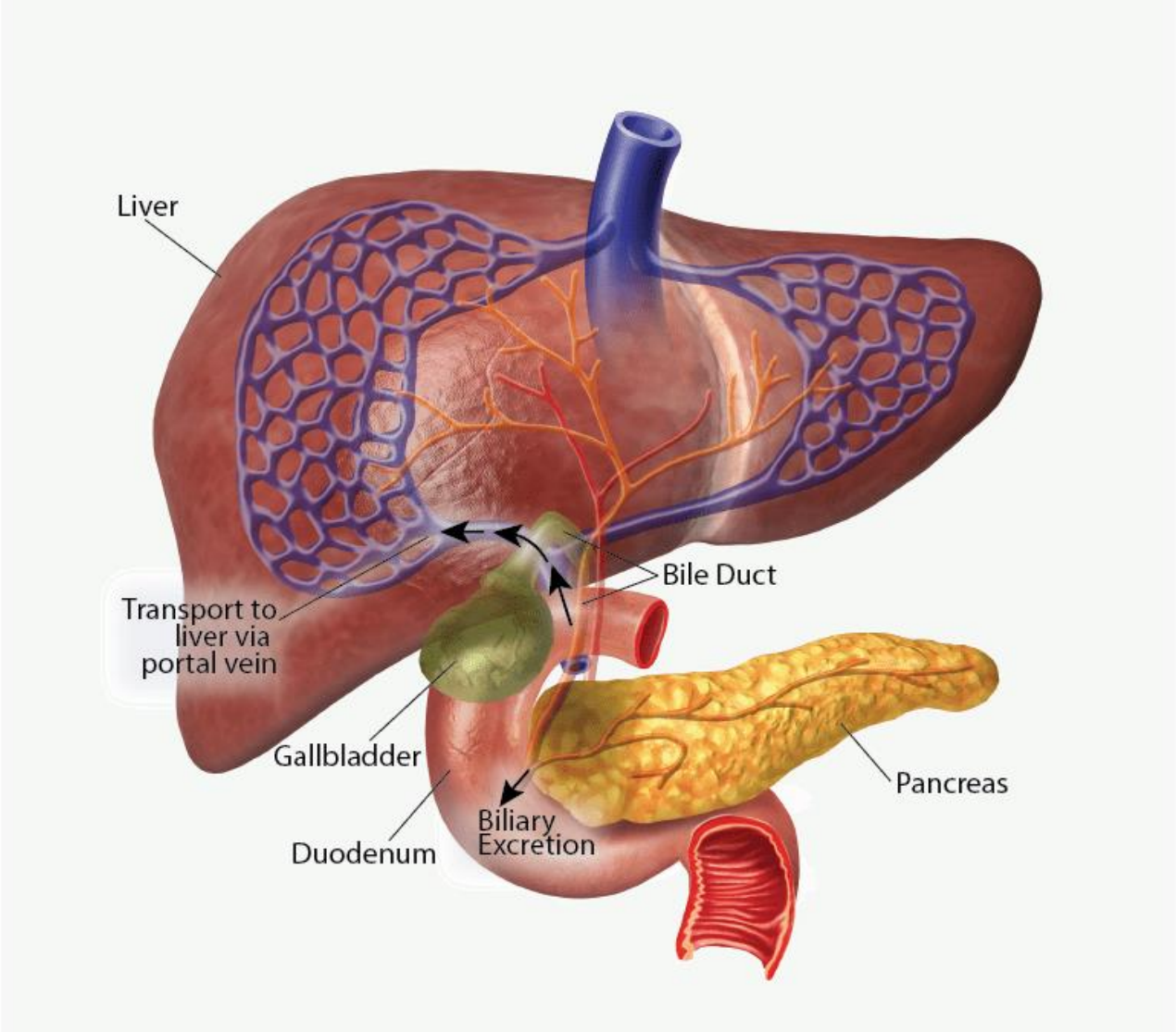
- Since most of the substances excreted in the bile are water soluble, they are not likely to be reabsorbed as such.

- However, enzymes in the intestinal flora are capable of hydrolyzing some glucuronide and sulfate conjugates, which can release the less polar compounds that may then be reabsorbed.

- This process of excretion into the intestinal tract via the bile and reabsorption and return to the liver by the portal circulation is known as the **enterohepatic circulation**

Enterohepatic circulation

- Enterohepatic circulation prolongs the life of the xenobiotic in the body. In some cases, the metabolite is more toxic than the excreted conjugate.
- Continuous enterohepatic recycling can occur and lead to very long half-lives of some substances. For this reason, drugs may be given orally to bind substances excreted in the bile.
- For example, a resin can be taken orally to bind with dimethylmercury, which had been secreted in the bile. The binding of the resin to dimethylmercury prevents its reabsorption and further toxicity.



Biliary excretion and enterohepatic circulation

Enterohepatic circulation

- Changes in the production and flow of bile into the liver affect the efficiency of biliary excretion. Liver disease usually causes a decrease in bile flow.
- Some drugs such as phenobarbital can produce an increase in bile flow rate.
- Administration of phenobarbital has been shown to enhance the excretion of methylmercury by this mechanism.

Intestinal Excretion

- Another way that xenobiotics can be eliminated via the feces is by direct **intestinal excretion**.

- While this is not a major route of elimination, a large number of substances can be excreted into the intestinal tract and eliminated via feces.

- Some substances, especially those that are poorly ionized in plasma (such as weak bases), may passively diffuse through the walls of the capillaries, through the intestinal submucosa, and into the intestinal lumen to be eliminated in feces.

Intestinal excretion

- Intestinal excretion is a relatively slow process and therefore, it is an important elimination route only for those xenobiotics that have slow biotransformation, or slow urinary or biliary excretion.

- Increasing the lipid content of the intestinal tract can enhance intestinal excretion of some lipophilic substances. For this reason, mineral oil (liquid paraffin, derived from petroleum) is sometimes added to the diet to help eliminate toxic substances, which are known to be excreted directly into the intestinal tract.

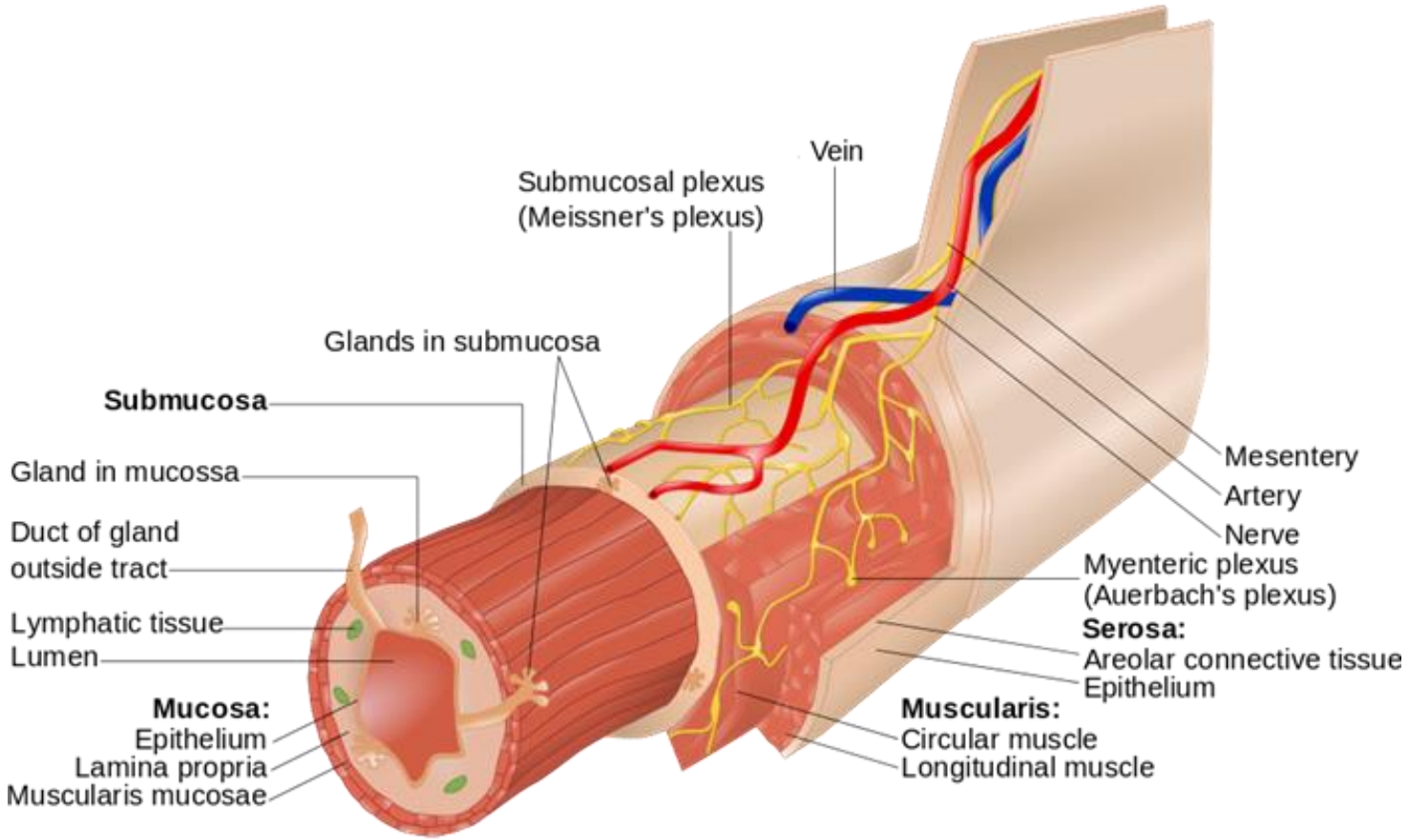


Image illustration Layers of the Alimentary Canal

Knowledge Check Questions

1) Substances excreted in the bile are primarily:

a) Small, lipid soluble molecules

b) Comparatively large, ionized molecules

c) Large, lipid soluble molecules

2) Many substances excreted in bile undergo enterohepatic circulation, which involves:

a) Excretion of substances into the circulating system rather than into the intestine

b) Excretion into the intestinal tract and reabsorption and return to the liver by the portal circulation

c) The recycling of xenobiotics between the liver and gall bladder

Knowledge Check Solutions

1) Comparatively large, ionized molecules - **This is the correct answer.**

The most likely substances to be excreted via the bile are comparatively large, ionized molecules, such as large molecular weight (greater than 300) conjugates.

2) Excretion into the intestinal tract and reabsorption and return to the liver by the portal circulation - **This is the correct answer.**

The process of excretion into the intestinal tract via the bile and reabsorption and return to the liver by the portal circulation is known as the enterohepatic circulation. The effect of this enterohepatic circulation is to prolong the life of the xenobiotic in the body.

Exhaled Air

- The lungs are an important route of excretion for xenobiotics (and metabolites) that exist in a gaseous phase in the blood.

- **Passive Diffusion**

- Blood gases are excreted by passive diffusion from the blood into the alveolus, following a concentration gradient. This type of excretion occurs when the concentration of the xenobiotic dissolved in capillary blood is greater than the concentration of the substance in the alveolar air.

- Gases with a low solubility in blood are more rapidly eliminated than those gases with a high solubility. Volatile liquids dissolved in the blood are also readily excreted via the expired air.

Exhaled Air

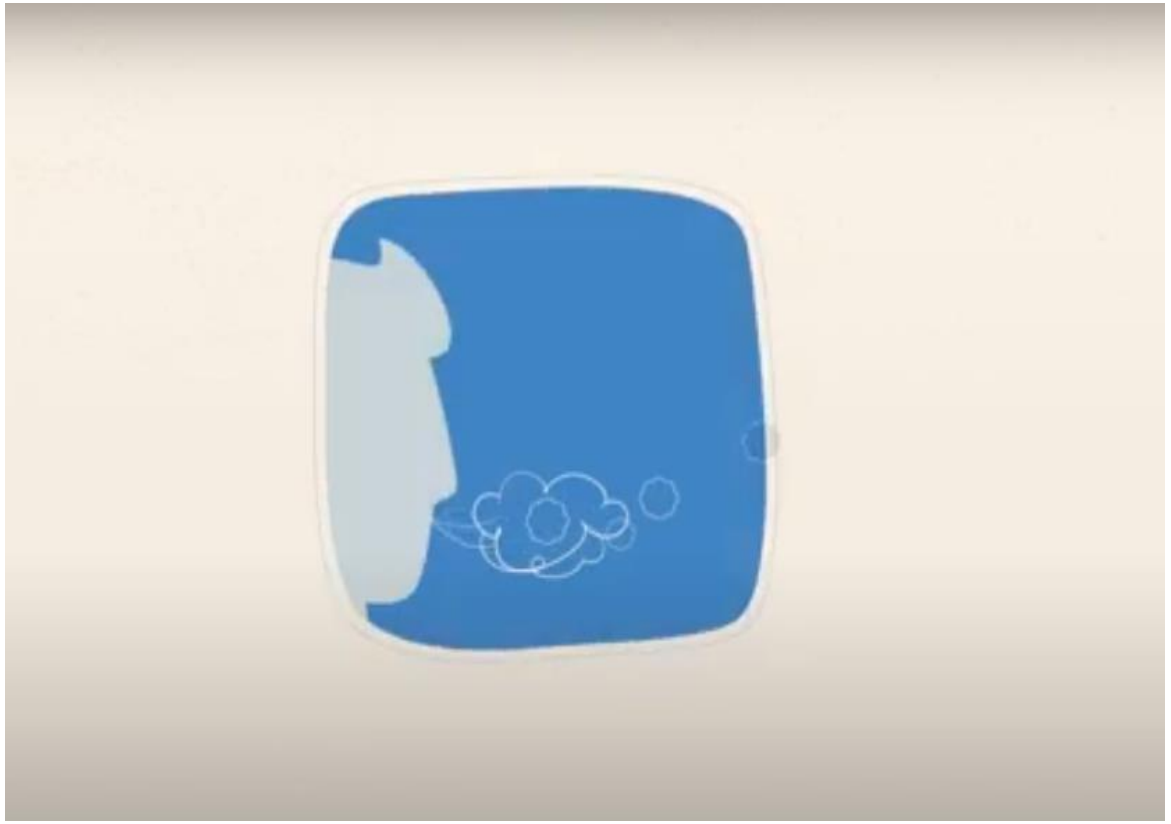
- For example, breathalyzer devices can measure blood alcohol concentration because as alcohol in the blood moves across the alveoli the alcohol in the blood evaporates and is exhaled.

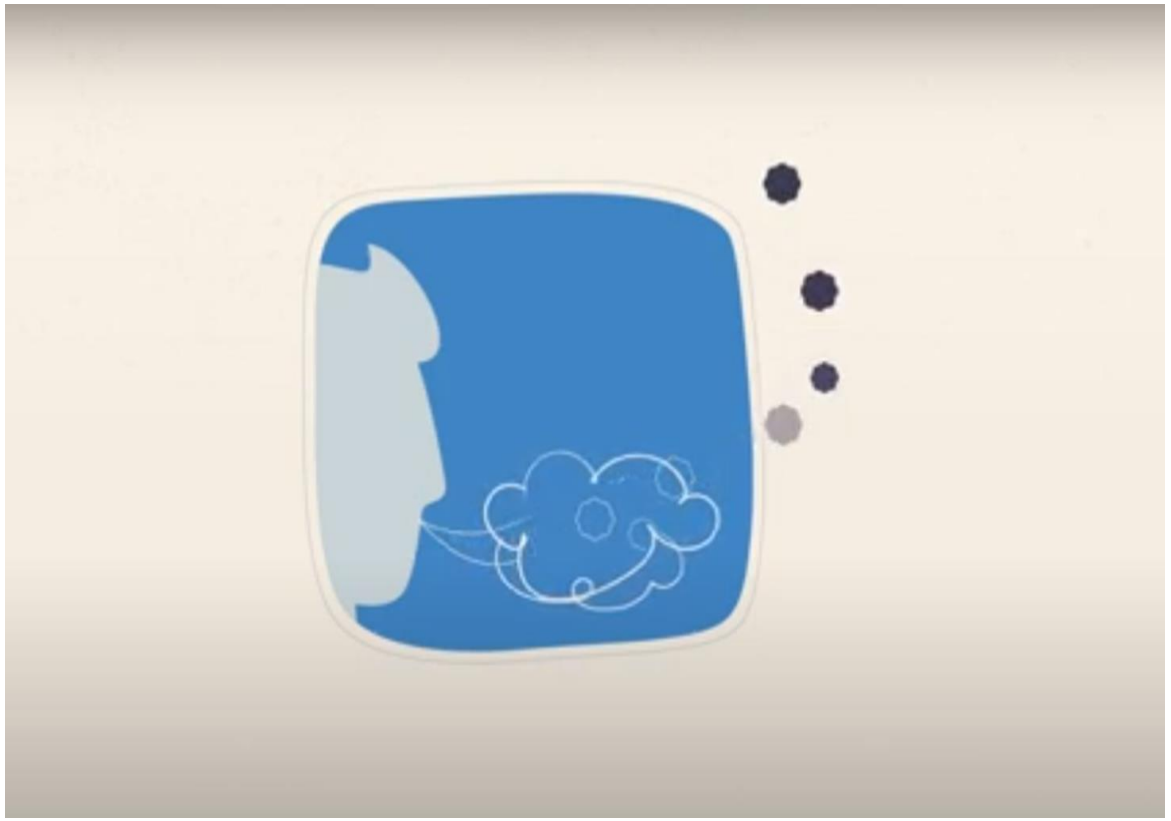
- The concentration of alcohol in the exhaled air relates to the level of alcohol in the blood.

Impact of Vapor Pressure

- The amount of a liquid excreted by the lungs is proportional to its vapor pressure.
- Exhalation is an exception to most other routes of excretion in that it can be a very efficient route of excretion for lipid soluble substances.
- This is due to the very close proximity of capillary and alveolar membranes, which are thin and allow for the normal gaseous exchange that occurs in breathing.
-

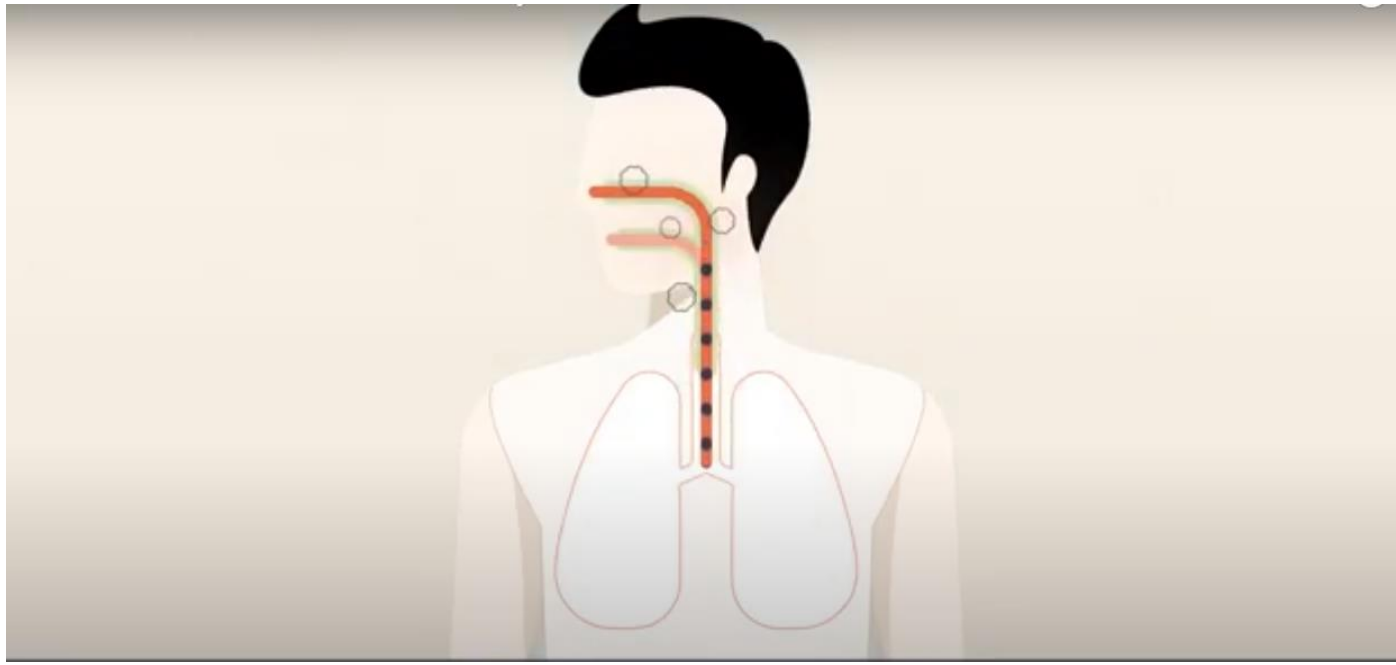
- The elimination with exhaled air.





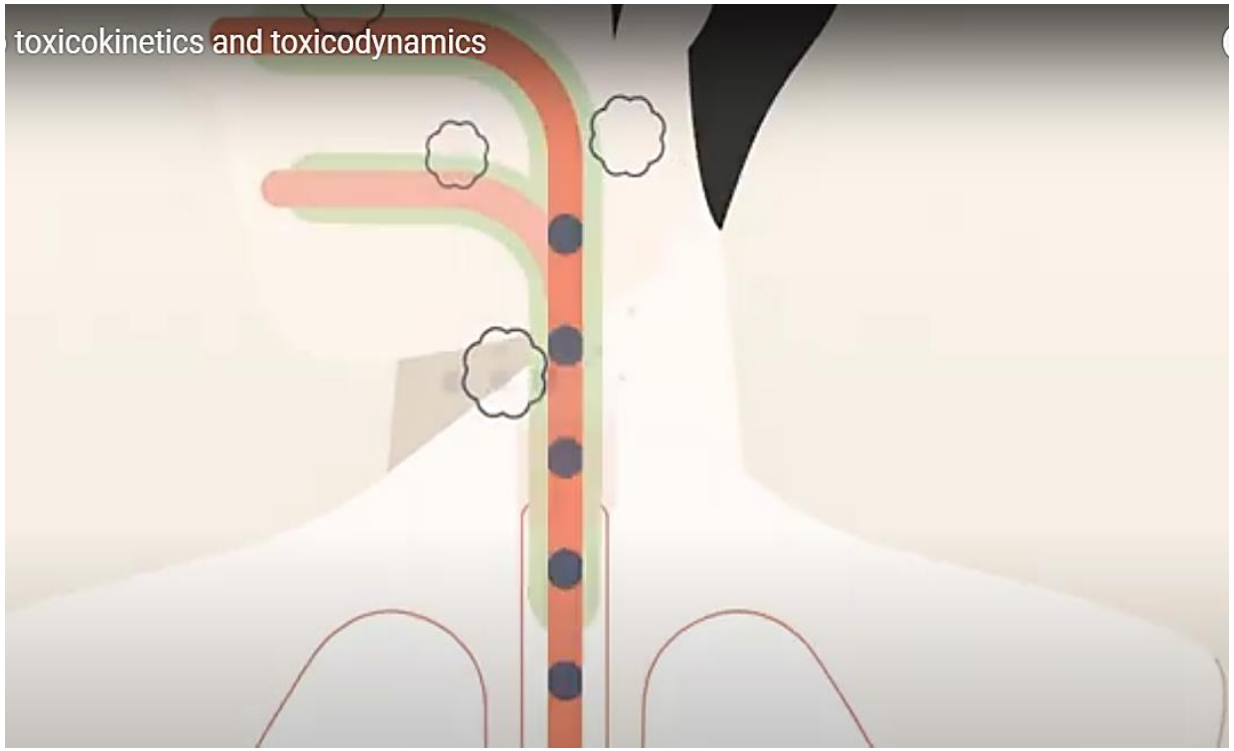
Etraction:

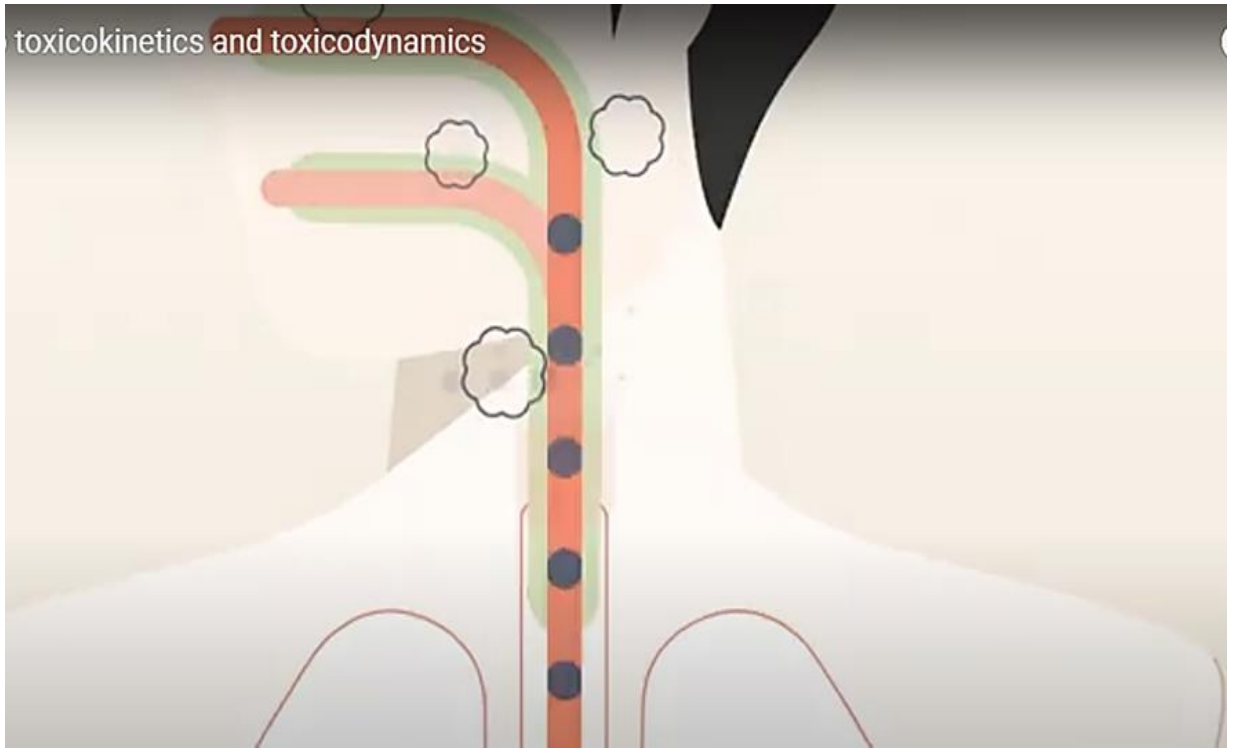
Extraction of large particles involves their capture by the mucosal lining in the upper respiratory or gastrointestinal tract. These particles are trapped by the mucous membrane, which acts as a physical barrier, preventing them from entering the bloodstream. The trapped particles are then moved away from the body via processes like ciliary action or swallowed and eliminated through feces, reducing the potential for harmful effects.



- Image illustration the big size particles are captured by mucosa in upper tract and eliminated.

Etraction:



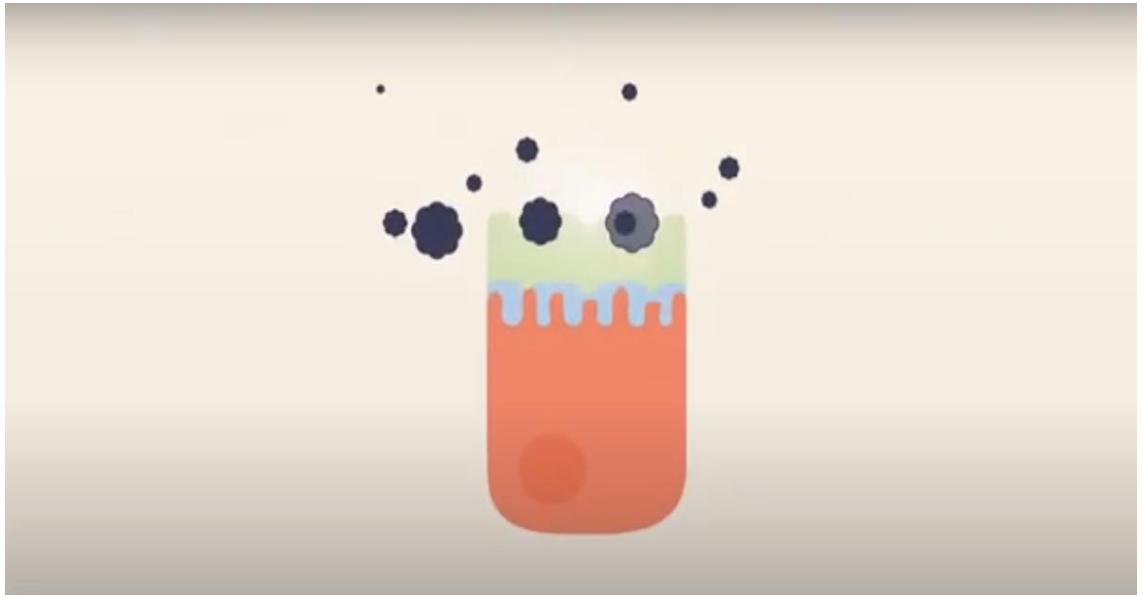


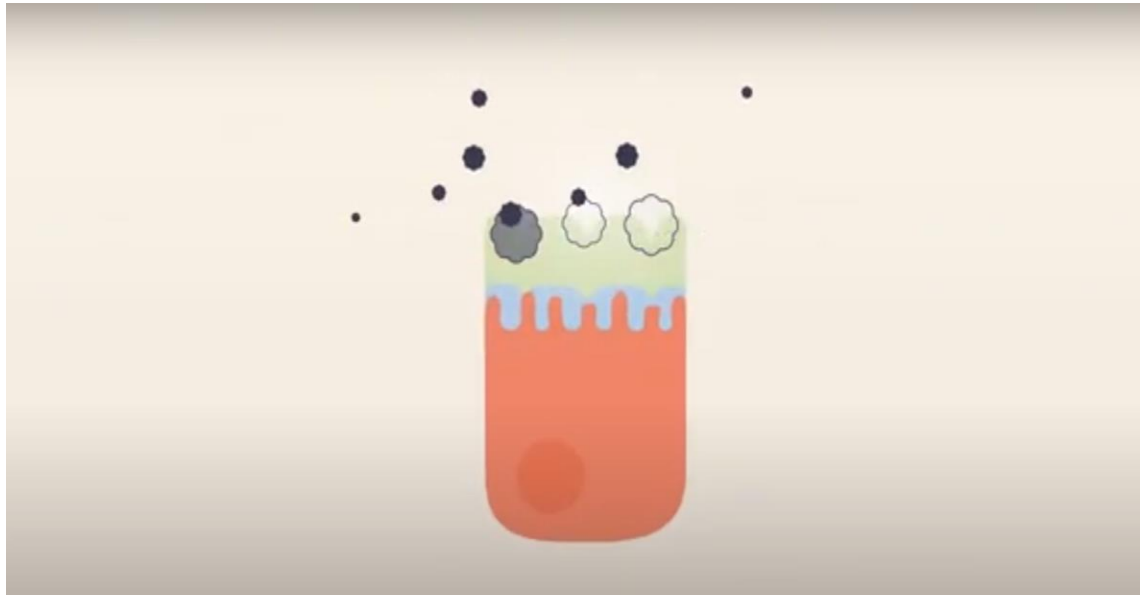
- Image illustration the big size particles are captured by mucosa in upper tract and eliminated.

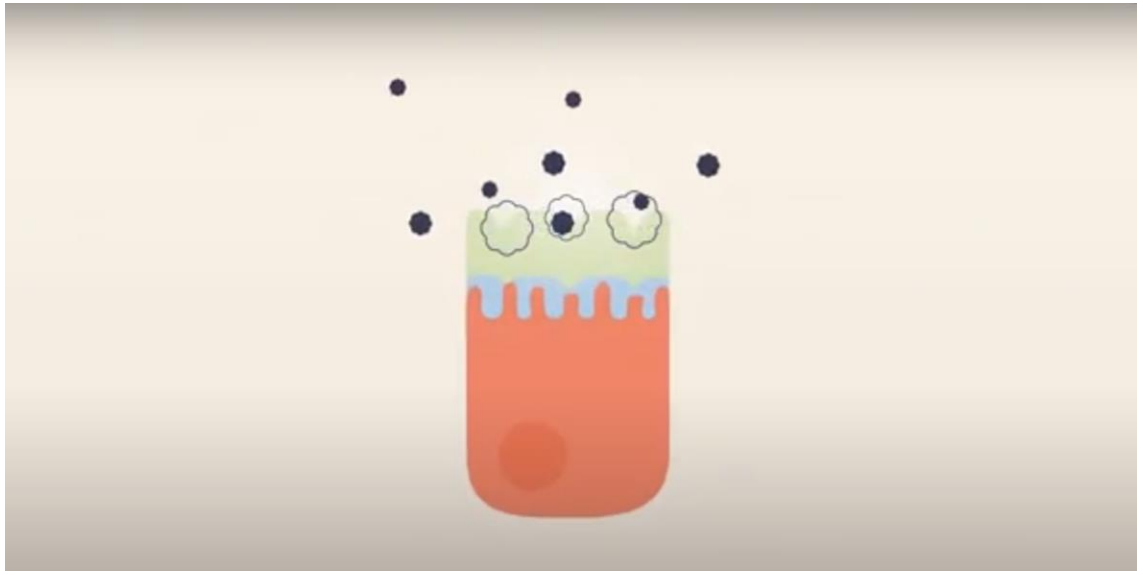
Extraction through the respiratory

- Large particles that enter the body, particularly through the respiratory or digestive systems, are often captured by the mucosal lining in the upper tract.
- The mucosa acts as a protective barrier, trapping these particles to prevent them from reaching deeper tissues or the bloodstream.
- Once trapped, the particles are moved along by ciliary action or swallowed, eventually being expelled from the body through mechanisms like coughing or digestion, and ultimately eliminated in the feces.
- This process helps reduce the potential for toxicity or irritation.

The upper tract and eliminated

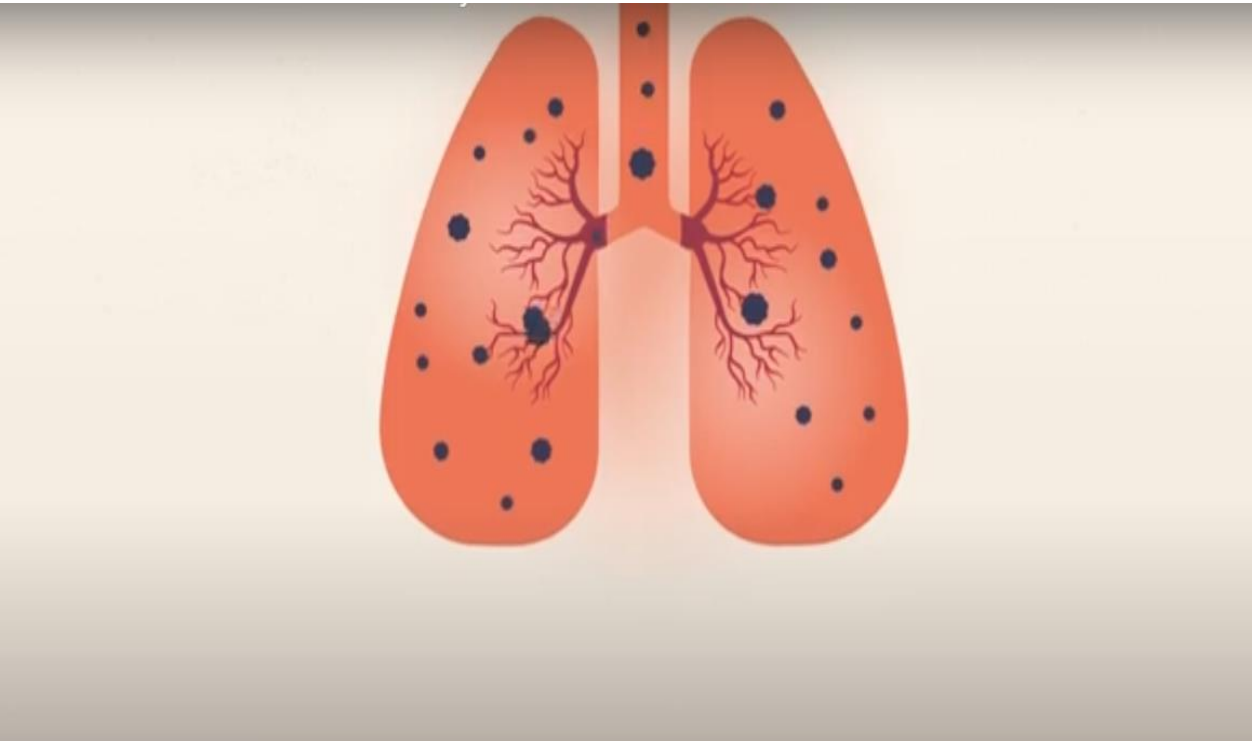


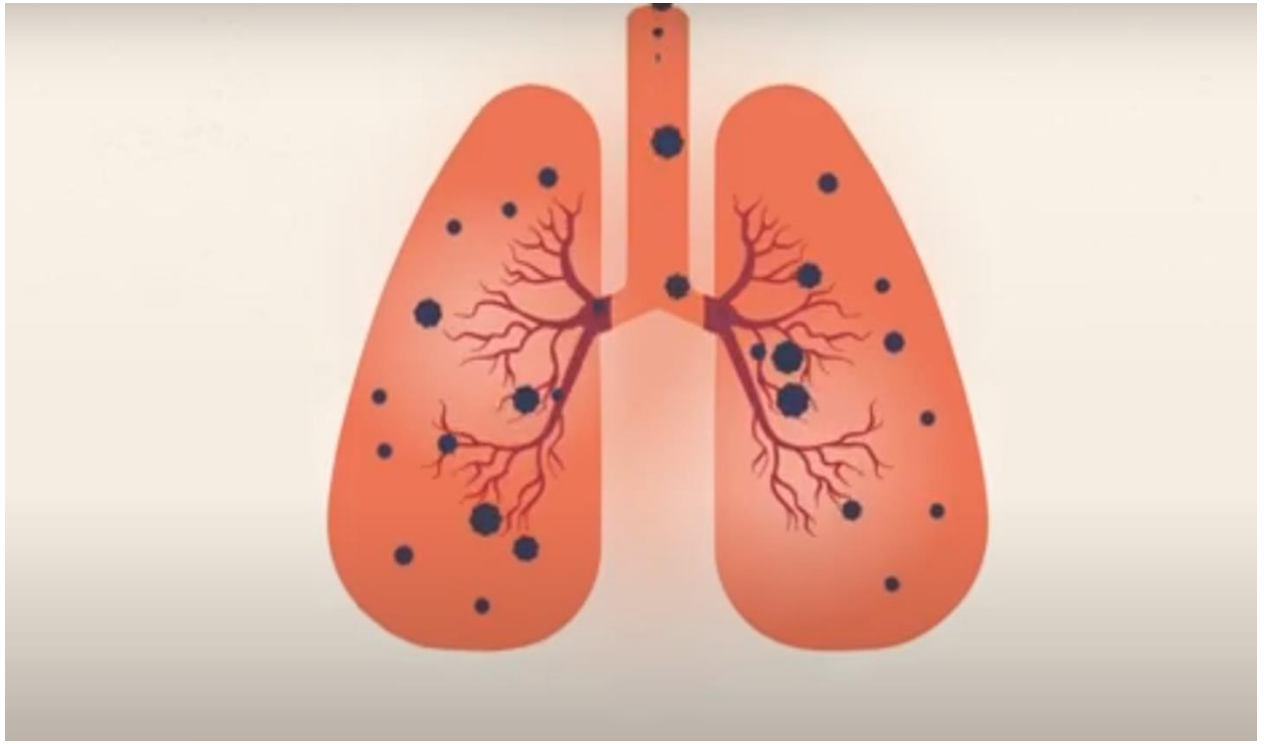




- Big size particles are captured by mucosa in upper tract and eliminated. Those reaching lungs are diffused to blood vessels

The upper tract big size particles elimination





- Image illustration the big size particles are captured by mucosa in upper tract and eliminated. Those reaching lungs are diffused to blood vessels

Large particles illumination from respiratory

- Large particles that are inhaled into the respiratory system are typically captured by the mucosal lining in the upper respiratory tract, including the nasal passages and throat.
- The mucosa contains mucus and cilia that trap and move these particles.
- Once trapped, the particles are usually expelled through mechanisms such as coughing or sneezing, or they are swallowed and eliminated through the digestive system.
-
- This process helps protect the lower respiratory tract from potential harm caused by these large particles.

Knowledge Check Questions

- **1) Xenobiotics are eliminated in exhaled air by:**

  a) Passive diffusion

  b) Active transport

  c) Facilitated transport

Answers

- 1) Passive diffusion - **This is the correct answer.**
  - Blood gases are excreted by passive diffusion from the blood into the alveolus, following a concentration gradient. This occurs when the concentration of the xenobiotic dissolved in capillary blood is greater than the concentration of the substance in the alveolar air.

Other Routes of Excretion

Several minor routes of excretion occur including mother's milk, sweat, saliva, tears, and semen.

◦ Excretion into Breast Milk

Excretion into milk can be important since toxicants can be passed with milk to the nursing offspring. In addition, toxic substances can pass from cow's milk to people. Toxic substances are excreted into milk by simple diffusion.

Both basic substances and lipid soluble compounds can be **excreted into milk (**The National Library of Medicine's **LactMed** is a resource for information on drugs, dietary supplements, and herbs that pass into breast milk).

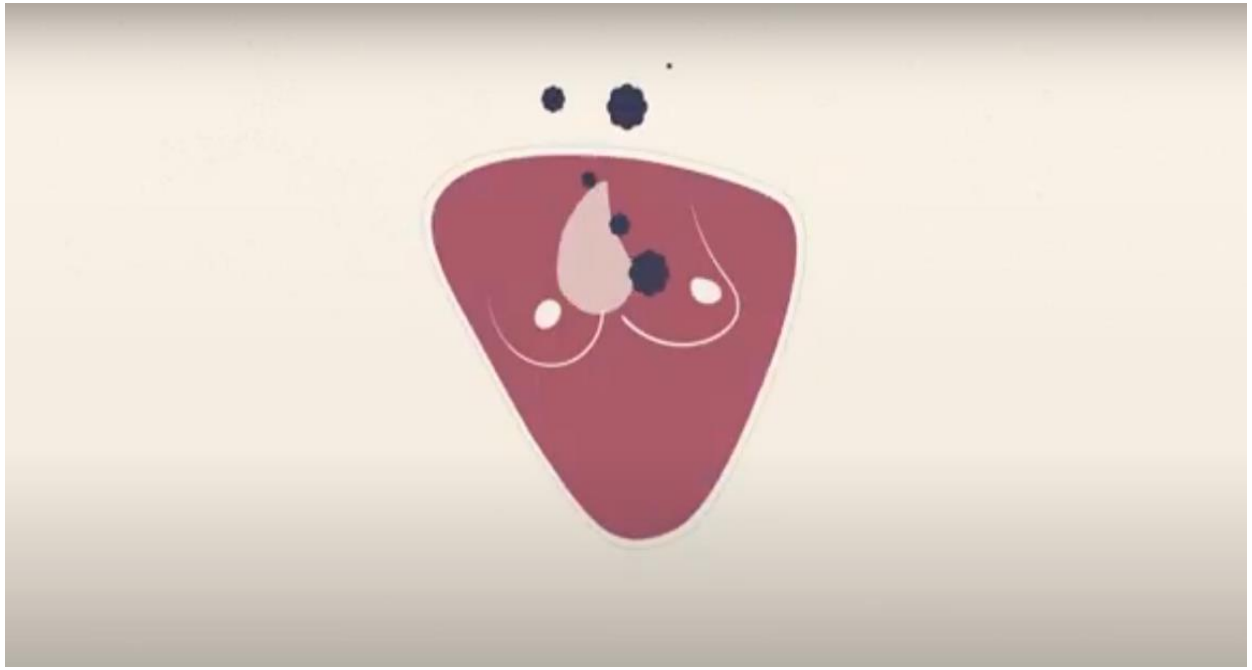
Elimination through bodily secretions involves the expulsion of certain chemicals or toxins through fluids and tissues such as saliva, sweat, breast milk, hair, and nails.

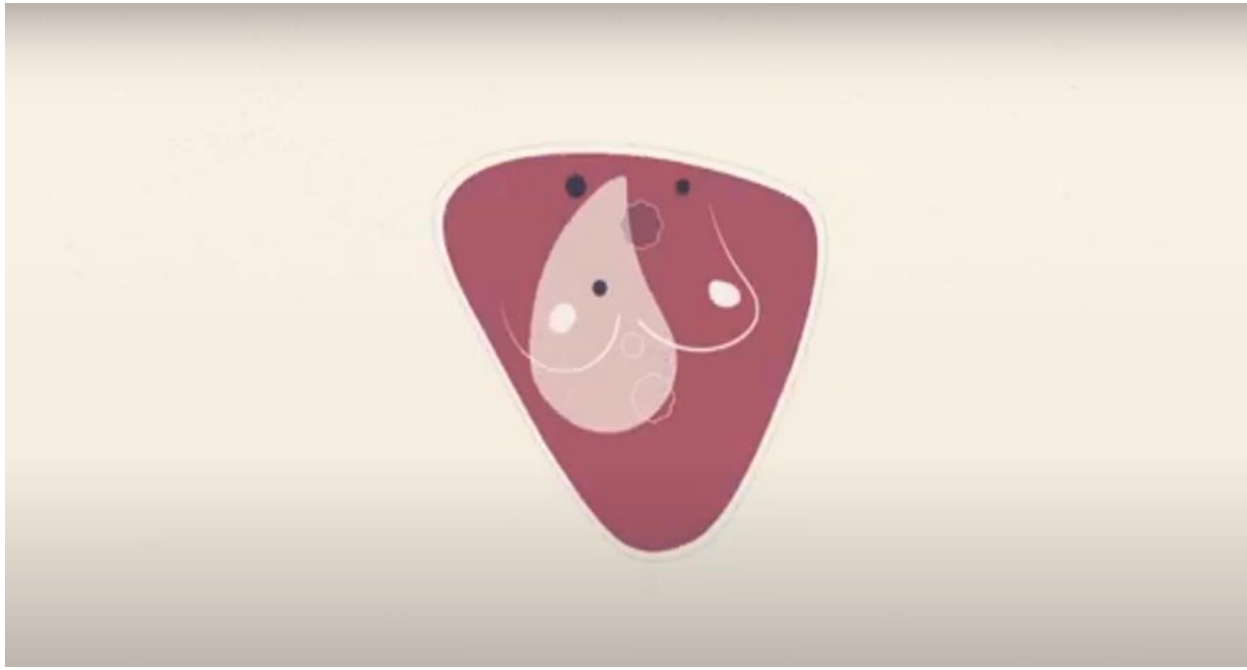
These processes help the body remove non-volatile, lipid-soluble substances that have entered the bloodstream.

For example, breast milk can be a route for the excretion of substances, impacting nursing infants.

Sweat helps eliminate some metabolic byproducts, while hair and nails incorporate substances during their growth, serving as markers of long-term exposure.

These pathways complement primary elimination routes like urine and feces, contributing to overall detoxification.





- The elimination through secretion such as salve swat, breast milk, hair and nails

Excretion into Breast Milk

- Basic substances can be concentrated in milk since milk is more acidic (pH approximately 6.5) than blood plasma.

- Since milk contains 3–4% lipids, lipid soluble xenobiotics can diffuse along with fats from plasma into the mammary gland and thus can be present in mother's milk.

- Substances such as lead, mercury, Bisphenol A (BPA), and phthalates that are chemically similar to calcium can also be excreted into milk along with calcium.

Volatile organic compounds (VOCs) found in indoor air can also be found in breast milk.

- Examples include MTBE (methyl tert-butyl ether), chloroform, benzene, and toluene. For benzene, toluene, and MTBE, the levels in breast milk followed the indoor air concentrations.

- However, the infant average daily dose by inhalation exceeded ingestion rates by 25-to-135 fold. Thus, the amount of VOC exposure from indoor air in nonsmoking households is much greater than the VOC exposure from breast milk.

- Strategies to lessen infant VOC exposure should focus on improving indoor air quality.

Excretion into All Other Body Secretions or Tissues

- Excretion of xenobiotics in **all other body secretions or tissues** (including the saliva, sweat, tears, hair, and skin) are of only minor importance. Under conditions of great sweat production, excretion in sweat may reach a significant degree.

- Some metals, including cadmium, copper, iron, lead, nickel, and zinc, may be eliminated in sweat to some extent.

- Xenobiotics that passively diffuse into saliva may be swallowed and absorbed by the gastrointestinal system. The excretion of some substances into saliva is responsible for the unpleasant taste that sometimes occurs with time after exposure to a substance.

Elimination Mechanisms

Renal Elimination: Processes in the kidneys.
Liver Elimination: Phase I & II reactions for water-soluble metabolites.

Other Routes: Excretion via lungs, sweat, and saliva.
Excretion Enhancements

Hemodialysis: For water-soluble, low protein-binding toxins.
Alkalinization of Urine: Enhancing excretion of specific drugs.
Multiple Doses of Activated Charcoal: For enterohepatic recirculation toxins.

Knowledge Check Questions

1) The following are minor routes of excretion:

a) Sweat and saliva

b) Urinary excretion, fecal excretion, and exhaled air

Answers

- 1) Sweat and saliva - **This is the correct answer.**

Several minor routes of excretion exist, primarily via mother's milk, sweat, saliva, tears, and semen. The main routes of excretion are via urine, feces, and exhaled air.

-

What We've Covered

This section made the following main points:
Excretion, as used in ToxTutor, pertains to the elimination of a xenobiotic and its metabolites by specific excretory organs.

- The primary organ systems involved in excretion are the:
    - Urinary system, which involves:
        - Filtration in the glomerulus.
        - Secretion in the proximal tubule section of the nephron to transport certain molecules out of the blood and into the urine.
        - Reabsorption in the proximal convoluted tubule of the nephron to reenter nearly all of the water, glucose, potassium, and amino acids lost during filtration back into the blood.

◦

What We've Covered

Gastrointestinal system, which occurs from two processes:

- Biliary excretion — generally active secretion by the liver into the bile and then into the intestinal tract, where it can be eliminated in the feces or reabsorbed.

- Intestinal excretion — an important elimination route only for xenobiotics that have slow biotransformation or slow urinary or biliary excretion.

- Respiratory system, which is important for xenobiotics and metabolites that exist in a gaseous phase in the blood:
  - Excreted by passive diffusion from the blood into the alveolus.

- Minor routes of excretion occur including breast milk, sweat, saliva, tears, and semen.

◦

What We've Covered

Excretion of Xenobiotics

- **Major Excretion Routes**
  - **Renal (Kidneys)**: Glomerular filtration, Tubular reabsorption, and secretion.
  - **Hepatic (Liver)**: Bile secretion and fecal excretion.
  - **Pulmonary (Lungs)**: Exhalation of volatile substances.
  - **Others**: Sweat, Saliva, Mother’s Milk.
- **Clearance (CL)**
  - Definition: Rate of xenobiotic elimination.
  - Organs involved: Liver, Kidneys, Intestines.

What is Distribution

- **Definition:** Movement from bloodstream to tissues.
- **Factors Influencing Distribution:** Tissue affinity, blood flow, and protein binding.
- **Examples:** Chemicals crossing the blood-brain barrier.

What are the primary routes of Excretion

- **Primary Routes:** Renal (urine), biliary (feces), and respiratory (lungs).
- **Factors Affecting Excretion:** Polarity, solubility, kidney function.
- **Importance:** Determines the duration of exposure.

What are the Factors Influencing Toxicity

- **Absorption Efficiency:** Higher absorption increases toxicity.
- **Metabolite Toxicity:** Metabolism can increase or reduce toxicity.
- **Excretion Rate:** Slower excretion increases toxic effects.

What is Dose-Response Relationship

- **Concept:** Toxic effect varies with dose.
- **Applications:** Used in establishing safe exposure levels.

Toxicokinetic Modeling

- **Purpose:** Predicts behavior of chemicals in the body.
- **Models:** One-compartment, multi-compartment.
- **Applications:** Used in regulatory toxicology and safety assessments.

Homework What are the factors related to the poison and patients

Factors related to the *poison*	Factors related to the *patient*
1. Amount taken 2. Route of administration 3. Form of the poison 4. Cumulation	1. Stomach 2. Age 3. Tolerance 4. Hypersensitivity.

Factors Related to the Poison:

1. **Chemical Nature**: Determines how the poison is absorbed, distributed, and eliminated (e.g., lipid-soluble vs. water-soluble).
2. **Dose**: The amount of poison ingested affects the severity of the toxic response.
3. **Route of Exposure**: Inhalation, ingestion, dermal, or injection routes affect absorption speed and impact.
4. **Formulation**: Solids, liquids, or gas forms can alter the rate of absorption and toxicity.
5. **Toxicokinetics and Toxicodynamics**: The poison's behavior in the body (absorption, distribution, metabolism, and excretion) and its physiological effects.

Factors Related to the Patient:

1. **Age**: Children and the elderly may have altered metabolism and vulnerability to toxins.
2. **Weight**: Body weight can influence the dosage and distribution of the toxin.
3. **Health Status**: Pre-existing conditions like liver or kidney disease can impair the metabolism and excretion of toxins.
4. **Genetics**: Genetic predispositions can affect how a person metabolizes and reacts to certain toxic substances.
5. **Tolerance/Previous Exposure**: Prior exposure can influence tolerance levels or trigger allergic reactions.
6. **Medications**: Current medications can interact with the poison and alter its effects.

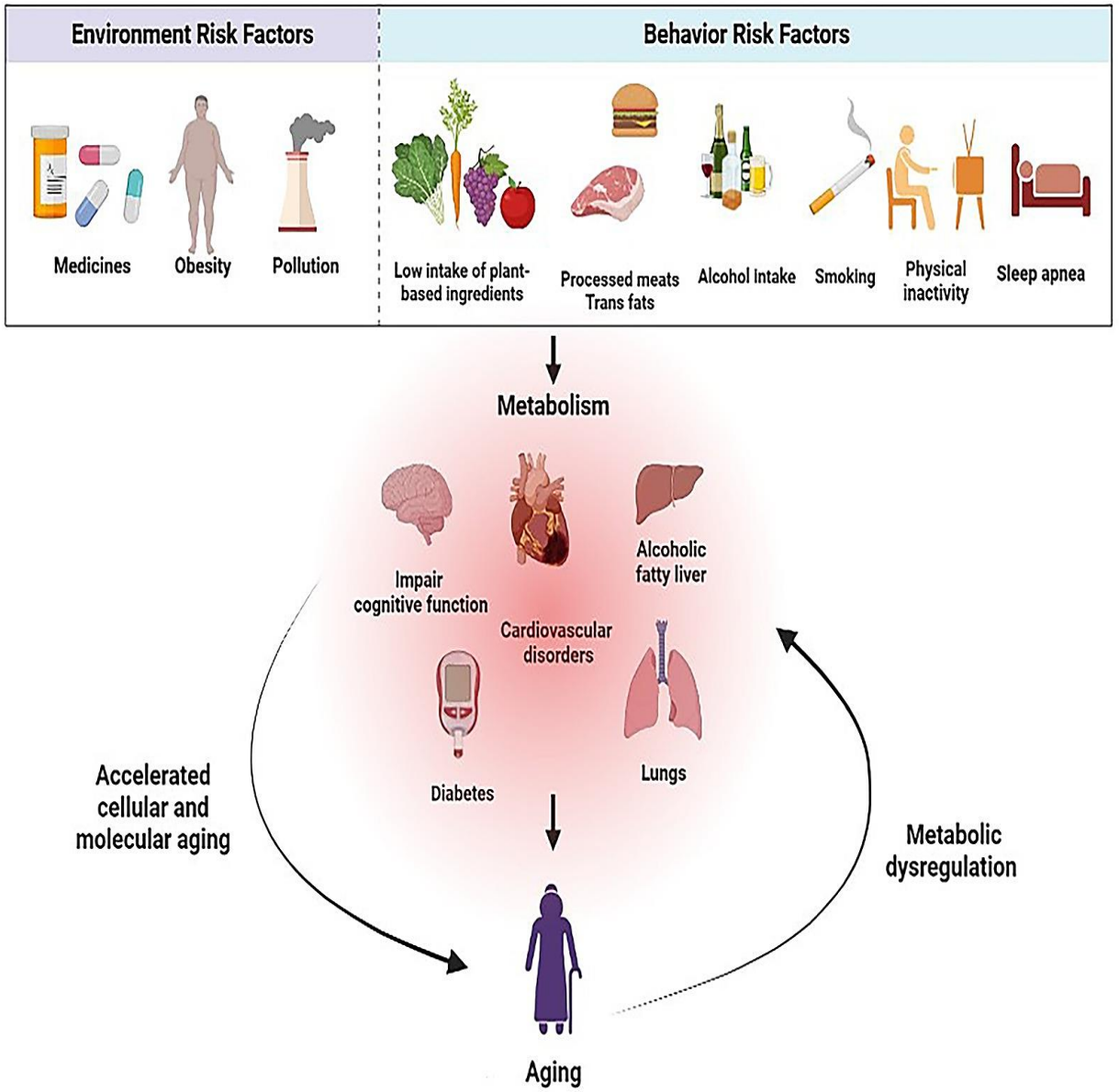


Image illustration Mechanism of the Factors Related to the Patient:

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What is **Xenobiotic Absorption**

- **Xenobiotic Absorption** refers to the process by which foreign substances—known as xenobiotics—enter the body. These compounds, which include drugs, environmental pollutants, and other chemicals not naturally produced by the body, can be absorbed through various routes, including the gastrointestinal tract, respiratory system, and skin. The efficiency of xenobiotic absorption depends on factors like the chemical's properties (e.g., solubility, molecular size), the body’s physiological characteristics (e.g., surface area and pH of the absorption site), and the specific route of entry.

What is **Absorption Sites**:

- **Absorption Sites**:
- **Oral/Gastrointestinal Tract**: Most common, especially for drugs and ingested toxins. The GI tract's large surface area and blood supply aid in efficient absorption.
- **Inhalation/Respiratory System**: The lungs offer a fast absorption route, particularly for gases and airborne particles.
- **Dermal/Skin**: Chemicals can penetrate the skin but typically at a slower rate unless the substance is lipid-soluble or there are enhancers.

What is Mechanisms of Absorption:

- Mechanisms of Absorption
- 1. Passive Diffusion: Common for lipophilic substances that can dissolve in cell membranes and move along a concentration gradient.Active Transport and Facilitated Diffusion: Used for some xenobiotics that resemble natural molecules, allowing transport via specific cellular mechanisms.Factors Influencing
- 2. Absorption:Chemical Properties: Lipophilic (fat-soluble) substances generally have higher absorption rates, while hydrophilic (water-soluble) compounds may need transport proteins.
- 3. Body Conditions: pH levels, enzyme presence, and motility of the GI tract or other tissues affect absorption efficiency.

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   Edition: 4th Edition (2010) This textbook provides an up-to-date overview of toxicological concepts, including chemical, environmental, and pharmaceutical toxicology.
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Thank you