
Absorption and Distribution of Toxicants

RONALD E. BAYNES and ERNEST HODGSON

6.1 INTRODUCTION

As illustrated in the previous chapter, the human body can be exposed to a variety of toxicants that may be present in various environmental media such as air, soil, water, or food. However, just simply being exposed to these hazardous chemicals does not necessarily translate into a toxicological response. The mammalian body has several inherent defense mechanisms and membrane barriers that tend to prevent the entry or absorption and distribution of these toxicants once an exposure event has occurred. However, if the toxicant is readily absorbed into the body, there are still other anatomical and physiological barriers that may prevent distribution to the target tissue to elicit a toxic response. As the toxicological response is often related to the exposed dose, interactions between the toxicant and the body's barriers and defense mechanisms will have an effect on toxicant movement in the body, and ultimately modulate the rate and extent of toxicant absorption and distribution to the target tissue.

The skin represents the largest organ in the human body, and one of its primary functions can be seen as a physical barrier to absorption of toxicants. The other major routes of toxicant entry into the body are through the respiratory and gastrointestinal tract, which can be seen to offer less resistance to toxicant absorption than the skin. In general, the respiratory tract offers the most rapid route of entry, and the dermal the least rapid. One reason for this major difference is primarily because membrane thickness, which is really the physical distance between the external environment (skin surface, air in the lung, or lumen of the gut) and the blood capillaries, varies across these portals of entry. The overall entry depends on both the amount present and the saturability of the transport processes involved.

Liver metabolism will have the most significant effect on toxicant bioavailability following gastrointestinal absorption, but microbial activity and various enzymes in the gastrointestinal tract and the skin can play a significant role in oral and dermal absorption, respectively. Physicochemical characteristics of the toxicant such as the chemical form can be a useful indicator of whether the toxicant will be absorbed and distributed in the body. In this regard toxicant molecular weight, ionization (pK_a), and octanol/water partition coefficient ($\log P$) are useful indexes of predicting chemical

transport from an environmental media across biological membranes to the blood stream. The reader should also be aware that for those toxicants that are readily ionized, the pH gradient across membranes can determine the extent of toxicant transport and accumulation in tissues.

Once the toxicant has been absorbed, the toxicant molecules can move around the body in two ways: (1) by bulk flow transfer (i.e., in the blood stream) and (2) by diffusional transfer (i.e., molecule-by-molecule over short distances). Disposition is the term often used to describe the simultaneous effects of distribution and elimination processes subsequent to absorption. The cardiovascular system provides distribution of all toxicants, regardless of their chemical nature, to various organs and tissues with various levels of affinities for toxicants. It should be remembered that organ mass and blood perfusion can vary, which can account for differential distribution of toxicants. Toxicant disposition can also be influenced by plasma protein binding in the blood stream. The nature of this toxicant-protein interaction is dependent on the chemical nature of the toxicant, the presence of other toxicants or drugs in the blood stream, as well as plasma protein levels. However, what distinguishes one toxicant pharmacokinetically from another is its diffusional characteristics. That is, its ability to cross nonaqueous diffusional barriers (e.g., cell membranes) from an aqueous compartment. This usually involves movement across several compartments separated by lipid membranes. It is therefore important to understand the *mechanisms by which drugs cross membranes* and the *physicochemical properties* of molecules and membranes that influence the movement of drugs from the environment to the body via either oral, inhalation, or dermal routes. These factors also influence movement from one compartment to another within the body during distribution as well as metabolism, and excretion.

We can quantitate this movement or transport from one compartment to another using mathematical models to describe transport rates. This in fact is what we do in pharmacokinetic analysis and modeling. *Pharmaco- or toxicokinetics* is therefore the quantitation of the time course of toxicants in the body during the various processes of absorption, distribution, and elimination or clearance (metabolism and/or excretion) of the toxicant. Stated differently, this is a study of how the body “handles” the toxicant as it is reflected in the plasma concentration at various time points. The two most important pharmacokinetic parameters that describe the disposition of a chemical are volume of distribution and systemic (body) clearance. *Pharmaco- and toxicodynamics* is the study of the biochemical and physiological effects of drugs and toxicants and determines their mechanism of action. Physiologically based pharmaco- or toxicokinetic models are used to integrate this information and to predict disposition of toxicants for a given exposure scenario. These concepts will be introduced at the end of this chapter.

6.2 CELL MEMBRANES

During absorption, distribution, and elimination processes the toxicant will encounter various cell membranes before interacting with the target tissue. Each step of these process involves translocation of the chemical across various membrane barriers, from the skin or mucosa through the capillary membranes, and through the cellular and organelle membranes (Figure 6.1). These membrane barriers vary from the relatively thick areas of the skin to the relatively thin lung membranes. In all cases, however, the membranes of tissue, cell, and cell organelle are relatively similar.

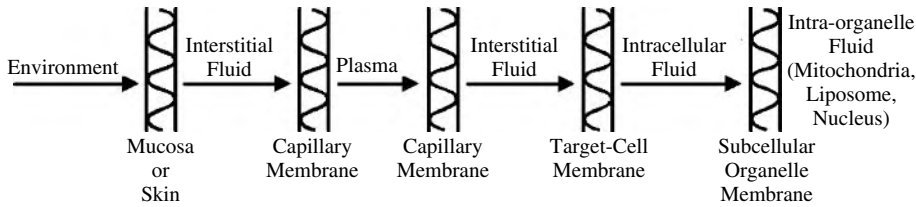


Figure 6.1 Schematic showing membranes that a chemical may need to cross during passage from the environment to the site of action. (Adapted from E. Hodgson and P. E. Levi, eds. *Introduction to Biochemical Toxicology*, 2nd ed., Appleton and Lange, 1994, p. 12.)

The cell membranes are predominantly a lipid matrix or can be considered a lipid barrier with an average width of a membrane being approximately 75 Å. The membrane is described as the fluid mosaic model (Figure 6.2) which consist of (1) a bilayer of phospholipids with hydrocarbons oriented inward (hydrophobic phase), (2) hydrophilic heads oriented outward (hydrophilic phase), and (3) associated intra- and extracellular proteins and transverse the membrane. The ratio of lipid to protein varies from 5:1 for the myelin membrane to 1:5 for the inner structure of the mitochondria. However, 100% of the myelin membrane surface is lipid bilayer, whereas the inner membrane of the mitochondria may have only 40% lipid bilayer surface. In this example the proportion of membrane surface that is lipid will clearly influence distribution of toxicants of varying lipophilicity.

The lipid constituents in the membrane permit considerable movement of macromolecules, and membrane constituents may move appreciably within membranes. Membrane fluidity, a function of lipid composition, can be altered by temperature and chemicals

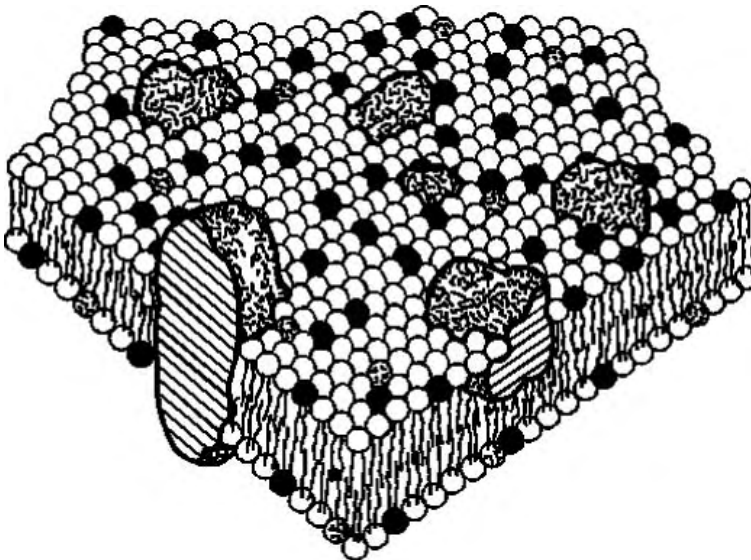


Figure 6.2 Schematic diagram of biological membrane. Head groups of lipids represented by spheres, tail ends by zigzag lines. Black, white, or stippled spheres indicate different kinds of lipids and illustrate asymmetry in certain cases. Large bodies are membrane-associated proteins. (Adapted from Singer and Nicolson, *Science* 175:720, 1972.)

(e.g., anesthetics). Several types of lipids are found in membranes, with phospholipids and cholesterol predominating. Sphingolipids comprise the primary minor component. Phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine are the primary phosphatides, and their two fatty acid hydrocarbon chains (typically 16 to 18, but varying from 12 to 22) comprise the nonpolar region. Some of the fatty acids are unsaturated and contribute appreciably to the fluidity of the membrane.

Proteins, which have many physiological roles in normal cell function, are intimately associated with lipids and may be located throughout lipid bilayers. These proteins may be located on either the surface or traverse the entire structure. Hydrophobic forces are responsible for maintaining the structural integrity of proteins and lipids within membranes, but movement within the membranes may occur. External and internal membrane proteins can function as receptors. Many proteins that traverse the membrane are transport proteins, and are involved in translocation of ligands; that is, they are involved in active and facilitated transport.

Complexes of intrinsic membrane proteins and lipids can form hydrophilic or hydrophobic channels that allow transport of molecules with different physicochemical characteristics. The amphipathic nature of the membrane creates a barrier for ionized, highly polar drugs, although it does not completely exclude them. The presence of pores of approximately 4 Å are believed to allow for ready movement of small molecules such as water. Thus certain molecules that ordinarily would be excluded can rapidly traverse the highly lipid membrane barrier.

It is worth noting that differences among membranes, such as the presence of different lipids, the amount of surface lipid, differences in size and shape of proteins, or physical features of bonding, may cause differences in permeability among membranes. These biochemical and biophysical differences are thought to be responsible for permeability differences in skin from different anatomical regions of the body.

6.3 MECHANISMS OF TRANSPORT

In general, there are four main ways by which small molecules cross biological lipid membranes:

1. *Passive diffusion.* Diffusion occurs through the lipid membrane.
2. *Filtration.* Diffusion occurs through aqueous pores.
3. *Special transport.* Transport is aided by a carrier molecule, which act as a “ferry-boat.”
4. *Endocytosis.* Transport takes the form of pinocytosis for liquids and phagocytosis for solids.

The first and third routes are important in relation to pharmacokinetic mechanisms. The aqueous pores are too small in diameter for diffusion of most drugs and toxicant, although important for movement of water and small polar molecules (e.g., urea). Pinocytosis is important for some macromolecules (e.g., insulin crossing the blood-brain barrier).

6.3.1 Passive Diffusion

Most drugs and toxicant pass through membranes by *simple diffusion* down a concentration gradient. The driving force being the concentration gradient across the membrane.

This diffusion process can continue until equilibrium, although in reality there is always movement but the net flux is zero. Eventually the concentration of unionized or unbound (free) toxicant is the same on either side of the membrane. In other words, there is no competition of molecules and there is generally a lack of saturation. Solubility in the lipid bilayer is important, and the greater the partition coefficient, the higher is the concentration in the membrane, and the greater is the rate of diffusion across the membrane. For ionized toxicants the steady state concentration is dependent on the differences in pH across the membrane. Most membranes are relatively permeable to water either by diffusion or by flow that results from hydrostatic or osmotic differences across the membrane, and bulk flow of water can also carry with it small and water soluble molecules by this mechanism. These substances generally have a molecular weight of less than 200. Although inorganic ions are small and will readily diffuse across some membranes, their hydrated ionic radius is relatively large. In such cases active transport is required (see below). Specific ion fluxes are also controlled by specific channels that are important in nerves, muscles, and signal transduction.

We can now quantitate the *rate* at which a toxicant can be transported by passive diffusion, and this can be described by Fick's law of diffusion as follows:

$$\text{Rate of diffusion} = \frac{D \times S_a \times P_c}{d} (C_H - C_L),$$

where D is the diffusion coefficient, S_a is the surface area of the membrane, P_c is the partition coefficient, d is the membrane thickness, and C_H and C_L are the concentrations at both sides of the membrane (high and low, respectively). The first part of this equation (DP_c/d) represents the permeability coefficient of the drug. The permeability expresses the ease of penetration of a chemical and has units of velocity, distance/time (cm/h).

The diffusion coefficient or diffusivity of the toxicant, D , is primarily dependent on solubility of the toxicant in the membrane and its molecular weight and molecular conformation. Depending on the membrane, there is a functional molecular size and/or weight cutoff that prevents very large molecules from being passively absorbed across any membrane. One would expect small molecular weight molecules to diffuse more rapidly than larger molecular weight toxicants. Therefore the magnitude of a toxicant's diffusion coefficient really reflects the ease with which it is able to diffuse through the membrane. The reader should also be aware that as a toxicant crosses from the donor or aqueous medium and through the membrane medium, there are really two diffusion environments and thus two diffusion coefficients to consider. Another important factor that can influence the diffusion coefficient is membrane viscosity. This physicochemical characteristic should remain constant in biological systems but can be modified in skin membranes exposed to various pharmaceutical or pesticide formulations. Formulation additives or excipients may enter the membrane barrier and reversibly or irreversibly change viscosity and thus diffusion coefficient of the drug or pesticide in the barrier membranes of the skin.

The partition coefficient, which will be described in more detail later in this chapter, is the relative solubility of the compound in lipid and water, and the compound's solubility really reflects the ability of the toxicant to move from a relatively aqueous environment across a lipid membrane. It is this factor that is often manipulated in pesticide and drug formulations to create a vehicle. Membrane permeability is therefore strongly correlated to the lipid solubility of the toxicant in the membrane as well as

the aqueous environment surrounding the membrane. Please be aware that there are instances where partition coefficient or lipid solubility of the toxicant may be very large, and there may be a tendency for the drug to sequester in the membrane. Membrane surface area and membrane thickness can also vary across different organs in the body, but one does not expect these two factors in Fick's equation to vary considerably. The final component of Fick's equation is the concentration gradient ($C_H - C_L$) across the membrane, which is the **driving force for diffusion**, and as will be demonstrated below in our discussion on first-order kinetics, is the most important factor dictating the rate of transport across most biological membranes.

First-Order Kinetics. When the rate of a process is dependent on a **rate constant** and a concentration gradient, a linear or first-order kinetic process will be operative. The reader should be aware that there are numerous deviations from the first-order process when chemical transport in vivo is analyzed, and this can be deemed an *approximation* since, in many barriers, penetration is slow and a long period of time is required to achieve steady state.

The rate of movement of a toxicant across a membrane may be expressed as the *change in amount of toxicant, A, (dA) or toxicant concentration, C, (dC) per unit of time (dt), which equals dA/dt*. Calculus can be used to express instantaneous rates over very small time intervals (*dt*). Thus rate processes may then be generally expressed as

$$\frac{dA}{dt} = \mathbf{K}A^n$$

where dA/dt is the rate of chemical (*X*) movement (e.g. absorption, distribution, elimination), \mathbf{K} is the rate constant of the process, and *n* is the kinetic order of the transport process (e.g., absorption). The *n* either equals 1 (first order) or 0 (zero order). Thus the first-order rate equation is written as

$$\frac{dA}{dt} = \mathbf{K}A^1 = \mathbf{K}A,$$

and the zero-order rate equation as

$$\frac{dA}{dt} = \mathbf{K}A^0 = \mathbf{K}.$$

We know from Fick's law that the rate of diffusion (now expressed as dA/dt) is

$$\frac{dA}{dt} = \frac{\mathbf{D} \cdot \mathbf{S}_a \cdot \mathbf{P}_c (A_1 - A_2)}{d}.$$

Once a toxicant crosses a membrane, it is rapidly removed from the "receiving side" (compartment B in Figure 6.3) either by uptake into the blood stream or elimination from the organism. Thus it is A_1 that is the primary driving force, and if we replace this with *A* in all equations, then

$$\frac{dA}{dt} = \left(\frac{\mathbf{D} \cdot \mathbf{S}_a \cdot \mathbf{P}_c}{d} \right) A.$$

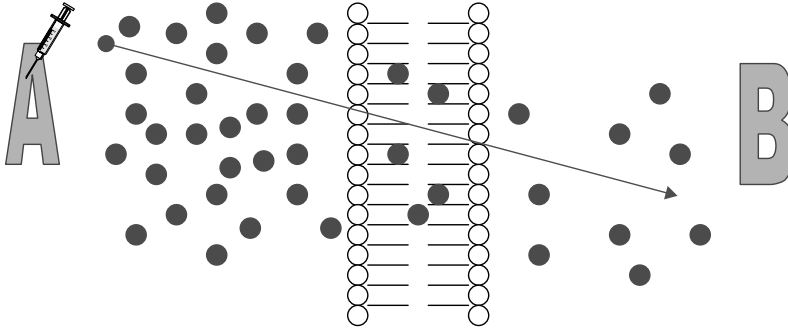


Figure 6.3 Illustration of concentration gradient generated by administration of a drug that can travel down this gradient from area A and across a biological membrane to area B.

If we let $K = (D \cdot S_a \cdot P_c / d)$, then, since A is present in the equation, n must equal 1, so we have a first-order rate process. Fick's law of diffusion, which is important for quantitating rates of absorption, distribution, and elimination, is thus the basis for using first-order kinetics in most pharmacokinetic models.

Therefore in a first-order process, the rate of drug movement is directly proportional to the amount of drug (A) in the body, which is usually a function of the dose. K is the first-order fractional rate constant with units of liters/time (time^{-1}) and represents the *fraction* of drug that is transported *per unit of time*. Thus in a *first-order* process, the rate of drug movement is proportional to dose but the fraction moved per unit of time is constant and *independent of dose*.

When first-order kinetics hold, a simple relationship exists between the penetration rate constant, K , and $t_{0.5}$ (time necessary for one-half of the applied dose to penetrate):

$$K = \frac{0.693}{t_{0.5}},$$

where the units of K are a percentage of the change/time unit. We can also derive the concentration of the toxicant if we know the volume or volume of distribution (V_d) of the toxicant compartment as

$$V_d(\text{volume}) = \frac{A(\text{mass})}{C(\text{mass/volume})}.$$

(V_d is discussed in more detail later in this chapter.)

6.3.2 Carrier-Mediated Membrane Transport

This mechanism is important for compounds that lack sufficient lipid solubility to move rapidly across the membrane by simple diffusion. A membrane-associated protein is usually involved, specificity, competitive inhibition, and the saturation phenomenon and their kinetics are best described by *Michaelis-Menton enzyme kinetic models*. Membrane penetration by this mechanism is more rapid than simple diffusion and, in the case of active transport, may proceed beyond the point where concentrations are equal on both

sides of the membrane. Generally, there are two types of specialized carrier-mediated transport processes:

Passive facilitated diffusion involves movement down a concentration gradient without an input of energy. This mechanism, which may be highly selective for specific conformational structures, is necessary for transport of endogenous compounds whose rate of transport by simple diffusion would otherwise be too slow. The classical example of facilitated diffusion is transport of glucose into red blood cells.

Active transport requires energy, and transport is against a concentration. Maintenance against this gradient requires energy. It is often coupled to energy-producing enzymes (e.g., ATPase) or to the transport of other molecules (e.g., Na⁺, Cl⁻, H⁺) that generate energy as they cross the membranes. Carrier-mediated drug transport can occur in only a few sites in the body, and the main sites are

- BBB, neuronal membranes, choroid plexus
- Renal tubular cells
- Hepatocytes, biliary tract

There are instances in which toxicants have chemical or structural similarities to endogenous chemicals that rely on these special transport mechanisms for normal physiological uptake and can thus utilize the same system for membrane transport. Useful examples of drugs known to be transported by this mechanism include levodopa, which is used in treating Parkinson's disease, and fluorouracil, a cytotoxic drug. Levodopa is taken up by the carrier that normally transports phenylalanine, and fluorouracil is transported by the system that carries the natural pyrimidines, thymine, and uracil. Iron is absorbed by a specific carrier in the mucosal cells of the jejunum, and calcium by a vitamin D-dependent carrier system. Lead may be more quickly moved by a transport system that is normally involved in the uptake of calcium.

For carrier-mediated transport, the rate of movement across a membrane will now be *constant*, since flux is dependent on the capacity of the membrane carriers and not the mass of the chemical to be transported. These processes are described by *zero-order* kinetic rate equations of the form:

$$\frac{dX}{dt} = KX^0 = K_0.$$

K_0 is now the *zero-order* rate constant and is expressed in terms of mass/time. In an active carrier-mediated transport process following zero-order kinetics, the rate of drug transport is always equal to K once the system is fully loaded or saturated. At subsaturation levels, the rate is *initially first order* as the carriers become loaded with the toxicant, but at concentrations normally encountered in pharmacokinetics, the rate becomes constant. Thus, as dose increases, the rate of transport does *not* increase in proportion to dose as it does with the fractional rate constant seen in first-order process. This is illustrated in the Table 6.1 where it is assumed that the first-order rate constant is 0.1 (10% per minute) and the zero-order rate is 10 mg/min.

In the case of first order, these amounts will subsequently diminish (10% of 900 is 90, etc.). In the case of zero order, the amount transported does not vary with time (constant rate of transport).

Table 6.1 Amount of Toxicant (mg) Transported in One Minute

Initial Toxicant Mass (mg)	First-Order Rate	Zero-Order Rate
1000	100	10
100	10	10
10	1	10

The plot in Figure 6.4 illustrates the differences in passive (linear) versus carrier-mediated (nonlinear) transport. At relatively low concentrations of drug, carrier-mediated processes may appear to be first order since the protein carriers are not saturated. However, at higher concentrations, zero-order behavior becomes evident. It is in plots such as this that the terms *linear* (first order) and *nonlinear* (zero order) come into existence.

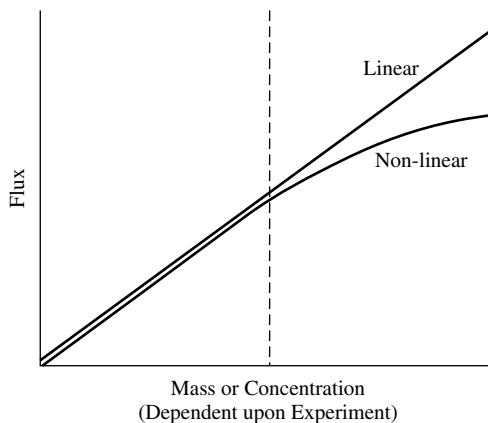


Figure 6.4 Plot depicting a linear relationship (first order) and nonlinear relationship (zero order) between chemical flux across a membrane and the initial mass or concentration of the chemical.

6.4 PHYSICOCHEMICAL PROPERTIES RELEVANT TO DIFFUSION

The following physicochemical properties are important for chemical diffusion. We have discussed several of these properties in previous sections of this chapter as they relate to the passive diffusion mechanism and its impacts on rate of toxicant transport across membranes.

- Molecular size and shape
- Solubility at site of absorption
- Degree of ionization
- Relative lipid solubility of ionized and unionized forms

Although molecular weight is important, it is less important than the drug's *lipid solubility* when it comes to assessing the rate of passive diffusion across membranes.

The permeability, P ($P = P_c \times D$), of a nonpolar substance through a cell membrane is dependent on two physicochemical factors: (1) *solubility in the membrane* (P_c), which can be expressed as a partition coefficient of the drug between the aqueous phase and membrane phase, and (2) *diffusivity or diffusion coefficient* (D), which is a measure of mobility of the drug molecules within the lipid. The latter may vary only slightly among toxicants, but the former is more important. Lipid solubility is therefore one of the most important determinants of the pharmacokinetic characteristics of a chemical, and it is important to determine whether a toxicant is readily ionized or not influenced by pH of the environment. If the toxicant is readily ionized, then one needs to understand its chemical behavior in various environmental matrices in order to adequately assess its transport mechanism across membranes.

6.4.1 Ionization

For the purposes of this discussion on membrane transport, chemicals can be broadly categorized into those that are ionized and those that are not ionized. Many drugs (e.g., antibiotics) and several toxicants (e.g., strychnine) are either weak acids or weak bases and can exist in solution as a mixture of nonionized and ionized forms. Generally, these drugs and toxicants must be in the uncharged or nonionized form to be transported by passive diffusion across biological membranes. This is because biological membranes are of a lipid nature and are less permeable to the ionized form of the chemical. The pH of the environment (e.g., lumen of the gastrointestinal tract and renal tubules) can influence transfer of toxicant that are ionizable by increasing or decreasing the amount of nonionized form of the toxicant. Aminoglycosides (e.g., gentamicin) are the exception to this general rule in that the uncharged species is insufficiently lipid soluble to cross the membrane appreciably. This is due to a preponderance of hydrogen-bonding groups in the sugar moiety that render the uncharged molecule hydrophilic. Note that some amphoteric drugs (e.g., tetracyclines) may be absorbed from both acidic and alkaline environments. In essence, the amount of drug or toxicant in ionized or nonionized form depends on the pKa (pH at which 50% of the drug is ionized) of the drug and the pH of the solution in which the drug is dissolved. *The pKa, which is the negative logarithm of the dissociation constant of a weak acid or weak base, is a physicochemical characteristic of the drug or toxicant.* When the pH of the solution is equal to the pKa, then 50% of the toxicant is in the ionized form and 50% is in the nonionized form. The ionized and nonionized fractions can be calculated according to the *Henderson-Hasselbach* equations listed below:

For weak acids : $\text{pKa} - \text{pH} = \log(\text{Nonionized form}/\text{Ionized form}),$

For weak bases : $\text{pKa} - \text{pH} = \log(\text{Ionized form}/\text{Nonionized form}).$

For an organic acid ($\text{RCOOH} \leftrightarrow \text{RCOO}^- + \text{H}^+$), acidic conditions (pH less than the pKa of the compound) will favor the formation of the nonionized RCOOH, whereas alkaline conditions (pH greater than pKa) will shift the equilibrium to the right. For an organic base ($\text{RNH}_2 + \text{H}^+ \leftrightarrow \text{RNH}_3^+$), the reverse is true, and decreasing the pH (increasing the concentration of H^+) will favor formation of the ionized form, whereas increasing the pH (decreasing the concentration of H^+) will favor formation of the nonionized form.

Table 6.2 Amount of Toxicant Absorbed at Various pH Values (%)

Compound	pKa	3.6–4.3	4.7–5.0	7.0–7.2	7.8–8.0
<i>Acids</i>					
Nitrosalicyclic	2.3	40	27	<02	<02
Salicyclic	3.0	64	35	30	10
Benzoic	4.2	62	36	35	05
<i>Bases</i>					
Aniline	4.6	40	48	58	61
Aminopyrene	5.0	21	35	48	52
Quinine	8.4	09	11	41	54

Memory aid: In general, weak organic acids readily diffuse across a biological membrane in an acidic environment, and organic bases can similarly diffuse in a basic environment. This is illustrated quite well in Table 6.2 for the chemical in rat intestine. There are the usual exceptions to the generalizations concerning ionization and membrane transport, and some compounds, such as pralidoxime (2-PAM), paraquat, and diquat, are absorbed to an appreciable extent even in the ionized forms. The mechanisms allowing these exceptions are not well understood.

Ion trapping can occur when at equilibrium the total (ionized + nonionized) concentration of the drug will be different in each compartment, with an acidic drug or toxicant being concentrated in the compartment with the relatively high pH, and vice versa. The pH partition mechanism explains some of the qualitative effects of pH changes in different body compartment on the pharmacokinetics of weakly basic or acidic drugs or toxicant as it relates to renal excretion and penetration of the blood-brain barrier. Alkalinization of urine in the lumen of renal tubules can enhance elimination of weak acids. However, this phenomenon is not the main determinant of absorption of drugs or toxicants from the gastrointestinal tract. In the gastrointestinal tract the enormous absorptive surface area of the villi and microvilli in the ileum, compared to the smaller absorptive area of the stomach, is of overriding importance.

6.4.2 Partition Coefficients

A second physicochemical parameter influencing chemical penetration through membranes is the relative lipid solubility of the potential toxicant that can be ascertained from its known partition coefficient. The partition coefficient is a measure of the ability of a chemical to separate between two immiscible phases. The phases consist of an organic phase (e.g., octanol or heptane) and an aqueous phase (e.g., water). The lipid solvent used for measurement is usually octanol because it best mimics the carbon chain of phospholipids, but many other systems have been reported (chloroform/water, ether/water, olive oil/water). The lipid solubility and the water solubility characteristics of the chemical will allow it to proportionately partition between the organic and water phase. The partition coefficients can be calculated using the following equation:

$$P = \frac{V_w}{V_o} \left[\frac{(C_{wo} - C_w)}{C_w} \right],$$

where P is the partition coefficient and usually expressed in terms of its logarithmic value ($\log P$), V_w and V_o are the volumes of aqueous and oil or organic phase, respectively, and C_{wo} and C_w are drug or toxic concentrations in the aqueous phase before and after shaking, respectively.

The lower the partition coefficient, the more water soluble, and the least permeable the toxicant is across a membrane. Regarding dermal absorption, partition coefficients can be predictive of absorption. However, toxicants with extremely high partition coefficients tend to remain in the membrane or skin. This explains why a strong correlation between permeability and the partition coefficient can exist for a hypothetical series of analogous chemicals for a specific range of partition coefficients, but the correlation does not exist for $\log P$ values greater than 6 in many instances. A $\log P$ of around 1 is often taken as desirable for skin penetration. The reader should also recall that this parameter is operative as the chemical diffuses across membranes (Figure 6.1) of varying lipid content during absorption, distribution, and elimination processes.

6.5 ROUTES OF ABSORPTION

Primary routes of entry of toxicants to the human body are dermal, gastrointestinal, and respiratory. Methods for studying these different routes are numerous, but they are perhaps best developed for the study of dermal absorption because this route is subject to more direct methodology, whereas methods for studying respiratory or gastrointestinal absorption require more highly specialized instrumentation. Additional routes encountered in experimental studies include intraperitoneal, intramuscular, and subcutaneous routes. When direct entry into the circulatory system is desired, intravenous (IV) or intra-arterial injections can be used to bypass the absorption phase. Information from this more direct route of entry (e.g., IV) should, however, be used in addition to data from the extravascular route of interest to adequately assess the true extent of absorption of a toxicant.

6.5.1 Extent of Absorption

It is often useful to determine *how much of the drug* actually penetrates the membrane barrier (e.g., skin or gastrointestinal tract) and gets into the blood stream. This is usually determined experimentally for oral and dermal routes of administration. The *area under the curve* (AUC) of the concentration-time profiles for oral or dermal routes is compared with the AUC for IV routes of administration. The AUC is determined by breaking the curve up into a series of trapezoids and summing all of the areas with the aid of an appropriate computer program (Figure 6.5).

The intravenous correction is very important if absolute bioavailability is desired. The ratio of these AUC values is absolute bioavailability, F :

$$F = \frac{(\text{AUC})_{\text{route}}}{(\text{AUC})_{\text{IV}}}$$

The relationship above holds if the same doses are used with both routes, but the bioavailability should be corrected if different doses are used:

$$F = \frac{\text{AUC}_{\text{route}} \times \text{Dose}_{\text{IV}}}{\text{AUC}_{\text{IV}} \times \text{Dose}_{\text{route}}}$$

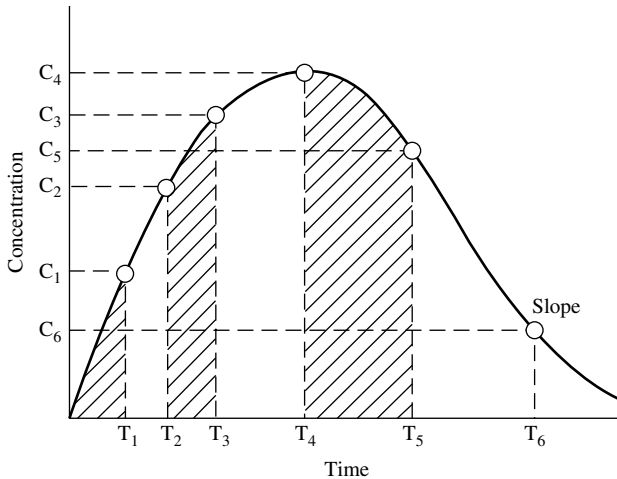


Figure 6.5 Plasma concentration time profile for oral exposure to a toxicant and depiction of AUCs determined by summation of trapezoids at several time periods.

Another technique is to monitor drug or toxicant excretion rather than blood concentrations, especially when blood or plasma concentrations are very low. Using the same equations, the AUC is now replaced by chemical concentrations in urine, feces, and expired air. Some chemicals are primarily excreted by the kidney and urine data alone may be necessary. The rate and extent of absorption are clearly important for therapeutic and toxicological considerations. For example, different formulations of the same pesticide can change the absorption rate in skin or gastrointestinal tract, and not bioavailability, but can result in blood concentrations near the toxic dose. Also different formulations can result in similar absorption rates but different bioavailability.

6.5.2 Gastrointestinal Absorption

The gastrointestinal tract (GIT) is a hollow tube (Figure 6.6a) lined by a layer of columnar cells, and usually protected by mucous, which offers minimal resistance to toxicant penetration. The distance from the outer membrane to the vasculature is about 40 μm , from which point further transport can easily occur. However, the cornified epithelium of the esophagus prevents absorption from this region of the GIT. Most of the absorption will therefore occur in the intestine ($\text{pH} = 6$), and to some extent in the stomach ($\text{pH} = 1-3$). Buccal and rectal absorption can occur in special circumstances. Note that secretions from the lachrymal duct, salivary gland, and nasal passages can enter the GIT via the buccal cavity. Therefore, following IV administration, a toxicant can enter the GIT if the drug is in these secretions.

The intestine can compensate the 2.5 log units difference between it and the stomach by the increased surface area in the small intestines. The presence of microvilli (Figure 6.6b) in the intestine is an increase of 600-fold in surface area compared to a hollow tube of comparable length. Note that there is no absorption, except for water, in the large intestine.

Most of the absorption in the GIT is by passive diffusion, except for nutrients; glucose, amino acids, and drugs that look like these substances are taken up by

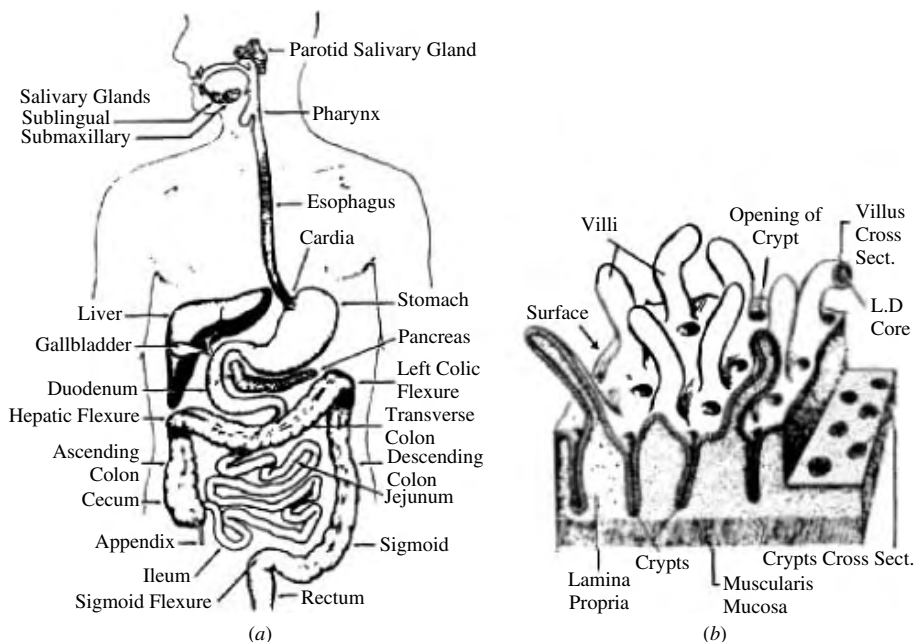


Figure 6.6 Schematic showing (a) alimentary canal and associated structures and (b) lining of the small intestine. (Sources:(a) Scholtelius and Scholtelius in *Textbook of Physiology*, Mosby, 1973; (b) Ham and Cormack, in *Histology*, 8th ed., Lippincott, 1979.)

active transport. For toxicants with structural similarities to compounds normally taken up by these active transport mechanisms, entry is enhanced. For example, cobalt is absorbed by the same active transport mechanism that normally transports iron, and 5-bromouracil is absorbed by the pyrimidine transport system.

Very lipid soluble toxicants and drugs, which are not miscible in the aqueous intestinal fluid, are presented as emulsions, and brought into solution through the action of detergent-like bile acids. The product of this mixing is large surface area micelles (hydrophobic interior) that deliver the lipids to the brush border of the intestine for diffusion across the membrane. As stated previously, the rate of passive transfer will be dependent on ionization and lipid solubility. Very strong bases (e.g., tubocurarine, succinylcholine) and strong acids are not readily absorbed in the GIT. These muscle relaxants therefore are given IV. The smaller the particle size of the toxicant, the greater is the absorption, and a chemical must be in aqueous solution for it to be absorbed in the GIT. A feature of the GIT that seems to contradict basic assumptions of absorption is the penetration of certain very large molecules. Compounds such as bacterial endotoxins, large particles of azo dyes, and carcinogens are apparently absorbed by endocytotic mechanisms.

GIT motility has a significant effect on GIT absorption of a toxicant. For example, excessively rapid movement of gut contents can reduce absorption by reducing residence time in the GIT, while the presence of food in the stomach can delay the progress of drugs from the stomach to the small intestine where most of the absorption will occur. Increased splanchnic blood flow after a meal can result in absorption of several drugs (e.g., propranolol), but in hypovolemic states, absorption can be reduced.

Biotransformation in the GIT prior to absorption can have a significant impact on bioavailability of a toxicant. The resident bacterial population can metabolize drugs in the GIT. Because of microbial fermentation in the rumen of ruminants and large intestine and cecum of horses and rabbits, it is often difficult to compare drug absorption profiles with carnivores (e.g., dogs) and omnivores (e.g., humans, pigs). Acid hydrolysis of some compounds can also occur, and enzymes in the intestinal mucosa can also have an effect on oral bioavailability. If the toxicant survive these microbial and chemical reactions in the stomach and small intestine, it is absorbed in the GIT and carried by the hepatic portal vein to the liver, which is the major site of metabolism. Chapters 7, 8, and 9 will discuss liver metabolism of toxicants in more detail. In brief, this activity in the liver can result in detoxification and/or bioactivation. Some drugs and toxicant that are conjugated (e.g., glucuronidation) in the liver are excreted via the biliary system back into the GIT. Once secreted in bile by active transport and excreted from the bile duct into the small intestine, this conjugated toxicant can be subjected to microbial beta-glucuronidase activity that can result in regeneration of the parent toxicant that is more lipophilic than the conjugate. The toxicant can now be reabsorbed by the GIT, prolonging the presence of the drug or toxicant in the systemic circulation. This is called *enterohepatic circulation*, which will be covered in greater detail in subsequent chapters.

6.5.3 Dermal Absorption

The skin is a complex multilayered tissue with a large surface area exposed to the environment. Skin anatomy, physiology, and biochemistry vary among species, within species, and even between anatomic sites within an individual animal or human. Logically these biological factors alone can influence dermal absorption. What is consistent is that the outer layer, the *stratum corneum* (SC), can provide as much as 80% of the resistance to absorption to most ions as well as aqueous solutions. However, the skin is permeable to many toxicants, and dermal exposure to agricultural pesticides and industrial solvent can result in severe systemic toxicity.

The anatomy of the skin is depicted in the schematic diagram of Figure 6.7. In mammalian skin there are really three distinct layers, which are the epidermis, dermis, and hypodermis or subcutaneous fat layer. Human skin is 3 mm thick, but it is the epidermis, which is only 0.1 to 0.8 mm, that provides the greatest resistance to toxicant penetration. The five layers of the epidermis, starting from the outside, are the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The basal cells of the epidermis proliferate and differentiate as they migrate outward toward the surface of the skin. It requires about 2 to 28 days for cells to migrate from the basal layer to the stratum corneum, where they are eventually sloughed off. These dead, keratinized cells are, however, very water absorbant (hydrophilic), a property that keeps the skin soft and supple. Sebum, a natural oil covering the skin, functions in maintaining the water-holding ability of the epidermis. The stratum corneum is the primary barrier to penetration, and it consists primarily of these dead keratin-filled keratinocytes embedded in an extracellular lipid matrix. The lipids are primarily sterols, other neutral lipids, and ceramides. This association between lipids and dead keratinized cells, which is often referred to as the “brick and mortar” model as depicted in Figure 6.7b, is used to simplify the composition of the stratum corneum that is integral to chemical transport through skin.

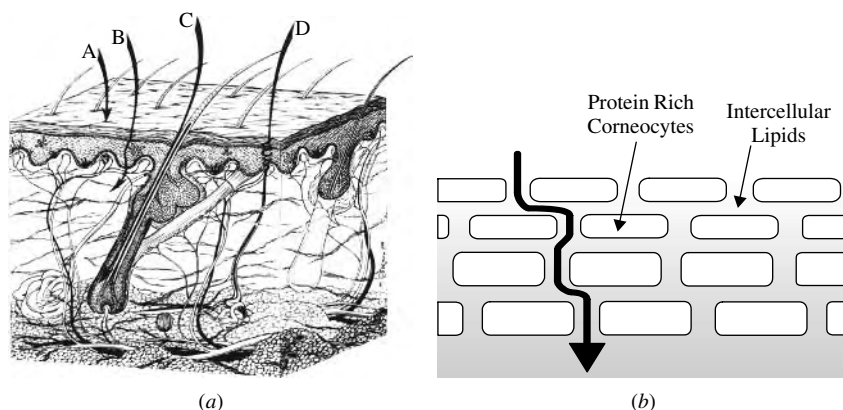


Figure 6.7 (a) Schematic diagram of the microstructure of mammalian skin and potential pathways for absorption by (A) intercellular, (B) transcellular, (C) transfollicular, or (D) sweat pore routes. (b) Brick-and-mortar" model of the stratum corneum depicting intercellular pathway (i.e., route A) between keratinocytes through the lipid domain of the stratum corneum.

A number of appendages are associated with the skin, including hair follicles, sebaceous glands, eccrine and apocrine sweat glands, and nails. Recently it was found that removal of the stratum corneum does not allow complete absorption; thus it is apparent that some role, although of lesser importance, is played by other parts of the skin. The dermis and subcutaneous areas of the skin are less important in influencing penetration, and once a toxicant has penetrated the epidermis, the other layers are traversed rather easily. The dermis is highly vascular, a characteristic that provides maximal opportunity for further transport once molecules have gained entry through the epidermis or through skin appendages. Most of the systemic absorption occurs at the capillary loops located at the epidermis-dermis junction. The blood supply of the dermis is under neural and humoral influences whose temperature-regulating functions could thus affect penetration and distribution of toxicants. Vasoactive drugs or environmental temperature can also influence absorption by altering blood flow to these capillaries. The subcutaneous layer of the skin is highly lipid in nature and serves as a shock absorber, an insulator, and a reserve depot of energy. The pH of the skin varies between 4 and 7 and is markedly affected by hydration.

Cutaneous biotransformation is mostly associated with the stratum basale layer where there can be phase I and phase II metabolism. However, the skin is not very efficient, compared to the liver. The epidermal layer accounts for the major portion of biochemical transformations in skin, although the total skin activity is low (2–6% that of the liver). Where activity is based on epidermis alone, that layer is as active as the liver or, in the case of certain toxicants, several times more active. For some chemicals, metabolism can influence absorption, and transdermal delivery systems of drugs utilize this activity. For example prodrug such as lipid esters are applied topically, and cutaneous esterases liberate the free drug. These basal cells and extracellular esterases have been shown to be involved in detoxification of several pesticides and bioactivation of carcinogens such as benzo(a)pyrene. For rapidly penetrating substances, metabolism by the skin is not presently considered to be of major significance, but skin may have an important first-pass metabolic function, especially for compounds that are absorbed slowly.

The *intercellular pathway* is now accepted as the major pathway for absorption. Recall that the rate of penetration is often correlated with the partition coefficient. In fact this is a very tortuous pathway, and the h (skin thickness) in Fick's first law of diffusion is really $10\times$ the measured distance. By placing a solvent (e.g., ether, acetone) on the surface or tape stripping the surface, the stratum corneum (SC) is removed, and absorption can be significantly increased by removing this outer barrier. This may not be the case for very lipophilic chemical. This is because the viable epidermis and dermis are regarded as aqueous layers compared to the SC. Note that the more lipophilic the drug, the more likely it will form a depot in the SC and be slowly absorbed over time and thus have a prolonged half-life.

The *transcellular pathway* has been discredited as a major pathway, although some polar substances can penetrate the outer surface of the protein filaments of hydrated stratum corneum. The *transfollicular pathway* is really an invagination of the epidermis into the dermis, and the chemical still has to penetrate the epidermis to be absorbed into the blood stream. This is also regarded as *minor* route. *Sweat pores* are not lined with the stratum corneum layer, but the holes are small, and this route is still considered a minor route for chemical absorption. In general, the epidermal surface is 100 to 1000 times the surface area of skin appendages, and it is likely that only very small and/or polar molecules penetrate the skin via these appendages.

Variations in areas of the body cause appreciable differences in penetration of toxicants. The rate of penetration is in the following order:

Scrotal > Forehead > Axilla >= Scalp > Back = Abdomen > Palm and plantar.

The palmar and plantar regions are highly cornified and are 100 to 400 times thicker than other regions of the body. Note that there are differences in blood flow and to a lesser extent, hair density, that may influence absorption of more polar toxicants.

Formulation additives used in topical drug or pesticide formulations can alter the stratum corneum barrier. Surfactants are least likely to be absorbed, but they can alter the lipid pathway by fluidization and delipidization of lipids, and proteins within the keratinocytes can become denatured. This is mostly likely associated with formulations containing anionic surfactants than non-ionic surfactants. Similar effects can be observed with solvents. Solvents can partition into the intercellular lipids, thereby changing membrane lipophilicity and barrier properties in the following order: ether/acetone > DMSO > ethanol > water. Higher alcohols and oils do not damage the skin, but they can act as a depot for lipophilic drugs on the skin surface. The presence of water in several of these formulations can hydrate the skin. Skin occlusion with fabric or transdermal patches, creams, and ointments can increase epidermal hydration, which can increase permeability.

The reader should be aware of the animal model being used to estimate dermal absorption of toxicants in humans. For many toxicants, direct extrapolation from a rodent species to human is not feasible. This is because of differences in skin thickness, hair density, lipid composition, and blood flow. Human skin is the least permeable compared to skin from rats, mice, and rabbits. Pig skin is, however, more analogous to human skin anatomically and physiologically, and pig skin is usually predictive of dermal absorption of most drugs and pesticides in human skin. Human skin is the best model, followed by skin from pigs, primates, and hairless guinea pigs, and then rats, mice, and rabbits. In preliminary testing of a transdermal drug, if the drug does

not cross rabbit or mice skin, it is very unlikely that it will cross human skin. There are several *in vitro* experimental techniques such as static diffusion (Franz) cells or flow-through diffusion (Bronough) cells. There are several *ex vivo* methods including the isolated perfused porcine skin flap (IPPSF), which with its intact microvasculature makes this model unique. *In vivo* methods are the golden standard, but they are very expensive, and there are human ethical and animal rights issues to be considered.

There are other factors that can influence dermal absorption, and these can include environmental factors such as air flow, temperature, and humidity. Preexisting skin disease and inflammation should also be considered. The topical dose this is usually expressed in per unit surface area can vary, and relative absorption usually decreases with increase in dose.

6.5.4 Respiratory Penetration

As observed with the GIT and skin, the respiratory tract can be regarded as an external surface. However, the lungs, where gas/vapor absorption occurs, are preceded by protective structures (e.g., nose, mouth, pharynx, trachea, and bronchus), which can reduce the toxicity of airborne substances, especially particles. There is little or no absorption in these structures, and residual volume can occur in these sites. However, cells lining the respiratory tract may absorb agents that can cause a toxicological response. The absorption site, which is the alveoli-capillary membrane, is very thin (0.4–1.5 μm). The membranes to cross from the alveolar air space to the blood will include: *type I cells to basement membrane to capillary endothelial cells* (Figure 6.8). This short distance allows for rapid exchange of gases/vapors. The analogous absorption distance in skin is 100 to 200 μm , and in GIT it is about 30 μm . There is also a large surface area (50 times the area of skin) available for absorption as well as significant blood flow, which makes it possible to achieve rapid adjustments in plasma concentration.

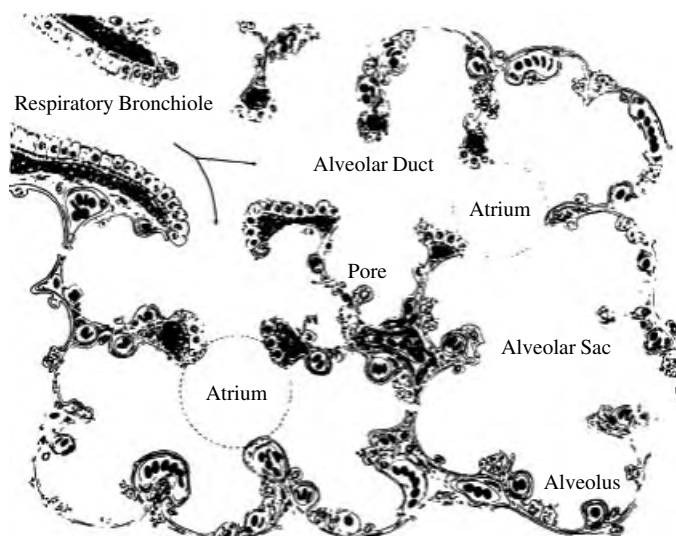


Figure 6.8 Schematic representation of the respiratory unit of the lung. (From Bloom and Fawcett, in *A Textbook of Histology*, Philadelphia: Saunders, 1975.)

Gases/vapors must get into solution in the thin fluid film in the alveoli for systemic absorption to occur. For this reason doses are often a measurement of partial pressures, which is important for gases/vapors.

The process of respiration involves the movement and exchange of air through several interrelated passages, including the nose, mouth, pharynx, trachea, bronchi, and successively smaller airways terminating in the alveoli, where gaseous exchange occurs. These alveoli consist mainly of type I pneumocytes, which represent 40% of all cells but cover > 90% of surface area, and type II pneumocytes, which represent 60% of all cells but cover 5% of surface area. Macrophages make up 90% of cells in alveolar space. The amount of air retained in the lung despite maximum expiratory effort is known as the residual volume. Thus toxicants in the respiratory air may not be cleared immediately because of slow release from the residual volume. The rate of entry of vapor-phase toxicants is controlled by the alveolar ventilation rate, with the toxicant being presented to the alveoli in an interrupted fashion approximately 20 times/min.

Airborne toxicants can be simplified to two general types of compounds, namely gases and aerosols. Compounds such as gases, solvents, and vapors are subject to gas laws and are carried easily to alveolar air. Much of our understanding of xenobiotic behavior is with anesthetics. Compounds such as aerosols, particulates, and fumes are not subject to gas laws because they are in particulate form.

The transfer of gas from alveoli to blood is the actual absorption process. Among the most important factors that determine rate and extent of absorption of a gas in lungs is the solubility of that gas. Therefore it is not the membrane partition coefficient that necessarily affects absorption as has been described for skin and GIT membranes, but rather the blood: gas partition coefficient or blood/gas solubility of the gas. A high blood: gas partition coefficient indicates that the blood can hold a large amount of gas. Keep in mind that it is the *partial pressure* at equilibrium that is important, so the more soluble the gas is in blood, the greater the amount of gas that is needed to dissolve in the blood to raise the partial pressure or tension in blood. For example, anesthetics such as diethyl ether and methoxyflurane, which are soluble (Table 6.3), require a longer period for this partial pressure to be realized. Again, the aim is to generate the same tension in blood as in inspired air. Because these gases are very soluble, detoxification is a prolonged process. In practice, anesthetic induction is slower, and so is recovery from anesthesia. For less soluble gases (e.g., NO, isoflurane, halothane), the partial pressure or tension in blood can be raised a lot easier to that of inspired gases, and detoxification takes less time than those gases that are more soluble.

There are several other important factors that can determine whether the gas will be absorbed in blood and then transported from the blood to the perfused tissue. The concentration of the gas in inspired air influences gas tension, and partial pressure can be increased by overventilation. In gas anesthesiology we know that the effects of

Table 6.3 Blood: Gas Partition Coefficient in Humans

Agent	Coefficient
Methoxyflurane	13.0–15.0
Halothane	2.3–2.5
Isoflurane	1.4
NO	0.5

respiratory rate on speed of induction are transient for gases that have low solubility in blood and tissues, but there is a significant effect for agents that are more soluble and take a longer time for gas tensions to equilibrate. In determining how much of the gas is absorbed, it's important to consider what fraction of the lung is ventilated and what fraction is perfused. However, one should be aware that due to diseased lungs, there can be differences between these fractions. For example, decreased perfusion will decrease absorption, although there is agent in the alveoli, and vice versa. The rate at which a gas passes into tissues is also dependent on gas solubility in the tissues, rate of delivery of the gas to tissues, and partial pressures of gas in arterial blood and tissues. After uptake of the gas, the blood takes the gas to other tissues. The mixed venous blood returned to the lungs progressively begins to have more of the gas, and differences between arterial (or alveolar) and mixed venous gas tensions decrease continuously.

While gases are more likely to travel freely through the entire respiratory tract to the alveoli, passage of aerosols and particles will be affected by the upper respiratory tract, which can act as an effective filter to prevent particulate matter from reaching the alveoli. Mucous traps particles to prevent entry to alveoli, and the mucociliary apparatus in the trachea traps and pushes particles up the trachea to the esophagus where they are swallowed and possibly absorbed in the GI tract.

In addition to upper pathway clearance, lung phagocytosis is very active in both upper and lower pathways of the respiratory tract and may be coupled to the mucus cilia. Phagocytes may also direct engulfed toxicants into the lymph, where the toxicants may be stored for long periods. If not phagocytized, particles $\leq 1 \mu\text{m}$ may penetrate to the alveolar portion of the lung. Some particles do not desquamate but instead form a dust node in association with a developing network of reticular fibers. Overall, removal

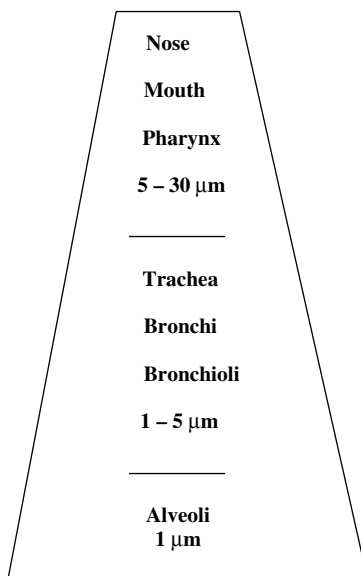


Figure 6.9 Schematic illustration of the regions where absorption may occur in the respiratory tract.

of alveolar particles is markedly slower than that achieved by the directed upper pulmonary mechanisms. This defense mechanism is not important for vapors/gases. The efficiency of the system is illustrated by the fact that on average, only 100 g of coal dust is found postmortem in the lungs of coal miners, although they inhale approximately 6000 g during their lifetime.

The deposition site of particles in the respiratory tract is primarily dependent on the *aerodynamic behavior* of the particles. The particle size, density, shape, hygroscopicity, breathing pattern, and lung airway structure are also important factors influencing the deposition site and efficiency. The *aerodynamic-equivalent diameter* (for particle $> 0.5 \mu\text{m}$) and *diffusion-equivalent diameter* ($< 0.5 \mu\text{m}$) are defined as the diameter of a *unit density sphere* having the same *settling velocity* (aerodynamic-equivalent) or the same *diffusion rate* (diffusion-equivalent) as the *irregularly shaped particle of interest*. Deposition occurs by five possible mechanisms: electrostatic precipitation, interception, impaction, sedimentation, and diffusion. The latter three are most important. Only particle sizes less than 10 to 20 μm that get past the nasopharyngeal regions and reach the alveoli are of medical concern. As particle size decreases below 0.5 μm , the aerosol begins to behave like a gas (Figure 6.9). For these particles, diffusion becomes the primary mechanism of deposition in the respiratory tract before it finally reaches the alveoli.

6.6 TOXICANT DISTRIBUTION

6.6.1 Physicochemical Properties and Protein Binding

Absorption of toxicants into the blood needs to be high enough so that it will have a significant effect at the site of action in other areas of the body. The distribution process that takes the absorbed drug to other tissues is dependent on various physiological factors and physicochemical properties of the drug. This process is therefore a reversible movement of the toxicant between blood and tissues or between extracellular and intracellular compartments. There are, however, several complicating factors that can influence the distribution of a toxicant. For example, *perfusion* of tissues is an important physiological process, as some organs are better perfused (e.g., heart, brain) than others (e.g., fat). There can also be significant *protein binding* that affects delivery of drug to tissues. To further complicate the issue, elimination processes such as excretion and biotransformation (discussed at a later time) is occurring simultaneously to remove the toxicant from the blood as well as the target site.

There are several physicochemical properties of the toxicant that can influence its distribution. These include lipid solubility, pKa, and molecular weight, all of which were described earlier in this chapter (Section 6.4) and will not be described here. For many toxicants, distribution from the blood to tissues is by simple diffusion down a concentration gradient, and the absorption principles described earlier also apply here. The concentration gradient will be influenced by the partition coefficient or rather the ratio of toxicant concentrations in blood and tissue. Tissue mass and blood flow will also have a significant effect on distribution. For example, a large muscle mass can result in increased distribution to muscle, while limited blood flow to fat or bone tissue can limit distribution. The ratio of blood flow to tissue mass is also a useful indicator of how well the tissue is perfused. The well perfused tissues include liver,

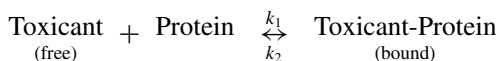
kidney, and brain, and the low perfused tissues include fat and bone where there is slow elimination from these tissues. Initial distribution to well-perfused tissues (e.g., heart, brain) occurs within the first few minutes, while delivery of drug to other tissues (e.g., fat, skin) is slower.

If the affinity for the target tissue is high, then the chemical will accumulate or form a depot. The advantage here is that if this is a drug, there is no need to load up the central compartment to get to the active site. However, if the reservoir for the drug has a large capacity and fills rapidly, it so alters the distribution of the drug that larger quantities of the drug are required initially to provide a therapeutic effective concentration at the target organ. If this is a toxicant, this may be an advantageous feature as toxicant levels at the target site will be reduced. In general, lipid-insoluble toxicants stay mainly in the plasma and interstitial fluids, while lipid-soluble toxicants reach all compartments, and may accumulate in fat. There are numerous examples of cellular reservoirs for toxicants and drugs to distribute. Tetracycline antibiotics have a high affinity for calcium-rich tissues in the body. The bone can become a reservoir for the slow release of chemicals such as lead, and effects may be chronic or there may be acute toxicity if the toxicant is suddenly released or mobilized from these depots. The antimalaria drug quinacrine accumulates due to reversible intracellular binding, and the concentration in the liver can be several thousand times that of plasma. Another antimalaria drug, chloroquine, has a high affinity for melanin, and this drug can be taken up by tissues such as the retina, which is rich in melanin granules, and can cause retinitis with a drug overdose. Lipophilic pesticides and toxicants (e.g., PCBs) and lipid soluble gases can be expected to accumulate in high concentration in fat tissue.

There are unique anatomical barriers that can limit distribution of toxicants. A classical example of such a unique barrier is the blood-brain barrier (BBB), which can limit the distribution of toxicants into the CNS and cerebrospinal fluid. There are three main processes or structures that keep drug or toxicant concentrations low in this region: (1) The BBB, which consist of capillary endothelial tight junctions and glial cells, surrounds the precapillaries, reduces filtration, and requires that the toxicant cross several membranes in order to get to the CSF. (Note that endothelial cells in other organs can have intercellular pores and pinocytotic vesicles.) (2) Active transport systems in the choroid plexus allow for transport of organic acids and bases from the CSF into blood. (3) The continuous process of CSF production in the ventricles and venous drainage continuously dilutes toxicant or drug concentrations. Disease processes such as meningitis can disrupt this barrier and can allow for penetration of antibiotics (e.g., aminoglycosides) that would not otherwise readily cross this barrier in a healthy individual. Other tissue/blood barriers include prostate/blood, testicles/blood, and globe of eye/blood, but inflammation or infection can increase permeability of these barriers. Toxicants can cross the placenta primarily by simple diffusion, and this is most easily accomplished if the toxicants are lipid-soluble (i.e., nonionized weak acids or bases). The view that the placenta is a barrier to drugs and toxicants is inaccurate. The fetus is, at least to some extent, exposed to essentially all drugs even if those with low lipid solubility are taken by the mother.

As was indicated earlier, the circulatory system and components in the blood stream are primarily responsible for the transport of toxicants to target tissues or reservoirs. Erythrocytes and lymph can play important roles in the transport of toxicants, but compared to plasma proteins, their role in toxicant distribution is relatively minor for most toxicants. Plasma protein binding can affect distribution because only the unbound

toxicant is free or available to diffuse across the cell membranes. The toxicant-protein binding reaction is reversible and obeys the laws of mass action:



Usually the ratio of unbound plasma concentration (C_u) of the toxicant to total toxicant concentration in plasma (C) is the fraction of drug unbound, f_u , that is,

$$f_u = \frac{C_u}{C}.$$

The constants k_1 and k_2 are the specific rate constants for association and dissociation, respectively. The association constant K_a will be the ratio k_1/k_2 , and conversely, the dissociation constant, K_d will be k_2/k_1 . The constants and parameters are often used to describe and, more important, to compare the relative affinity of xenobiotics for plasma proteins.

There are many circulating proteins, but those involved in binding xenobiotics include albumin, α_1 -acid glycoprotein, lipoproteins, and globulins. Because many toxicants are lipophilic, they are likely to bind to plasma α - and β -lipoproteins. There are mainly three classes of lipoproteins, namely high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low density lipoprotein (VLDL). Iron and copper are known to interact strongly with the metal-binding globulins transferrin and ceruloplasmin, respectively. Acidic drugs bind primarily to albumin, and basic drugs are bound primarily to α_1 -acid glycoprotein and β -globulin. Albumin makes up 50% of total plasma proteins, and it reacts with a wide variety of drugs and toxicants. The α_1 -acid glycoprotein does not have as many binding sites as albumin, but it has one high-affinity binding site. The amount of toxicant drug that is bound depends on free drug concentration, and its affinity for the binding sites, and protein concentration. Plasma protein binding is nonselective, and therefore toxicants and drugs with similar physicochemical characteristics can compete with each other and endogenous substances for binding sites. Binding to these proteins does not necessarily prevent the toxicant from reaching the site of action, but it slows the rate at which the toxicant reaches a concentration sufficient to produce a toxicological effect. Again, this is related to what fraction of the toxicant is free or unbound (f_u).

Toxicants complex with proteins by various mechanisms. Covalent binding may have a pronounced effect on an organism due to the modification of an essential molecule, but such binding is usually a very minor portion of the total dose. Because covalently bound molecules dissociate very slowly, if at all, they are not considered further in this discussion. However, we should recognize that these interactions are often associated with carcinogenic metabolites. Noncovalent binding is of primary importance to distribution because the toxicant or ligand can dissociate more readily than it can in covalent binding. In rare cases the noncovalent bond may be so stable that the toxicant remains bound for weeks or months, and for all practical purposes, the bond is equivalent to a covalent one. Types of interactions that lead to noncovalent binding under the proper physiological conditions include ionic binding, hydrogen bonding, van der Waals forces, and hydrophobic interactions. There are, however, some transition metals that have high association constants and dissociation is slow.

We know more about ligand-protein interactions today because of the numerous protein binding studies performed with drugs. The major difference between drugs and most toxicants is the frequent ionizability and high water solubility of drugs as compared with the non-ionizability and high lipid solubility of many toxicants. Thus experience with drugs forms an important background, but one that may not always be relevant to other potentially toxic compounds.

Variation in chemical and physical features can affect binding to plasma constituents. Table 6.4 shows the results of binding studies with a group of insecticides with greatly differing water and lipid solubilities. The affinity for albumin and lipoproteins is inversely related to water solubility, although the relation may be imperfect. Chlorinated hydrocarbons bind strongly to albumin but even more strongly to lipoproteins. Strongly lipophilic organophosphates bind to both protein groups, whereas more water-soluble compounds bind primarily to albumin. The most water-soluble compounds appear to be transported primarily in the aqueous phase. Chlordecone (Kepone) has partitioning characteristics that cause it to bind in the liver, whereas DDE, the metabolite of DDT, partitions into fatty depots. Thus the toxicological implications for these two compounds may be quite different.

Although highly specific (high-affinity, low-capacity) binding is more common with drugs, examples of specific binding for toxicants seem less common. It seems probable that low-affinity, high-capacity binding describes most cases of toxicant binding. The number of binding sites can only be estimated, often with considerable error, because of the nonspecific nature of the interaction. The number of ligand or toxicant molecules bound per protein molecule, and the maximum number of binding sites, n , define the definitive capacity of the protein. Another consideration is the binding affinity K_{binding} (or $1/K_{\text{diss}}$). If the protein has only one binding site for the toxicant, a single value, K_{binding} , describes the strength of the interaction. Usually more than one binding site is present, each site having its intrinsic binding constant, k_1, k_2, \dots, k_n . Rarely does one find a case where $k_1 = k_2 = \dots = k_n$, where a single value would describe the affinity

Table 6.4 Relative Distribution of Insecticides into Albumin and Lipoproteins

Insecticide	Percent Bound	Percent Distribution of Bound Insecticide		
		Albumin	LOL	HDL
DDT	99.9	35	35	30
Deildrin	99.9	12	50	38
Lindane	98.0	37	38	25
Parathion	98.7	67	21	12
Diazinon	96.6	55	31	14
Carbaryl	97.4	99	<1	<1
Carbofuran	73.6	97	1	2
Aldicarb	30.0	94	2	4
Nicotine	25.0	94	2	4

Source: Adapted from B. P. Maliwal and F. E. Guthrie, *Chem Biol Interact* 35:177–188, 1981.

Note: LOL, low-density lipoprotein; HOL, high-density lipoprotein.

constant at all sites. This is especially true when hydrophobic binding and van der Waals forces contribute to nonspecific, low-affinity binding. Obviously the chemical nature of the binding site is of critical importance in determining binding. The three-dimensional molecular structure of the binding site, the environment of the protein, the general location in the overall protein molecule, and allosteric effects are all factors that influence binding. Studies with toxicants, and even more extensive studies with drugs, have provided an adequate elucidation of these factors. Binding appears to be too complex a phenomenon to be accurately described by any one set of equations.

There are many methods for analyzing binding, but equilibrium dialysis is the most extensively used. Again, the focus of these studies is to determine the percentage of toxicant bound, the number of binding sites (n), and the affinity constant (K_a). The examples presented here are greatly simplified to avoid the undue confusion engendered by a very complex subject.

Toxicant-protein complexes that utilize relatively weak bonds (energies of the order of hydrogen bonds or less) readily associate and dissociate at physiological temperatures, and the law of mass action applies to the thermodynamic equilibrium:

$$K_{\text{binding}} = \frac{[TP]}{[T][P]} = \frac{1}{K_{\text{diss}}},$$

where K_{binding} is the equilibrium constant for association, $[TP]$ is the molar concentration of toxicant-protein complex, $[T]$ is the molar concentration of free toxicant, and $[P]$ is the molar concentration of free protein. This equation does not describe the binding site(s) or the binding affinity. To incorporate these parameters and estimate the extent of binding, double-reciprocal plots of $1/[TP]$ versus $1/[T]$ may be used to test the specificity of binding. The $1/[TP]$ term can also be interpreted as moles of albumin per moles of toxicant. The slope of the straight line equals $1/nK_a$ and the intercept of this line with the x -axis equals $-K_a$. Regression lines passing through the origin imply infinite binding, and the validity of calculating an affinity constant under these circumstances is questionable. Figure 6.10 illustrates one such case with four pesticides, and the insert illustrates the low-affinity, "unsaturable" nature of binding in this example.

The two classes of toxicant-protein interactions encountered may be defined as (1) specific, high affinity, low capacity, and (2) nonspecific, low affinity, high capacity. The term high affinity implies an affinity constant (K_{binding}) of the order of 10^8 M^{-1} , whereas low affinity implies concentrations of 10^4 M^{-1} . Nonspecific, low-affinity binding is probably most characteristic of nonpolar compounds, although most cases are not as extreme as that shown in Figure 6.10.

An alternative and well-accepted treatment for binding studies is the Scatchard equation especially in situations of high-affinity binding:

$$\nu = \frac{nk[T]}{1 + k[T]},$$

which is simplified for graphic estimates to

$$\frac{\nu}{[T]} = k(n - \nu),$$

where ν is the moles of ligand (toxicant) bound per mole of protein, $[T]$ is the concentration of free toxicant, k is the intrinsic affinity constant, and n is the number of sites exhibiting such affinity. When $\nu/[T]$ is plotted against ν , a straight line is obtained

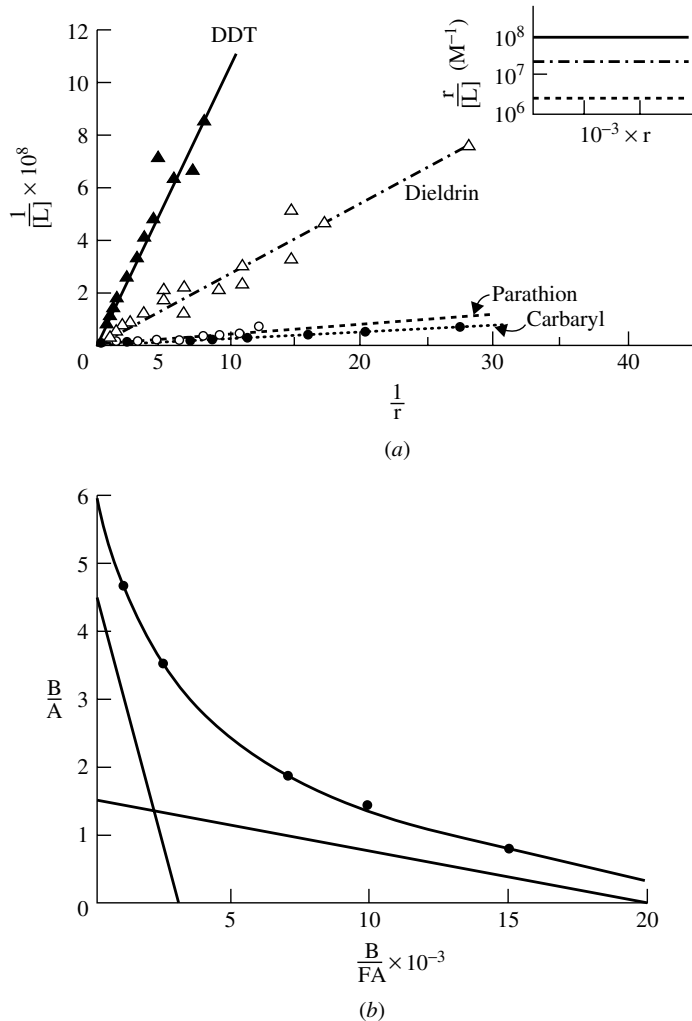


Figure 6.10 Binding of toxicants to blood proteins: (a) Double-reciprocal plot of binding of rat serum lipoprotein fraction with four insecticides. Insert illustrates magnitude of differences in slope with Scatchard plot. (b) Scatchard plot of binding of salicylate to human serum proteins. (Sources: (a) Skalsky and Guthrie, *Pest. Biochem. Physiol.* **7**: 289, 1977; (b) Moran and Walker, *Biochem. Pharmacol.* **17**: 153, 1968.)

if only one class of binding sites is evident. The slope is $-k$, and the intercept on the v -axis becomes n (number of binding sites). If more than one class of sites occurs (probably the most common situation for toxicants), a curve is obtained from which the constants may be obtained. This is illustrated in Figure 6.10b, for which the data show not one but two species of binding sites: one with low capacity but high affinity, and another with about three times the capacity but less affinity. Commonly used computer programs usually solve such data by determining one line for the specific binding and one line for nonspecific binding, the latter being an average of many possible solutions.

When hydrophobic binding of lipid toxicants occurs, as is the case for many environmental contaminants, binding is probably not limited to a single type of plasma

protein. For example, the binding of the chlorinated hydrocarbon DDT is strongest for lipoproteins and albumin, but other proteins account for a significant part of overall transport. Similar results have been observed for several compounds with a range of physiochemical properties.

The presence of another toxicant and/or drug that can bind at the same site can also increase the amount of free or unbound drug. This is an example of drug interaction that can have serious toxicological or pharmacological consequences. In general, when bound concentrations are less than 90% of the total plasma concentrations, plasma protein binding has little clinical importance. Plasma protein binding *becomes important when it is more than 90%*. For example, if a toxicant is 99% bound to plasma proteins, then 1% is free, but if there is toxicant interaction (e.g., competitive binding) that results in 94% bound, 6% is now free. Note that because of this interaction, the amount of available toxicant to cause a toxicological response *has increased sixfold*. Such a scenario may result in severe acute toxicity. Extensive plasma protein binding can influence renal clearance if glomerular filtration is the major elimination process in the kidney, but not if it is by active secretion in the kidney. Binding can also affect drug clearance if the extraction ratio (*ER*) in the liver is low, but not if the *ER* is high for that toxicant. Plasma protein binding can vary between and within chemical classes, and it is also species specific. For example, humans tend to bind acidic drugs more extensively than do other species.

There are several other variables that can alter plasma protein concentrations. These include malnutrition, pregnancy, cancer, liver abscess, renal disease, and age can reduce serum albumin. Furthermore α_1 -glycoprotein concentrations can increase with age, inflammation, infections, obesity, renal failure, and stress. Small changes in body temperature or changes in acid-base balance may alter chemical protein-binding characteristics. Although termination of drug or toxicant effect is usually by biotransformation and excretion, it may also be associated with redistribution from its site of action into other tissues. The classical example of this is when highly lipid-soluble drugs or toxicants that act on the brain or cardiovascular system are administered by IV or by inhalation.

6.6.2 Volume of Distribution (V_d)

Usually after a toxicant or drug is absorbed it can be distributed into various physiologic fluid compartments. The total body water represents 57% of total body mass (0.57 L/kg) (Table 6.5). The plasma, interstitial fluid, extracellular fluid, and intracellular fluid represent about 5, 17, 22, and 35% body weight, respectively. The extracellular fluid comprises the blood plasma, interstitial fluid, and lymph. Intracellular fluid includes

Table 6.5 Volume of Distribution into Physiological Fluid Compartments

Compartment	Volume of Distribution in L/kg Body Weight (Ls/70 kg Body weight)
Plasma	0.05(3.5 L)
Interstitial fluid	0.18(12.6 L)
Extracellular fluid	0.23(16.1 L)
Intracellular fluid	0.35(24.5 L)
Total body water	0.55(39 L)

the sum of fluid contents of all cells in the body. There is also transcellular fluid that represents 2% body weight, and this includes cerebrospinal, intraocular, peritoneal, pleural, and synovial fluids, and digestive secretions. Fat is about 20% body weight, while the GIT contents in monogastrics make up 1% body weight, and in ruminants it can constitute 15% body weight.

It is sometimes useful to quantitate how well a drug or toxicant is distributed into these various fluid compartments, and in this context the apparent volume of distribution can be a useful parameter. The apparent volume of distribution, V_d , is defined as the volume of fluid required to contain the total amount, A , of drug in the body at the same concentration as that present in plasma, C_p ,

$$V_d = \frac{A}{C_p}.$$

In general, the V_d for a drug is to some extent descriptive of its distribution pattern in the body. For example, drugs or toxicants with relatively small V_d values may be confined to the plasma as diffusion across the capillary wall is limited. There are other toxicants that have a slightly larger V_d (e.g., 0.23 L/kg), and these toxicants may be distributed in the extracellular compartment. This includes many polar compounds (e.g., tubocurarine, gentamicin, $V_d = 0.2\text{--}0.4$ L/kg). These toxicants cannot readily enter cells because of their low lipid solubility. If the V_d for some of these toxicants is in excess of the theoretical value, this may be due to limited degree of penetration into cells or from the extravascular compartment. Finally there are many toxicants distributed throughout the body water ($V_d \geq 0.55$ L/kg) that may have V_d values much greater than that for total body water. This distribution is achieved by relatively lipid-soluble toxicants and drugs that readily cross cell membranes (e.g., ethanol, diazepam; $V_d = 1$ to 2 L/kg). Binding of the toxicant anywhere outside of the plasma compartment, as well as partitioning into body fat, can increase V_d beyond the absolute value for total body water. In general, toxicants with a large V_d can even reach the brain, fetus, and other transcellular compartments. In general, toxicants with large V_d are a consequence of extensive tissue binding. The reader should be aware that we are talking about tissue binding, and not plasma protein binding where distribution is limited to plasma for obvious reasons.

The fraction of toxicant located in plasma is dependent on whether a toxicant binds to both plasma and tissue components. Plasma binding can be measured directly, but not tissue binding. It can, however, be inferred from the following relationship:

$$\begin{aligned} \text{Amount in body} &= \text{Amount in plasma} + \text{Amount outside plasma} \\ V_d \times C &= V_p \times C + V_{TW} \times C_{TW} \end{aligned}$$

where V_d is the apparent volume of distribution, V_p the volume of plasma, V_{TW} the apparent volume of tissue, and C_{TW} the tissue concentration. If the preceding equation is divided by C , it now becomes

$$V_d = V_p + V_{TW} \times \frac{C_{TW}}{C}$$

Recall that $f_u = C_u/C$ occurs with plasma, and also that the fraction unbound in tissues is $f_{uT} = C_{uT}/C_{TW}$.

Assuming at equilibrium that unbound concentration in tissue and plasma are equal, then we let the ratio of f_u/f_{uT} replace C_{TW}/C and determine the volume of distribution as follows:

$$V_d = V_p + V_{TW} \times \left(\frac{f_u}{f_{uT}} \right).$$

It is possible to predict what happens to V_d when f_u or f_{uT} changes as a result of physiological or disease processes in the body that change plasma and/or tissue protein concentrations. For example, V_d can increase with increased unbound toxicant in plasma or with a decrease in unbound toxicant tissue concentrations. The preceding equation explains why: because of both plasma and tissue binding, some V_d values rarely correspond to a real volume such as plasma volume, extracellular space, or total body water. Finally interspecies differences in V_d values can be due to differences in body composition of body fat and protein, organ size, and blood flow as alluded to earlier in this section. The reader should also be aware that in addition to V_d , there are volumes of distribution that can be obtained from pharmacokinetic analysis of a given data set. These include the volume of distribution at steady state ($V_{d,ss}$), volume of the central compartment (V_c), and the volume of distribution that is operative over the elimination phase ($V_{d,area}$). The reader is advised to consult other relevant texts for a more detailed description of these parameters and when it is appropriate to use these parameters.

6.7 TOXICOKINETICS

The explanation of the pharmacokinetics or toxicokinetics involved in absorption, distribution, and elimination processes is a highly specialized branch of toxicology, and is beyond the scope of this chapter. However, here we introduce a few basic concepts that are related to the several transport rate processes that we described earlier in this chapter. Toxicokinetics is an extension of pharmacokinetics in that these studies are conducted at higher doses than pharmacokinetic studies and the principles of pharmacokinetics are applied to xenobiotics. In addition these studies are essential to provide information on the fate of the xenobiotic following exposure by a define route. This information is essential if one is to adequately interpret the dose-response relationship in the risk assessment process. In recent years these toxicokinetic data from laboratory animals have started to be utilized in physiologically based pharmacokinetic (PBPK) models to help extrapolations to low-dose exposures in humans. The ultimate aim in all of these analyses is to provide an estimate of tissue concentrations at the target site associated with the toxicity.

Immediately on entering the body, a chemical begins changing location, concentration, or chemical identity. It may be transported independently by several components of the circulatory system, absorbed by various tissues, or stored; the chemical may effect an action, be detoxified, or be activated; the parent compound or its metabolite(s) may react with body constituents, be stored, or be eliminated—to name some of the more important actions. Each of these processes may be described by rate constants similar to those described earlier in our discussion of first-order rate processes that are associated with toxicant absorption, distribution, and elimination and occur

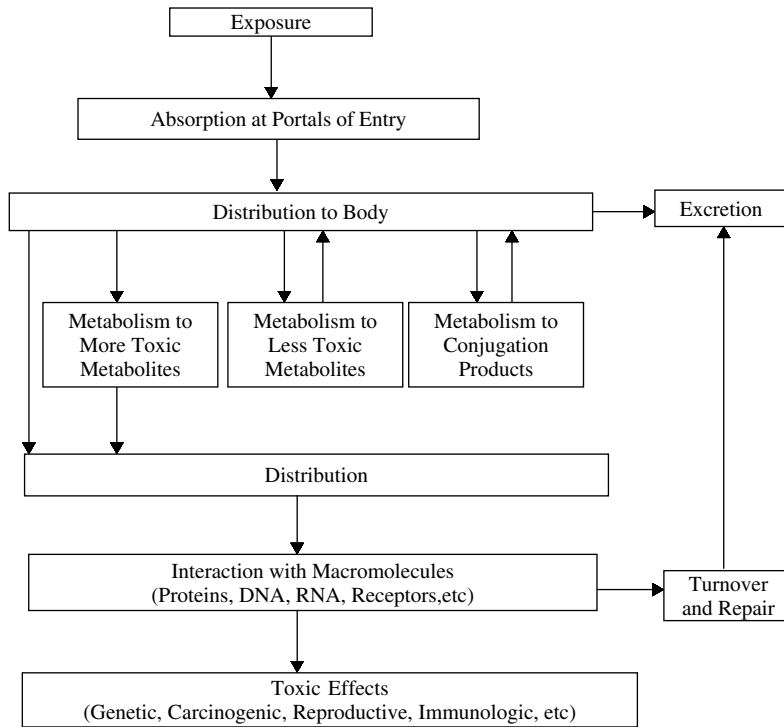


Figure 6.11 Sequence of events following exposure of an animal to exogenous chemicals.

simultaneously. Thus at no time is the situation stable but is constantly changing as indicated in Figure 6.11.

It should be noted, however, that as the toxicant is being absorbed and distributed throughout the body, it is being simultaneously eliminated by various metabolism and/or excretion mechanisms, as will be discussed in more detail in the following chapters. However, one should mention here that an important pharmacokinetic parameter known as *clearance* (C_l) can be used to quantitatively assess elimination of a toxicant. Clearance is defined as the rate of toxicant excreted relative to its plasma concentration, C_p :

$$C_l = \frac{\text{Rate of toxicant excretion}}{C_p}$$

The rate of excretion is really the administered dose times the fractional elimination rate constant K_{el} described earlier. Therefore we can express the preceding equation in terms of K_{el} and administered dose as volume of distribution, V_d :

$$C_l = K_{el} \cdot \frac{\text{Dose}}{C_p} = K_{el} \cdot (V_d \cdot C_p) / C_p = K_{el} \cdot V_d$$

In physiological terms we can also define clearance as the volume of blood cleared of the toxicant by an organ or body per unit time. Therefore, as the equations above indicate, the body clearance of a toxicant is expressed in units of volume per unit time (e.g., L/h), and can be derived if we know the volume of distribution of the toxicant

and fractional rate constant. In many instances this can only be derived by appropriate pharmacokinetic analysis of a given data set following blood or urine sample collection and appropriate chemical analyses to determine toxicant concentrations in either of these biological matrices.

Each of the processes discussed thus far—absorption, distribution, and elimination—can be described as a rate process. In general, the process is assumed to be first order in that the rate of transfer at any time is proportional to the amount of drug in the body at that time. Recall that the rate of transport (dC/dt) is proportional to toxicant concentration (C) or stated mathematically:

$$\frac{dC}{dt} = KC,$$

where K is the rate constant (fraction per unit time). Many pharmacokinetic analyses of a chemical are based primarily on toxicant concentrations in blood or urine samples. It is often assumed in these analyses that the rate of change of toxicant concentration in blood reflects quantitatively the change in toxicant concentration throughout the body (first-order principles). Because of the elimination/clearance process, which also assumed to be a first-order rate process, the preceding rate equation now needs a negative sign. This is really a decaying process that is observed as a decline of toxicant concentration in blood or urine after intravenous (IV) administration. The IV route is preferred in these initial analyses because there is no absorption phase, but only chemical depletion phase. However, one cannot measure infinitesimal change of C or time, t ; therefore there needs to be integration after rearrangement of the equation above:

$$\frac{-dC}{C} = kdt \quad \text{becomes} \quad \int \frac{-dC}{C} = k \int dt,$$

which can be expressed as

$$C = C^0 e^{-kt},$$

where e is the base of the natural logarithm. We can remove e by taking the \ln of both sides:

$$\ln C^t = \ln C^0 - kt.$$

Note that K is the slope of the straight line for a semilog plot of toxicant concentration versus time (Figure 6.12). In the preceding equation it is the elimination rate constant that is related to the half-life of the toxicant described earlier in this chapter. The derived C^0 can be used to calculate the volume of distribution (V_d) of the toxicant as follows:

$$V_d = \frac{\text{Dose}}{C^0}.$$

However, toxicokinetic data for many toxicants do not always provide a straight line when plotted as described above. More complicated equations with more than one exponential term with rate constants may be necessary to mathematically describe the concentration-time profile. These numerous rate constants are indicative of chemical transport between various compartments in the body and not only to a single central compartment as suggested in the simple equation and semilog plot described in

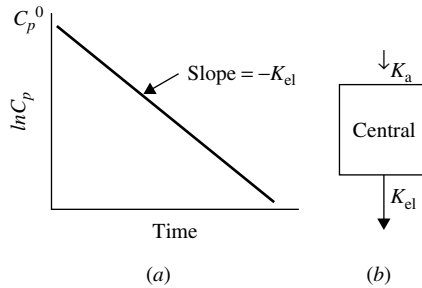


Figure 6.12 (a) Semilog plot of plasma concentration (C_p) versus time. C_p^0 is the intercept on the y-axis, and K_{el} is the elimination rate constant. (b) Single compartment model with rate constants for absorption, K_a and for elimination, K_{el} .

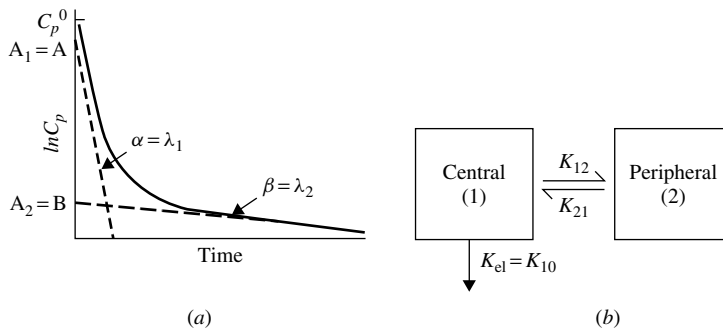


Figure 6.13 (a) Semilog plot of plasma concentration for (C_p) versus time representative of a two-compartment model. The curve can be broken down into an α or λ_1 distribution phase and β or λ_2 elimination phase. (b) Two-compartment model with transfer rate constants, K_{12} and K_{21} , and elimination rate constant, K_{el} .

Figure 6.12. In some instances the data may fit to a bi-exponential concentration-time profile (Figure 6.13). The equation to describe this model is

$$C = Ae^{-\alpha t} + Be^{-\beta t}.$$

In other instances, complex profiles may require a three- or multi-exponential concentration-time profile (Figure 6.14). The equation to describe the three-profile case is

$$C = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}.$$

In the physiological sense, one can divide the body into “compartments” that represent discrete parts of the whole-blood, liver, urine, and so on, or use a mathematical model describing the process as a composite that pools together parts of tissues involved in distribution and bioactivation. Usually pharmacokinetic compartments have no anatomical or physiological identity; they represent all locations within the body that have similar characteristics relative to the transport rates of the particular toxicant. Simple first-order kinetics is usually accepted to describe individual

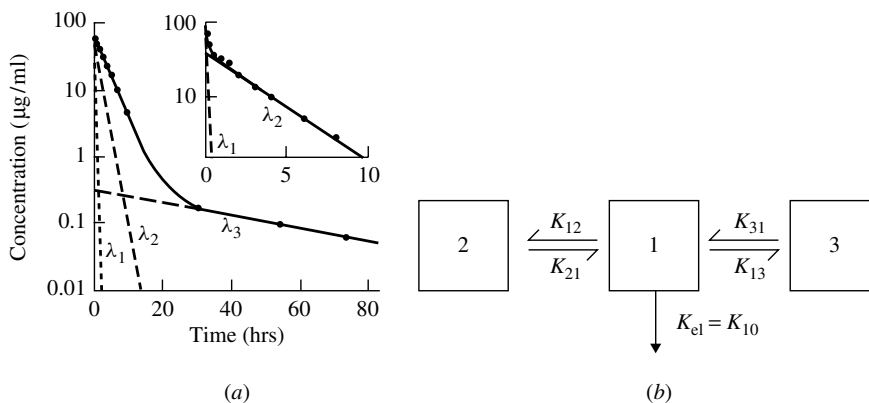


Figure 6.14 (a) Semilog plot of plasma concentration for (C_p) versus time representative of a three- or multi-compartment model. The curve can be broken down into three phases, λ_1 , λ_2 , and λ_3 . (b) Three-compartment model with transfer rate constants, K_{12} , K_{21} , K_{13} , K_{31} , and elimination rate constant, $K_{el} = K_{10}$. As these models can get more complicated, the α , β , and γ nomenclature may get replaced with λ_n as indicated in the profile.

rate processes for the toxicant after entry. The resolution of the model necessitates mathematical estimates (as a function of time) concerning the absorption, distribution, biotransformation, and excretion of the toxicant.

Drugs and toxicants with multi-exponential behavior depicted in Figure 6.14 require calculation of the various micro constants. An alternative method involves using model-independent pharmacokinetics to arrive at relevant parameters. Very briefly, it involves determination of the area under the curve (AUC) of the concentration-time profiles. The emergence of microcomputers in recent years has greatly facilitated this approach.

In conclusion, pharmacokinetics is a study of the time course of absorption, distribution, and elimination of a chemical. We use pharmacokinetics as a tool to analyze plasma concentration time profiles after chemical exposure, and it is the derived rates and other parameters that reflect the underlying physiological processes that determine the fate of the chemical. There are numerous software packages available today to accomplish these analyses. The user should, however, be aware of the experimental conditions, the time frame over which the data were collected, and many of the assumptions embedded in the analyses. For example, many of the transport processes described in this chapter may not obey first-order kinetics, and thus may be nonlinear especially at toxicological doses. The reader is advised to consult other texts for more detailed descriptions of these nonlinear interactions and data analyses.

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