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# Xenobiotic Distribution: A Comprehensive Review and Toxicological Implications

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## ABSTRACT

*Xenobiotics is derived from the Greek words 'Xenos', meaning foreign and strange, and 'bios', which means life. Concerning the environment, xenobiotics can be defined as chemically synthesized compounds that do not occur in nature and thus are 'foreign' to the biosphere. Relating to the organisms, a xenobiotic is any substance foreign to life/living organism. Thus, a xenobiotic is a foreign chemical substance found within an organism that is not naturally produced by or expected to be present within the organism. The definition of xenobiotics as compounds 'foreign to life' exhibiting unnatural structural features does not necessarily mean that they are toxic compounds, but many are indeed harmful to living organisms. Specifically, drugs such as antibiotics are xenobiotics are xenobiotics because the human body does not produce them itself, nor are they part of a normal food. Natural compounds can also become xenobiotics if another organism takes them up. The body removes xenobiotics by xenobiotic metabolism, which consists of their deactivation and excretion, which happens mostly in the liver. Enzymes are involved in the metabolism of xenobiotics. Excretion routes are urine, feces, breath, and sweat. Xenobiotics may be grouped as carcinogens, drugs, environmental pollutants, food additives, hydrocarbons, and pesticides.*

**Keywords:** Xenobiotics, Biosphere, Antibiotics, Carcinogens, Drugs, Environmental pollutants, Food additives, Hydrocarbons, Pesticides.

# INTRODUCTION

Xenobiotics are compounds that are foreign to a living system. Toxic xenobiotics interfere with critical metabolic processes, causing structural damage to cells or altering the cellular genetic material. The specific biochemical sites of actions that disrupt metabolic processes are well characterised by many xenobiotics although mechanisms of cellular injury are not (Wallace and Starkov, 2000).

The capacity of a xenobiotic to produce injury is affected by many factors including its absorption, distribution, elimination, site of activation or detoxification, site of action, and capability of cross membranes to access a particular organ. Sites of action include the active sites of enzymes, DNA, and lipid membranes (Brittebo, 1993). The route of exposure to a xenobiotic may confine damage primarily to one organ, for example, pulmonary injury that follows inhalation or GI injury that follows a caustic ingestion. Hepatocellular injury results when a toxic xenobiotic is delivered to the liver, either by the portal venous system following ingestion or by the hepatic artery carrying blood with xenobiotics absorbed from other sites of exposure (Nelson, 2004). Various factors affect the ability of a xenobiotic to access a particular organ. For example, many potentially toxic xenobiotics fail to produce CNS injury because they cannot cross the blood–brain barrier. Two potent biologic xenobiotics—ricin (from *Ricinus communis*) and α-amanitin (from *Amanita phalloides*)—block protein synthesis through the inhibition of RNA polymerase. However, they cause different clinical effects because of access to different tissues. Ricin has a special binding protein that enables it to gain access to the endoplasmic reticulum in GI mucosal cells, where it inhibits cellular protein synthesis and causes severe diarrhea. 4α-Amanitin is transported into hepatocytes by bile salt transport systems, where inhibition of protein synthesis results in cell death (Kroncke *et al.,* 1986).

The electrical charge on a toxin also affects its ability to enter a cell. Unlike the ionized (charged) form of a xenobiotic, the uncharged form is lipophilic and passes easily through lipid cell membranes to enter the cells. The pKa of an acidic xenobiotic (HA↔A − + H +) is the pH at which 50% of the molecules are charged (A − form) and 50% are uncharged (HA form). A xenobiotic with a low pKa is more likely to be absorbed in an acidic environment where the uncharged form predominates (Kalgutkar *et al.,* 2005).

## Storage Depots of Xenobiotics

**Plasma proteins depot**: albumin (many toxicants), transferin (iron), ceruloplasmin (copper), lipoproteins (lipid-soluble compounds) (Kalgutkar *et al.,* 2005)

**Liver and kidney**: active metabolizing tissues, sites of biotransformation

**Body fat depot**: e.g., neutral fat and myelin store lipophilic toxicants such as pesticides, organophosphate compounds, DTT (Kalgutkar *et al.,* 2005).

**Bone**: store fluoride, lead, cadmium (itai-itai/ouchouch), radiostrontium, radium, plutonium (Kalgutkar *et al.,* 2005).

## *Characteristics of Xenobiotics*

Most xenobiotics are:

- Lipophilic
- Penetrate membranes by diffusion
- Transported by lipoproteins in blood
- Required chemical conversion to facilitate excretion (Nelson, 2004)

## *Fate of Xenobiotics in the Body*

Knowledge of the fate of a drug, its disposition (absorption, distribution, metabolism, and excretion, known by the acronym ADME) and pharmacokinetics (the mathematical description of the rates of these processes and of concentration-time relationships), plays a central role throughout pharmaceutical research and development (Kalgutkar *et al.,* 2005). ADME studies provide the only basis for critical judgments from

situations where the behavior of the drug is understood to those where it is unknown: this is most important in bridging from animal studies to the human situation (Boberg *et al.,* 1983).

Humans and other animals are exposed daily to many xenobiotics, that is, compounds that are foreign to the normal energy-yielding metabolism of the body. Exposure to these xenobiotics may occur deliberately, as in the case of drugs and food additives; accidentally, as in the case of food contaminants and pesticides, or coincidentally, as in the case of industrial chemicals and environmental pollutants. In this paper, the terms drug, xenobiotic, and foreign compound will be used interchangeably (Burchell and Coughtrie, 1992).

In the present context, the importance of ADME (absorption, distribution, metabolism, and excretion) principles in drug development will be emphasized, but it should be appreciated that these have comparable applicability in the safety assessment of all types of chemicals to which humans might be exposed (Caldwell, 1993).

To achieve its effect, whether therapeutic or toxic, a drug and/or its metabolites must be present in appropriate concentrations at its sites of action. The concentration of xenobiotic attained will depend on the dose, formulation, and route of administration, the rate and extent of absorption, its distribution through the body and binding to tissues, biotransformation, and excretion. It is the purpose of this presentation to give an overview of these processes and to comment upon the factors influencing them and their biological significance (Koymans *et al.,* 1993).

# ABSORPTION

The processes of absorption are those that lead to the entry of a xenobiotic into the systemic circulation of the body. The most important site of absorption is the gastrointestinal tract, although absorption through the skin, the main barrier between the internal milieu and the external environment, and the respiratory tract, which is important for volatile compounds and materials present in aerosols and dust particles, can also occur. Regardless of the site of absorption, xenobiotics must cross cell membranes to enter the systemic circulation. Mechanistically this can occur in 1 of 2 ways (Abernathy and Flockhart, 2000). Small, lipophilic compounds can cross the cell membrane by passive diffusion along a concentration gradient (Benet *et al.,* 1990). Large, highly- polar or charged xenobiotics cannot cross the cell membranes by simple diffusion and hence, are dependent on the presence of active carrier-mediated transport mechanisms (Price-Evans, 1993).

**The Effect of pH and pKa on Absorption from the Gastrointestinal Tract:** Many xenobiotics are weak acids or bases and are thus present in solution in both non-ionized and ionized forms. The non-ionized molecules tend to be lipid-soluble and cross membranes by passive diffusion, whereas the ionized forms have low lipid solubility and cannot cross the cell membrane (Benet *et al.,* 1990). The partition of weak electrolytes across membranes will thus be a function of the pKa of the xenobiotic and the pH gradient across the membrane. The low pH in the stomach favors absorption of weak acids. Weak bases are ionized and, thus, generally not absorbed from the stomach. In the intestine, absorption is rapid for weak acids ($pK > 3$) or weak bases ($pK < 7.8$) (Abernathy & Flockhart, 2000).

**First-Pass Elimination:** The extent to which xenobiotics undergo first-pass elimination will have a major influence on the exposure to the compound following oral administration. The enzymes contributing to the metabolism of xenobiotics are also found in organs other than the liver, such as the lung and skin, albeit usually at a lower level. Thus, xenobiotics entering the body by routes other than the gastrointestinal tract can also be subject to first-pass metabolism (Wilce & Parker, 1994).

# DISTRIBUTION

Following entry of a xenobiotic to the systemic circulation, its distribution into the various tissues of the body will be influenced by tissue hemodynamics, passive diffusion across lipid membranes. The presence of carrier-mediated active transport processes recognizing the xenobiotic protein binding in the blood and tissues (Wilkinson, 1987). Most tissue membranes behave as typical lipid barriers allowing small lipophilic

molecules to cross cell membranes. Equilibrium drug concentration ratios are maintained by diffusion of drugs into and out of tissues. Drugs can accumulate in tissues at a higher concentration than predicted by simple diffusion under the influence of pH gradients, binding to intracellular constituents, or partitioning into lipid depots (Benet *et al.,* 1990).

Active uptake processes tend to show stereoselectivity and can be particularly important for xenobiotics that may be analogs of nutrients. The operation of specific uptake mechanisms for xenobiotics may play an important role in the toxicity of some compounds. For example, amantanide and phalloidin are toxic cyclopeptides of the fungus Amanita phalloides (Abernathy and Flockhart, 2000). The toxins enter the liver via an active transport system involved in the transport of bile acids. Once inside the cells, the toxins bind to microfilamentous F-actin and destroy the mechanical stability of the liver cell membrane. This results in hemorrhagic liver swelling and animals die within 2-3 hours of intravenous dosing with the peptides (Koymans *et al.,* 1993).

Co-administration of bile salts with the toxins reduces their hepatic uptake by this active transport mechanism and thereby limits the toxicity of the compounds. Distribution of xenobiotics can also be limited by binding to plasma proteins. Acidic drugs tend to bind to albumin, and basic drugs tend to bind to acid glycoprotein (Meijer and Groothuis, 1991). As only unbound drug is in equilibrium across membranes, a drug that is extensively and strongly bound to plasma proteins has only limited access to the tissues (Timbrell, 1993).

**Drug Reservoirs:** Accumulation of a drug within a tissue can act as a reservoir serving to prolong its duration of action. If the stored xenobiotic is in equilibrium with that in plasma and is released as its plasma concentration falls, then the concentration of xenobiotic in plasma will be sustained and the pharmacological effects of the xenobiotic will be prolonged (Benet *et al.,* 1990). Thus, the storage of a drug can prolong its action either within the tissue where the drug is held or at a distant site reached following re-diffusion into the systemic circulation (Hladky, 1990). The concepts of drug reservoirs and how they influence the concentration of a xenobiotic at its target tissue are well illustrated by the behavior of the lipophilic anesthetic thiopental, which is given by bolus intravenous injection. Because of the high blood flow to the brain and its lipid solubility, thiopental reaches its maximum concentration in its target tissue within 1 minute of intravenous injection. When the injection is stopped, the plasma concentration falls as the drug distributes into tissues such as muscle (Benet *et al.,* 1990). A third distributive phase for thiopental occurs as the result of a slow, blood flow-limited uptake into poorly perfused tissues such as fat. On repeated administration, fat and other poorly perfused tissues can accumulate large amounts of thiopental. These reservoirs are then capable of maintaining plasma and, hence, brain concentrations of thiopental at levels above those needed for anesthesia (Benet *et al.,* 1990). Toxicity testing is often performed using much higher doses of xenobiotics than humans are exposed to. As well as leading to saturation of metabolic pathways, it must be appreciated that these high doses can lead to changes in tissue distribution like those seen following multiple dosing of thiopentone (Hladky, 1990).

## Metabolism of Xenobiotics

The study of xenobiotic metabolism was established as a scientific discipline by the seminal publication of Williams in 1949 (Williams, 1949). Biotransformation is the physiochemical alteration of a xenobiotic, usually because of enzyme action. Most definitions also include that this action converts lipophilic substances into more polar, excretable substances (Timbrell, 2000, Manahan, 2003). The chemical nature of the xenobiotic determines whether it will undergo biotransformation; however, most undergo some degree of biotransformation. The hydrophilic nature of ionized compounds such as carboxylic acids enables the kidneys to rapidly eliminate them. Very volatile compounds, such as enflurane, are expelled promptly via the lungs. Neither of these groups of xenobiotics undergo significant enzymatic metabolism (Hladky, 1990).

Biotransformation usually results in “detoxification,” a reduction in the toxicity, by the conversion to hydrophilic metabolites of the xenobiotic that can be renally eliminated (Manahan, 2003). However, this is

not always the case. Many parent xenobiotics are inactive and must undergo "metabolic activation," a classic concept introduced in 1947 (Miller and Miller, 1947). When metabolites are more toxic than the parent xenobiotic, biotransformation has resulted in "toxification". Biotransformation via acetylation or methylation may enhance the lipophilicity of a xenobiotic (Timbrell, 2000).

The predominant pathway for the biotransformation of an individual xenobiotic is determined by many factors including the availability of cofactors, changes in the concentration of the enzyme caused by induction, and the presence of inhibitors. The predominant pathway is also affected by the rate of substrate metabolism, reflected by the Km (Michaelis-Menten dissociation constant) of the biotransformation enzyme (Timbrell, 2000).

Biotransformation is often divided into phase I and phase II reactions, terminology first introduced in 1959 (Williams, 1959). Phase I reactions prepare lipophilic xenobiotics for the addition of functional groups or add the groups, converting them into more chemically reactive metabolites. This is usually followed by phase II synthetic reactions that conjugate the reactive products of phase I with other molecules that render them more water soluble, further detoxifying the xenobiotics and facilitating their elimination. However, biotransformation often does not follow this stepwise process, and it has been suggested that phase I and II terminology be eliminated (Josephy *et al.,* 2005).

Some xenobiotics undergo only a phase I or a phase II reaction prior to elimination. Phase II reactions can precede phase I. While virtually all phase II synthesis reactions cause inactivation, a classic exception is fluoroacetate being metabolized to fluorocitrate, a potent inhibitor of the tricarboxylic acid cycle (Abernathy and Flockhart, 2000).

Biotransformed xenobiotics cannot be eliminated until they are moved back across cell membranes, out of the cells. Membrane transporters are proteins that move agents across the membranes without altering their chemical compositions, a process called a phase III reaction because it typically occurs after biotransformation. However, membrane transport does not always occur after phase I or II reactions. Some parent compounds are transported across membranes without any biotransformation at all (Josephy *et al.,* 2005).

# PHASE I BIOTRANSFORMATION REACTIONS

Oxidation is the predominant phase I reaction, adding reactive functional groups suitable for conjugation during phase II. These groups include hydroxyl (OH), sulfhydryl (–SH), amino (–NH 2), aldehyde (–COH), or carboxyl (–COOH) moieties. Non-carbon elements such as nitrogen, sulfur, and phosphorus are also oxidized in phase I reactions (Manahan, 2003).

Other phase I reactions include hydrolysis (the splitting of a large molecule by the addition of water that is divided among the 2 products), hydration (incorporation of water into a complex molecule), hydroxylation (the attachment of –OH groups to carbon atoms), reduction, dehalogenation, dehydrogenation, and dealkylation (Timbrell, 2000; Manahan, 2003).

The CYP enzymes are the most numerous and important of the phase I enzymes. A common oxidation reaction catalyzed by CYP enzymes is illustrated by the hydroxylation of a xenobiotic R–H to R–OH (Farabee, 2009). Membrane-bound flavin mono-oxygenase (FMO), an NADPH-dependent oxidase located in the endoplasmic reticulum, is an important oxidizer of amines and other compounds containing nitrogen, sulfur, or phosphorus (Manahan, 2003).

The alcohol, aldehyde, and ketone oxidation systems use predominantly cytosolic enzymes that catalyze these reactions using NADH/ NAD + (Timbrell, 2000; Lieber, 2005). Two classic phase I oxidation reactions are the metabolism of ethanol to acetaldehyde by alcohol dehydrogenase (ADH) followed by the metabolism of acetaldehyde to acetic acid by aldehyde dehydrogenase (ALDH) (Lieber, 2005). Some populations, particularly Asians, are deficient in ALDH, resulting in increased acetaldehyde concentrations and symptoms of the acetaldehyde syndrome (Lieber, 2005).

# PHASE II BIOTRANSFORMATION REACTIONS

Phase II biotransformation reactions are synthetic, catalyzing conjugation of the products of phase I reactions or molecules with sites amenable to conjugation. Conjugation usually terminates the pharmacologic activity of the xenobiotic and greatly increases their water solubility and excretability (Timbrell, 2000, Manahan, 2003, Zamek-Gliszczynski *et al.,* 2006).

Conjugation occurs most commonly with glucuronic acid, sulfates, and glutathione. Less common phase II reactions include amino acid conjugation, such as glycine, glutamic acid, and taurine; acetylation; and methylation (Pavek and Dvorak, 2008). Glucuronidation is the most common phase II synthesis reaction (Manahan, 2003). It occurs only within microsomal membranes. Glucuronyl transferase has relatively low substrate affinity, but it has high capacity at higher substrate concentrations (Zamek-Gliszczynski *et al.,* 2006). The glucuronic acid, donated by uridine diphosphate glucuronic acid (UDPG), is conjugated with the nitrogen, sulfhydryl, hydroxyl, or carboxyl groups of substrates. Smaller conjugates usually undergo renal elimination, whereas larger ones undergo biliary elimination (Lewis, 2000).

Sulfation complements glucuronidation because it is a high affinity but low-capacity reaction that occurs primarily in the cytosol. For example, the affinity of sulfate for phenol is very high (the Km is low), so that when low doses of phenol are administered, the predominant excretion product is the sulfate ester. Because the capacity of this reaction is readily saturated, glucuronidation becomes the main method of detoxification when high doses of phenol are administered (Manahan, 2003; Zamek-Gliszczynski *et al.,* 2006). Sulfate conjugates are highly ionized and very water soluble. Of note, sulfation is reversible by the action of sulfatases within the liver. The resultant metabolites may be resulfated and the cycle may repeat itself further (Zamek-Gliszczynski *et al.,* 2006).

Glutathione *S* -transferases are important because they catalyze the conjugation of the tripeptide glutathione (glycine-glutamate-cysteine, or GSH) with a diverse group of reactive, electrophilic metabolites of phase I CYP enzymes. The reactive compounds initiate an attack on the sulfur group of cysteine, resulting in conjugation with GSH that detoxifies the reactive metabolite. Of the three phase II reactions addressed, hepatic concentrations of glutathione by far account for the greatest number of cofactors used. While intracellular glutathione is difficult to deplete, when it does occur, severe hepatotoxicity often follows (Zamek-Gliszczynski *et al.,* 2006). Some GSH conjugates are directly excreted. More commonly, the glycine and glutamate residues are cleaved, and the remaining cysteine is acetylated to form an *N* -acetylcysteine (mercapturic acid) conjugate that is readily excreted in the urine. A familiar example of this detoxification is the avid binding of *N* -acetyl- *p* -benzoquinoneimine (NAPQI), the toxic metabolite of acetaminophen, by glutathione (Brittebo, 1993). As with the CYP enzymes, many phase II enzymes are inducible. For example, UDP-glucuronosyltransferase which executes glucuronidation is inducible via PXR, CAR, and AhR nuclear receptors after binding with rifampin, phenobarbital, and PAHs, respectively. Its activity varies 6-fold to 15-fold in liver microsomes (Urquhart *et al.,* 2007).

## Membrane Transporters

Because they usually occur after phase I and II biotransformation, their actions are sometimes called phase III metabolism (Josephy *et al.,* 2005). Their physiologic role is to transport sugars, lipids, amino acids, and hormones to regulate cellular solute and fluid balance. However, they affect drug disposition just as do biotransformation processes by facilitating or preventing the passage of xenobiotics through membranes (Kim, 2002). Uptake transporters translocate drugs into cells while efflux transporters export xenobiotics, often against concentration gradients, out of cells (Ho and Kim, 2005).

Most transporters are in the adenosine triphosphate binding cassette (ABC) family of transmembrane proteins that use energy from ATP hydrolysis (Ho and Kim, 2005; Callaghan, 2008). This family includes the P-glycoprotein family. Some transporters move substrates both into and out of cells. Organs important for drug disposition have multiple transporters that have overlapping substrate capabilities, a redundancy that enhances protection. In the small intestine, P-glycoprotein is important because it can actively extrude

xenobiotics back into the intestinal lumen (Callaghan, 2008). The degree of phenotypic expression of P-glycoprotein affects the bioavailability of many xenobiotics including paclitaxel, digoxin, and protease inhibitors. Hepatocyte efflux transporters move biotransformed xenobiotics into bile. Transporters in endothelial cells of the blood–brain barrier prevent CNS entry of substrate xenobiotics (Ho and Kim, 2005, Callaghan, 2008). As with biotransformation enzymes and nuclear receptors, membrane transporters may be inhibited or induced. Digoxin, a high affinity substrate for P-glycoprotein, has increased bioavailability when administered with P-glycoprotein inhibitors such as clarithromycin or atorvastatin (Ho and Kim, 2005). Loperamide is a substrate for P-glycoprotein that limits its intestinal absorption or CNS entry. Coadministration with quinidine, a P-glycoprotein inhibitor, results in increased opioid CNS effects of loperamide (Ho and Kim, 2005). As with the biotransformation enzymes, polymorphisms exist for membrane transporters. However, the clinical significance of these is not clear (Chinn and Kroetz, 2007).

# CONCLUSION

Exposure to a xenobiotic via air, food, or water, or by contact with the skin can lead to transfer of that xenobiotic to the blood and circulation to the tissues of the body. Lipid-soluble compounds are usually absorbed faster than water-soluble xenobiotics because the cell (plasma) membrane is more lipoid than aqueous.

Xenobiotics can be held in the body by being stored in the fatty tissues and by being bound to proteins. The body can excrete only water-soluble xenobiotics in the urine and bile; lipid soluble xenobiotics can be excreted via the lung only if they are highly volatile. The concentration of a xenobiotic in the blood determines in large part the concentration of that xenobiotic in most tissues.

Fast rates of absorption into the blood and slow rates of excretion from the body can lead to high concentrations of xenobiotics in the body. Humans are exposed to a wide variety of xenobiotics. Some, including therapeutic drugs, are harmless at low doses and toxic only at high doses. The toxicity of those xenobiotics that interrupt important biologic functions or cause cellular injury is dose related and often rapidly evident. The diverse mechanisms of toxic injury have been discussed in general terms. The capacity of xenobiotics to cause injury is clearly a function of many factors specific to the xenobiotic, the tissue injured, and the individual.

## Conflict of Interest

The authors declare no conflicts of interest.

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