Chapter 7

Absorption of Toxicants and Models of Disposition
Toxicant Entry into the Body

• To produce a systemic effect, a toxicant has to defeat barriers to absorption and enter into the internal compartments of the body; otherwise, all effects are confined to the site of exposure, that is, all toxicity will be local (e.g., irritation to skin or respiratory tract).

• An orally consumed toxicant, or one that enters into the respiratory system, is not considered to be “internal” until it moves across the epithelial cellular membranes that line the respective systems, thus gaining entry into the internal fluid compartments of the body.
Figure 7-1 Absorption and fate of a toxicant

- Toxicant
  - Exposure
    - Respiratory Inhalation
    - Gastrointestinal Ingestion
    - Skin Dermal
  - Absorption
    - Blood/Lymph
  - Distribution
    - Body Tissues and Organs
      - Storage
      - Metabolism
      - Toxicity
      - Elimination
Toxicant Entry into the Body

Principally, toxicants enter the body through one of three systems:

1. *The respiratory system*
2. *The gastrointestinal system*
3. *The integumentary system*
The Respiratory System

• The lungs are an important entry point for toxic gases, solvents, aerosols, and particulates.

• Pulmonary tissue is highly vascularized and has a large surface area (approximately 100 m² in adults) for toxicant absorption.
The Gastrointestinal System

• The gastrointestinal tract has a large surface area (approximately 300 m² in adults).

• The pH, which can influence the absorption of many chemicals, is variable, ranging from approximately 1–3 in the stomach to approximately 6 in the small intestine.
The Integumentary System

• The skin, with its surface area of approximately 2 m², is not highly permeable to most water-soluble chemicals, but lipid-soluble compounds are well absorbed via passive diffusion.

• Damage to the integrity of the skin increases absorption and may lead to greater systemic toxicity.
Cell Membranes

• Cell membranes (a.k.a. plasma membranes) are similar in all cells; they are composed of a phospholipid bilayer approximately 7–9 nm thick.
• They contain proteins that have structural, receptor, or enzymatic function.
• The bilayer is oriented in a way such that the polar phosphate heads, which are hydrophilic, extend into the aqueous phases (extracellular fluid or intracellular fluid) and the hydrophobic (lipophilic) lipid tails toward each other.
Cell Membranes, cont.

• Contained within the phospholipid bilayer are proteins that may assist in the movement of chemicals (e.g., some proteins form aqueous pores, whereas others serve as transport proteins for chemicals).

• For a toxicant to enter into the internal body fluid compartments or to enter, leave, or move to other cells requires passage across several cell membranes.
Figure 7-2 Cell membrane crossings for a toxicant from exposure site to target
Movement of Toxicants Across Cell Membranes

• Toxicants move across cell membranes by either simple diffusion or specialized transport.

• Specialized transport mechanisms included active transport, special transport (facilitated or carrier-mediated diffusion and active transport), and endocytosis.
Movement of Toxicants Across Cell Membranes, cont.

• The primary mechanism is simple diffusion. Several primary factors determine net diffusion (amount of chemical moved) and the diffusion rate:
  – Size of the molecule
  – Molecular charge and degree of ionization
  – Water solubility
  – Concentration differences across the cell membrane
Figure 7-3a Simple Diffusion
Figure 7-3b Diffusion through protein pores
Figure 7-3c
Facilitated Diffusion
Figure 7-3d Active Transport
Figure 7-3e Endocytosis
Figure 7-3f Exocytosis
Skin Absorption

• The skin can be a significant route of exposure for toxicants, especially at the workplace.
• The outer layer of the skin (stratum corneum) is the first line of defense between dermal exposure and systemic toxicity.
• The term *percutaneous absorption* refers to absorption from the surface of the skin into the blood of the cutaneous vessels, which reside in the dermis.
Skin Absorption, cont.

• The skin is relatively impermeable to aqueous solutions and ions; however, it can be a significant route of exposure for chemicals that are lipophilic in nature.

• The skin or integument consists of an outer epidermis, a middle dermis, and a layer of subcutaneous connective tissue.
Did You Know?

Due to the large surface area of the skin, percutaneous absorption has the potential to contribute significantly to the total bioavailability of some compounds. Many chemicals that are very lipophilic can rapidly enter into the blood from the skin and can actually be measured in the expired breath within minutes of dermal exposure. This can be done in the laboratory by connecting a human subject directly with an ion-trap mass spectrometer system to provide continuous real-time analysis of the individual chemical components in the expired air.

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Gastrointestinal Absorption

• Chemicals entering the gastrointestinal tract must first cross the mucosa somewhere along the tract before gaining entry into the blood.
• Only by absorption from the gastrointestinal tract can a chemical exert a toxic effect that could be considered as systemic.
Gastrointestinal Absorption

• The degree of absorption is dependent on:
  – Site
  – pH
  – time
  – the physicochemical properties of the chemical

• Toxicant absorption in the oral cavity and the esophagus is generally poor for many chemicals because of the relatively short residence compared to the slower transport through the stomach and the gastrointestinal tract.
Gastrointestinal Absorption

• The absorption of chemicals from the stomach and intestinal tract first pass through the liver circulation before entering into the general circulation of the body, and therefore they cannot escape hepatic metabolism.

• It is in the liver where a significant amount of toxicant is removed from the venous blood and excreted into the bile, metabolically converted (first-pass metabolism), or stored.
Gastrointestinal Absorption

• Unchanged toxicant or its metabolite can be excreted into the bile and back into the small intestine where they may be absorbed (in the case of the first-pass metabolite) or reabsorbed (in the case of the unmetabolized toxicant).

• This process may continue once again and would tend to reduce the rate of elimination of toxicant from the body.

• This is referred to as enterohepatic circulation.
Figure 7-5
Entero-hepatic circulation
Case in Point

Most people are aware that iron is an essential mineral. Iron may be supplemented as a standalone pill composed of elemental iron or as part of a multivitamin. Iron supplements contain ferrous sulfate, ferrous fumarate, or ferrous gluconate salts; ferrous fumarate contains the highest percentage of elemental iron. These supplements are used to treat iron deficiencies, including certain types of anemia common in pre- and postpartum women.
People who ingest too much iron may develop iron toxicity. Chronic overload can be due to excessive supplement intake; however, diseases such as hereditary hemochromatosis and other conditions may also cause iron overload. Acute iron poisoning is usually the result of excessive ingestion of iron tablets. Multivitamins that contain iron as part of their overall formulation, including children’s chewable ultivitamins, rarely contain enough iron to result in toxicity.
Iron toxicity triggers systemic damage because it disrupts cellular respiration by interfering with mitochondrial respiratory enzymes. Symptoms of acute ingestion may include gastrointestinal, hepatic, central nervous system, and metabolic effects. Weeks after recovery, the stomach, digestive tract, and liver can develop scarring from the previous irritation.
Respiratory Absorption

• The respiratory system constitutes a very important route of exposure for airborne contaminants (e.g., toxic gases, particulates, aerosols, volatile organic solvents).

• Toxicants that are contained within our breathing zone may be absorbed in the nasopharyngeal, tracheobronchial, or pulmonary exchange surfaces of the lungs, depending on the physical and chemical properties of the toxicant.
Figure 7-6
Toxicant absorption from the respiratory system
Respiratory Absorption

• A rapidly absorbed toxicant is quickly distributed throughout the body.
  – Consider the rapidity of poisonings that can occur from respiratory exposure to nitrous oxide (laughing gas), hydrocyanic acid (HCN), ether, or chloroform.
Respiratory Absorption

• Lipophilic and low-molecular-weight gases are quickly absorbed.
  – The greater the degree of lipophilicity, the greater the potential rate of absorption.
  – For hydrophilic chemicals the rate of absorption decreases with increasing molecular size.
Respiratory Absorption, cont.

• For volatile chemicals one can experimentally measure the retention of the chemical in the body by measuring the difference in the concentration between inspired and expired air.

• Particles are also taken into the respiratory system during breathing; depending on the characteristics of the particulates and their interaction with the cells in the lungs, this determines the extent of their retention, absorption, and potential to produce local or systemic toxicity.
Respiratory Absorption, cont.

• In the lungs pulmonary macrophages can engulf particulates, some of which may be cleared into the lymphatic system, or may remain within the lungs for an indefinite period of time, as is the case for asbestos and coal dust.

• Material that remains within the respiratory system may produce local toxicity in which they take the form of:
  – lung cancer, chronic bronchitis, lung fibrosis, and emphysema
Other Exposure Routes

• Intravenous and intraarterial routes provide direct entry of chemicals into the blood vascular system.
  – This is important clinically when rapid action must be taken to stabilize a patient.
  – This exposure pathway results in 100% of the dose being absorbed.
Other Exposure Routes

• Injection of a chemical into the skin is a method to facilitate its systemic absorption.
  – Both intradermal and subcutaneous injections are common clinical routes for the delivery of chemicals.
  – Systemic absorption via intradermal injection is generally much slower than by subcutaneous injection because the tissue here is very well vascularized, thus facilitating rapid absorption into the systemic circulation.
Other Exposure Routes, cont.

• Injection directly into the muscle is referred to as intramuscular and is a common route for the delivery of many pharmaceuticals and vaccines.

  – Skeletal muscle is well vascularized, and absorption via this route of administration is comparable with the subcutaneous route.
Other Exposure Routes, cont.

• The direct injection of chemicals into the body by any route is referred to as a parenteral route of delivery.
  – In laboratory studies, animals are often injected with chemicals directly into either the abdominal cavity or into the chest cavity, and these methods are referred to as intraperitoneal and intrapleural injections, respectively.
  – These exposure routes, rarely used clinically, generally result in a relatively slow absorption of chemicals into the blood.
There are specific aspects of disposition that are of primary importance:

– The duration and concentration of the substance at the site of entry
– The rate of absorption (determined by the ability of the substance to pass through cell membranes)
– The total amount of toxicant absorbed
– The distribution within the body and presence at specific sites
Chemical Disposition & Toxicokinetics

- There are specific aspects of disposition that are of primary importance:
  - The efficiency of biotransformation
  - The toxicity of the metabolites
  - The storage of the toxicant and its metabolites within the body
  - The rate and sites of elimination
Models of Disposition

- The movement of toxicants throughout the body, over time, has been described by the use of models of disposition.
- Models of disposition integrate the processes of:
  - distribution
  - Metabolism
  - elimination
Different theoretical models

- One-compartment model
- Two-compartment model
- Multicompartment model
- Physiologically based model
- Most toxicants follow a theoretical two- or greater compartment model of disposition.
One-compartment model

• The toxicant when introduced into the body would be distributed evenly and instantaneously into a single homogeneous compartment.

• In this simple model, the body is depicted as a single homogeneous compartment.
Figure 7-7 One-compartment model.

Absorption $k_a$ → Central Compartment $A$ → Elimination $k_e$
Two-compartment model

• The toxicant is distributed from the blood (central compartment) into a peripheral compartment (e.g., the kidney) where it can be eliminated or returned back to the blood.
• A *half-life* is described as the time required to reduce the blood or plasma concentration by 50%.
Figure 7-8 One-compartment model of disposition

Absorption

\[ k_a \]

Central

\[ A_1 \]

Peripheral

\[ A_2 \]

Elimination

\[ k_e \]

\[ k_{12} \]

\[ k_{21} \]
Physiologically Based Kinetic Model

• These models are defined by:
  – physiological volumes
  – blood flows
  – partition coefficients
  – metabolic rate
  – Age
  – Sex
  – body weight
  – percentage of body fat
  – ventilation rate
  – cardiac output

• Thus they can be very complex in nature.
Figure 7-11
Physiologically based kinetic model.