General Toxicologic Principles

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INTRODUCTION

Toxicology is the study of the nature, effects, and detection of poisons and the treatment of poisoning. For the purposes of this textbook, we define *clinical toxicology* as the diagnosis and treatment of the poisoned patient. Many of the basic principles of toxicology, such as the inherent toxicity of various forms of a chemical, variations in dose–response curves, different mechanisms of toxic action, variations in individual and species sensitivities to chemicals, and how differences in kinetics of chemicals (sometimes referred to as "toxicokinetics") need to be applied to the successful diagnosis and treatment of poisoning. In clinical toxicology there is a need for the application of good critical care and medical practices (e.g., stabilizing, monitoring, and treating a patient) to achieve a successful outcome.

DEFINITIONS

All special areas of study have unique terminology that is important to master to fully appreciate the discipline. The following definitions provide some needed terminology in order to more effectively utilize this textbook.

Toxicant

A poison or poisonous agent; an intoxicant; any solid, liquid or gas that, when introduced into or applied to the body, can interfere with the life processes of cells or the organism by its own inherent qualities (toxicity) without acting mechanically and irrespective of temperature.

Toxin

A poisonous material that is synthesized or derived from an animal or plant; also referred to as a *biotoxin*. Zootoxins, bacterial toxins, and phyto (or plant) toxins are subcategories of toxins.

Toxicity

The poisonous characteristics of a substance; the degree to which something is poisonous. Perhaps the best known measure of toxicity of a chemical is its lethal dose or LD_{50} (Table 1.1).

Acute Toxicity

Intoxication that results from the effects of a single dose or multiple doses of a toxicant given during a 24-hour period (e.g., a dog got into a box of chocolates or a cat was left in a room contaminated by chemical fumes overnight). The LD_{50} of a chemical is most often determined during acute exposure studies in which a single dose of a chemical is given.

Subacute Toxicity

Exposure to multiple doses of a toxin or toxicant given for greater than 24 hours but no longer than 30 days (e.g., an animal owner administers ibuprofen to dog for a week).

Subchronic Toxicity

Repeated or continuous exposures to toxicants for a duration of 1–3 months (e.g., a patient on weekly chemotherapy for cancer).

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Table 1.1. Classification scheme for relative toxicity

Classification	Toxicity (LD_{50} in mg/kg body weight)
Extremely toxic	<1 mg/kg
Highly toxic	1–50 mg/kg
Moderately toxic	50–500 mg/kg
Slightly toxic	0.5–5.0 g/kg
Practically nontoxic	5–15 g/kg
Relatively harmless	>15 g/kg

Chronic Toxicity

Intoxication that results from prolonged exposure, with the duration of exposure being 3 months or longer (e.g., repeated exposure of a cat to low levels of lead as a result of environmental contamination and grooming of contaminated paws or hair).

Dose

The quantity of drug or toxicant administered at one time irrespective of body weight.

Dosage

The regimen governing the size, amount, frequency, and number of doses of a therapeutic agent to be administered to a patient; most commonly measured in milligrams per kilogram (mg/kg), milligrams per pound (mg/lb), or milligrams per square meter of body surface area (mg/m^2).

Lethal Dosage (LD)

The lowest dosage that causes death. An LD can be expressed as a percentage of individuals dying (e.g., an LD_{10} means 10% of individuals will die from this dosage).

Median Lethal Dosage (LD_{50})

The quantity of an agent that will kill 50% of the test subjects to which it is administered. Note that the LD_{50} is a fairly rough estimate of overall toxicity and will not tell us at what dosage the first individual will develop signs of toxicosis (minimum toxic dosage or MTD) or die (minimum lethal dosage or MLD).

Parts per Million (ppm)

A weight-for-weight (w/w) concentration equal to 1 mg/kg or 1 g/ton (tonne). Used most commonly to express the concentration of toxicants or trace elements in water, feeds, solvents, and tissues. Note that mg/kg can refer to either a concentration in a material or a dosage in a patient; its meaning is dependent on the context of its use.

Parts per million (ppm), parts per billion (ppb), and parts per trillion (ppt) are the most commonly used terms to describe very small amounts of contaminants in our environment. They are measures of concentration or the amount of one material in a larger amount of another material; for example, the weight of a toxic chemical in a certain weight of food. The following example might help conceptually. If you divide a pie equally into 10 pieces, each piece would be one part per 10 or one-tenth of the total pie. If, instead, you cut this pie into a million pieces, each piece would be very small and would represent a millionth of the total pie or one part per million of the original pie. If you cut each of these million pieces into a thousand little pieces, each of these new pieces would be one part per billion of the original pie. To give you an idea of how little this would be, a pinch of salt in 10 tons of potato chips is also one part (salt) per billion parts (chips). In the pie example, the pieces of the pie are made up of the same material as the whole. However, if there were a contaminant in the pie at a level of one part per billion, one of these invisible pieces of pie would be made up of the contaminant and the other 999,999,999 pieces would be pure pie. Similarly, one part per billion of an impurity in a biological or environmental sample represents a tiny fraction of the total amount of the sample (e.g., water, food, whole blood, urine, or tissue).

Hazard (Risk)

The likelihood that a chemical will cause harm under certain conditions. The hazard can vary for the same chemical. For example, the hazard or risk of intoxication is greater if a potentially toxic product or chemical is not stored properly and thereby the chance for accidental exposure is increased due to greater accessibility. Or the risk of intoxication of a compound may be low if the compound comes in contact with the skin but high if it is ingested.

CLASSIFICATION OF TOXICANTS

Toxins and toxicants are classified in a variety of ways; no one way is better than another and a combination of classification schemes is used in this textbook. Poisons can be classified based on the organ systems that are primarily affected (e.g., hepatotoxicants, neurotoxicants, nephrotoxicants, etc.). The limitation to this scheme is that many toxins or toxicants affect more than one organ system.

Alternatively, poisons can be classified based on their chemical structure. For example, alkaloids are cyclic compounds that contain a nitrogen molecule within the ring. Toxic alkaloids are common in plants (e.g., nicotine in *Nicotiana* spp. or coniine in *Conium maculatum*). A third classification scheme categorizes poisons according to their use or location. For example, pesticides are subcategorized into rodenticides, insecticides, herbicides, fungicides, avicides, parasiticides, etc. based on the type of target organism for which they were developed. Poison categories based on location might include those found in homes, yards, or industrial sites. Within each of these categories are chemically diverse compounds with quite distinct target organs or mechanisms of toxic action. Finally, poisons can also be categorized according to their mechanism of toxic action. For example, some poisons cause damage via free radical formation or lipid peroxidation of cellular membranes and others inhibit protein synthesis.

SPECTRUM OF UNDESIRED EFFECTS

Toxicants cause damage through a variety of mechanisms, including altering cell and organelle membrane integrity, altering cell energy production, inhibiting protein synthesis or enzyme activity, or damaging DNA (Osweiler 1996). Other undesired effects that need to be considered are discussed below.

Idiosyncratic Reactions

Idiosyncratic reactions to chemicals are defined as genetically determined abnormal reactivity to a chemical (Aleksunes and Eaton 2019). Most commonly, this is caused by an acquired or congenital enzyme deficiency that prevents a toxicant from being processed properly. In some cases, the reason for an idiosyncratic reaction is unknown. See the discussion on genetic polymorphisms below.

Immediate vs. Delayed Reactions

Immediate effects can be defined as those that occur rapidly after a single exposure to a chemical. In contrast, delayed toxic effects are those that occur after some period of time (often, but not always, following repeated exposures). For example, many chemicals can induce cancer, but only after a long latency period of years (Aleksunes and Eaton 2019; Osweiler 1996). The focus of this textbook is on immediate adverse effects.

Reversible vs. Irreversible Damage

If a chemical damages a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible. Tissues such as the gastrointestinal tract and the liver, which have high regenerative capabilities, are less likely to suffer irreversible damage than other tissues, such as nervous tissue, which has much more limited regenerative capacity. However, even highly regenerative tissues such as the liver can suffer irreversible damage, particularly as a result of fibrosis in response to chemically induced damage.

Local vs. Systemic Effects

Local effects of a chemical are those that typically occur at the site of first contact between the biological system and the chemical. Good examples of chemicals with primarily local effects include acid and alkali corrosives. Systemic effects require the absorption and distribution of a chemical to a distant site where damage occurs. Most chemicals discussed in this textbook have systemic effects. It is possible for some chemicals to have both local and systemic effects. A good example of this occurs following exposure to iron salts. The reactivity of iron damages mucosal cells along the gastrointestinal tract; systemic absorption of iron results in more widespread damage to multiple organs.

INTERACTION OF CHEMICALS

Because animals and people are exposed to multiple chemicals at any given time, it is necessary to consider how different chemicals might interact with each other to modify toxic responses. Chemical interactions occur by a number of mechanisms that can include alterations of absorption, biotransformation (metabolism), protein binding, or elimination (Aleksunes and Eaton 2019). An example of two chemicals interacting to affect toxicity of one involves the combination of piperonyl butoxide and pyrethrin/pyrethroid insecticides. Piperonyl butoxide interferes with the metabolism, and therefore the detoxification, of the insecticides (Volmer 2004).

In general, types of interactions between chemicals that can influence the toxicity of one or more of the chemicals are classified as additive, synergistic, or antagonistic (Table 1.2). Additive interaction means the effect of two chemicals is equal to the sum of the effect of the two chemicals taken separately (e.g., $2+3 = 5$). This is usually due to the two chemicals acting on the body in the same way. An example of additive toxicity would be exposure to two different organophosphorus insecticides at the same time. Both have the same mechanism of toxic action (i.e., inhibition of acetylcholinesterase activity). Synergistic interaction means that the effect of two chemicals

Table 1.2. Interactions of toxicants: when multiple chemical exposures occur, a variety of interactions may occur between those chemicals

Additive **2+2 = 4**	Exposure to two or more toxicants results in the sum of the expected individual responses
Synergistic **2+2 = 10**	Exposure of two or more toxicants results in response in great excess than the sum of their individual responses
Antagonistic **2+2 = 1**	Exposure to two toxicants results in effects that are less than the sum of their individual responses
Potentiated **0+2 = 4**	Exposure to a normally nontoxic agent in combination with a toxicant results in enhanced toxicity of the toxicant

taken together is greater than the sum of their separate effects at the same dosages (e.g., 2+2 = 20). One example of synergism is simultaneous exposure to the hepatotoxicants ethanol and carbon tetrachloride. In this case the damage to the liver is greater than that expected from summing the toxicities of each individual chemical. Antagonistic interaction means that the effect of two chemicals is less than the sum of the effect of the individual chemicals (e.g., 4+6 = 8). This can be due to the second chemical increasing the excretion of the first or perhaps as a result of the first directly blocking the toxic actions of the second. Antagonism forms the basis for many antidotal drugs. For example, atropine blocks cholinergic receptors that are stimulated following exposure to organophosphorus or carbamate insecticides.

One other term, *potentiation*, is used to describe chemical interactions. Potentiation occurs when one substance does not have a toxic effect on a certain organ or system but, when added to another chemical, makes the second chemical much more toxic (Aleksunes and Eaton 2019). For example, isopropanol is not hepatotoxic. However, when combined with carbon tetrachloride, the hepatoxicity of carbon tetrachloride is greatly enhanced.

Finally, *tolerance* is another term worth noting. It is defined as the state of decreased responsiveness to the toxic effect of a chemical as a result of prior exposure to that chemical or to a structurally related chemical (Aleksunes and Eaton 2019). Tolerance can occur either as a result of a decreased amount of a chemical reaching its site of toxic action or as a result of reduced responsiveness of a target to the chemical. The former can occur, for example, when exposure to a chemical increases the levels of metabolic enzymes in the liver, resulting in enhanced metabolism and detoxification of that chemical with subsequent exposures. The latter can occur as a result of down-regulation of receptor numbers for chemicals that cause adverse effects due to receptor stimulation.

CHARACTERISTICS OF EXPOSURE

Every day, animals (including humans) are exposed to poisons in the air they breathe, the food they eat, and the water they drink. Even agents necessary for life such as oxygen, water, and sodium can be toxic under certain circumstances. The fact that we don't all develop signs of poisoning on a daily basis underscores the basic concept of toxicology: the dose makes the poison. However, many factors are involved in determining whether a sufficient dose of a poison reaches its site of action in order to invoke a toxicosis. Agent factors to consider include the toxicant, its physical properties (i.e., liquid vs. solid vs. gas, pH, etc.), its chemical structure, and its stability or reactivity. Host factors to consider include species and/or breed, age, weight, and general health status of the animal. The most important factors that must be considered in determining whether a toxicosis will develop are those surrounding the introduction of toxicant to host: the exposure. Without exposure to a poison, there will be no poisoning, so it is important to understand the characteristics of exposures to toxicants that help to determine whether a toxicosis will develop.

Route and Site of Exposure

In veterinary medicine most exposures to toxicants occur via ingestion (gastrointestinal tract). However, exposures to toxicants can occur via other routes, including inhalation (lungs), transdermal (skin), injection, ocular, and other minor parenteral routes (intramammary, etc.). Toxicants injected intravenously produce the most rapid response, with inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and dermal following in descending order of speed of response (Aleksunes and Eaton 2019). Not all poisons are toxic by all routes of exposure; in fact, most toxicants have a narrow range of routes by which they can gain access to the body. For instance, elemental mercury (quicksilver) is virtually nontoxic by dermal or oral routes; however, inhalation of the vapors can result in respiratory irritation as well as systemic absorption of mercury vapors

via the lungs, which can, over time, result in central nervous system dysfunction from mercury toxicosis (Tchounwou et al. 2023).

Duration and Frequency of Exposure

Some toxicants can cause clinical effects with single exposures, but others may require repeated exposures over time before a toxicosis develops; the clinical syndromes of each of these types of exposures may be quite different. In small animal medicine, most toxicoses that present to the veterinary hospital are acute because they are most often due to a single exposure to a toxicant.

There can be significant differences between clinical syndromes demonstrated by patients, depending on whether the exposure was acute or chronic. For example, acute arsenic toxicosis causes severe gastrointestinal hemorrhage, shock, and, often, death in dogs, whereas sub-acute to chronic exposure is expected to cause renal failure.

The frequency of exposure also can dictate the degree and severity of a toxicosis. For instance, a cat given 10 mg/kg of aspirin on a daily basis will quickly develop a toxicosis, but if the same dose is given every third day, toxicosis is unlikely.

DOSE–RESPONSE RELATIONSHIP

The basic concept in toxicology is "the dose makes the poison." This concept is essential in assessing the risks of exposures to toxicants, and it is often overlooked by the lay public, who typically perceive substances as either "toxic" or "nontoxic." Virtually any substance can be toxic under the appropriate circumstances. A veterinary technician who understands and is able to apply the basic concepts of toxicology to clinical situations will be able to provide objective and rational input into the development of risk assessments for patient exposures to potential toxicants.

The dose–response relationship is the correlation of the exposure characteristics with the spectrum of toxic effects that a particular toxicant can produce. Knowing the dose–response relationship allows us to predict what type of reaction might be expected from an exposure. For example, methylxanthines in chocolate can cause serious clinical effects if sufficient amounts are ingested (Gwaltney-Brant 2001). A canine patient ingesting chocolate equal to 5 mg/kg of methylxanthines is not expected to have any serious clinical problems, but a dosage of 50 mg/kg could put the dog at risk for serious cardiovascular effects.

There are two components to the dose–response relationship: the population component and the individual component. Most dose–response relationships are made by grouping the responses of individuals to develop a population dose–response curve. As with all statistical studies of populations, the curve is bell-shaped, and the majority of individuals (the "normal" population) fall under the middle area of the curve. However, there are always individuals on the lower or upper limits of the curve (i.e., *outliers*), meaning they are more or less sensitive, respectively, to the toxicant and they will respond at lower or higher levels than the "normal" population (Figure 1.1). For instance, most dogs ingesting 20–30 mg/kg of methylxanthines from chocolate will develop agitation, restlessness, polydipsia, and gastrointestinal upset (Gwaltney-Brant 2001). However, at this dose, some dogs will show none of these clinical effects and appear clinically normal (less sensitive), while other dogs may develop signs at doses below 20 mg/kg (more sensitive). So, while knowing the dose–response relationship for a toxicant, it is important to also realize that there will be occasions when an individual patient fails to "read the same book" as the rest of us and responds differently than the norm. Some potential reasons for these individual variations will be discussed later in the chapter.

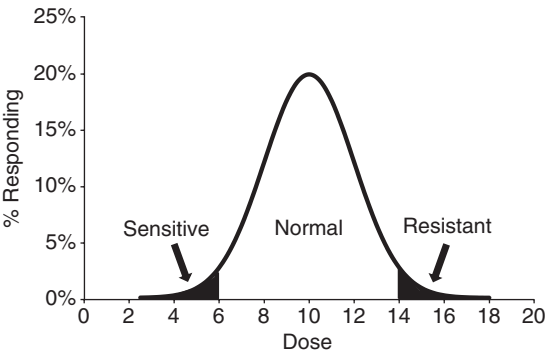

Figure 1.1. Illustration of dose–response curve. The majority of responders fall into the "Normal" range, but a small percentage of "Sensitive" individuals will respond at lower doses and another small percentage of "Resistant" individuals will not respond until the dose is much higher.

Therapeutic Index

Medications provide an excellent example of the dose–response relationship. If too small a dose of medication is taken, it will not have the desired therapeutic effect, and if too high a dose is taken, signs of toxicosis may be seen. The goal is to find a dose that

Figure 1.2. The margin of safety is the ratio of the lethal dose to 1% of the population to the effective dose to 99% of the population. It is used to measure drug safety. Bigger is better.

is effective and yet carries a low risk of intoxication. When comparing the relative safety of two similar drugs, a measurement called the *therapeutic index* is often used. This index is a ratio of the dose known to produce a toxic effect in 50% of the population (TD_{50}) to the dose known to produce a desirable therapeutic dose in 50% of the population (ED_{50}) (Aleksunes and Eaton 2019). The larger the ratio, the greater the relative safety.

Another parameter that also compares a toxic dose (TD_1; the dose at which 1% will experience toxic effect) with an effective dose (ED_{99}; dose that is effective in 99% of the population) is the *margin of safety*. A drug with a wide margin of safety will have low risk of adverse effects in the vast majority of patients (Figure 1.2).

Variation in Toxic Responses

In discussing dose–response, one must keep in mind that there will always be individuals who do not respond in the same fashion as the majority of the population. An individual may show a higher or lower sensitivity to toxicosis than expected or may not show a therapeutic effect from a medication. Some reasons for these individual variations have been elucidated, but others still remain to be discovered (see *idiosyncratic* definition above).

Species Differences

Response to toxicants can vary tremendously between different species, with compounds that are relatively nontoxic to one species being quite toxic in a different species. These species differences can be the result of differences in physiology or toxicant absorption, metabolism, and/or elimination. For instance, cats evolved as true carnivores that did not need to metabolize plant-derived compounds such as phenols, and they therefore did not evolve the necessary enzymes required to eliminate phenolic compounds from the feline body. As a result, cats have diminished ability to metabolize certain phenolic compounds, making them more susceptible to toxicosis from xenobiotics (such as acetaminophen) that contain phenols. Cats are also highly susceptible to developing methemoglobinemia and Heinz body anemia because their hemoglobin molecules contain eight reactive sulfhydryl groups (compared to four in dogs and two in humans), which can bind to oxidative agents, such as disulfides found in onions and other *Allium* spp., that can denature hemoglobin. Additionally, a relative deficiency of methemoglobin reductase enzymes in their red blood cells makes it difficult for them to reverse the hemoglobin damage (Osweiler 2013). Because species differences are common and many are not fully elucidated, care must be taken when attempting to extrapolate toxicity data from one species and apply it to another.

Genetic Polymorphisms

The influence of genetics on an individual's response to xenobiotics is the subject of much study in the human pharmaceutical world. *Genetic polymorphism* is the term for hereditary differences in a single gene that occur in more than 1% of the population (Aleksunes and Eaton 2019). Genetic polymorphisms are significant causes of individual variation in response to toxicants. Although a large number of genetic polymorphisms relating to xenobiotics have been identified in humans, less study has been done in companion animals. Perhaps the best known toxicology-related genetic polymorphism in the veterinary world is the sensitivity of some dogs to macrolide antiparasitic agents (e.g., ivermectin, moxidectin, etc.). Individuals within certain genetic lines of collies, Shetland sheepdogs, Old English sheep dogs, and several related breeds carry an autosomal recessive defect in a gene that codes for a blood–brain barrier P-glycoprotein (Lanusse et al. 2018; Mealey et al. 2023). This defect results in a faulty "pump" that normally excludes certain xenobiotics (including macrolides) from entering the central nervous system (CNS). As a result, macrolide agents are able to enter the CNS and cause clinical signs of intoxication at dosages that are not toxic to dogs without this defect. Likewise, other drugs that are normally excluded from the CNS by this pump but can gain access to the CNS in P-glycoprotein-defective dogs include digoxin, doxorubicin, and vincristine (Mealey et al. 2023). Similar P-glycoprotein defects and macrolide sensitivities have been identified in cats, resulting from different P-glycoprotein gene mutations than those found in dogs (Mealey et al. 2023).

Age

Age-related responses to toxicants must be considered when dealing with pediatric and geriatric patients because behavioral, physiological, and pathological

differences in these special populations can have a profound influence on sensitivity to toxicants. When assessing the risk of an exposure to a toxicant, pediatric and geriatric animals should be considered at increased risk, and treatment should be considered at lower levels of exposure than would occur with a young adult animal.

Pediatric Patients

Nursing puppies and kittens may be exposed to toxicants not only through ingestion or inhalation of toxicants in their environments but by exposure to toxicants that the nursing dam may have ingested if these toxicants are passed through the milk (Peterson 2013). By their inquisitive nature, young animals are more inclined to be exposed to toxicants in their environment that adult animals have learned to avoid (e.g., skunk spray). Younger animals have a variety of physiological differences making them more susceptible to toxicosis, including:

- increased intestinal permeability to some toxicants (e.g., lead)
- increased gastric pH, which enhances the absorption of some toxicants
- decreased intestinal motility, which allows toxicants to stay in the gastrointestinal tract longer and provides more opportunity for absorption of toxicants
- decreased plasma protein concentrations to bind toxicants, allowing more free toxicant in the blood to reach target tissues
- less body fat to sequester lipid soluble toxicants
- decreased glomerular filtration rate, which results in decreased excretion of toxicants and their metabolites
- decreased hepatic function and metabolic enzymes to detoxify toxicants.

Geriatric Patients

As animals age, they experience physiological and metabolic changes that can alter the way that they respond to toxicants. Additionally, these animals may be on medications for degenerative disorders typical of elderly animals (e.g., arthritis), and interaction between the medication and toxicant may occur. Aging results in decreased kidney and liver function. Because these two organ systems are the predominant means of toxicant elimination, the aging animal has a decreased capacity to efficiently remove toxicants from the body. Geriatric animals share some of the same metabolic derangements seen in pediatric animals, including decreased intestinal motility, decreased plasma protein production, decreased glomerular filtration rate, and decreased hepatic function. Additionally, elderly animals may have decreased cardiovascular function, making them less able to handle the stresses of intoxication. Concurrent disease processes are more common in older patients and may increase the susceptibility to organ damage by toxicants (e.g., preexisting renal dysfunction may make a patient more susceptible to the toxic effects of nonsteroidal anti-inflammatory drugs) or compromise the animal's ability to respond to a toxicant. The behavior of a geriatric patient on some medications might be altered such that there is an increased risk for toxicant exposure (e.g., dogs on corticosteroid therapy often experience polyphagia and may ingest something they normally would avoid).

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

Pregnant animals exposed to toxic agents represent a special case when doing a risk assessment. Not only do the immediate needs of the patient need to be considered, but the potential effects of the toxicant (and any agents used to treat the dam) on the fetuses must be taken into account before a treatment plan is initiated. Pregnancy itself can cause some physiological changes in the dam, including decreased intestinal motility, decreased plasma protein concentrations, and alterations in renal and hepatic function (Kutzler 2013). These changes can impact the absorption, distribution, metabolism, and elimination of toxic compounds, making the dam more or less susceptible to a particular toxicant. Pregnant animals may spontaneously abort their pregnancies due to stress, direct effects of toxicants on the reproductive organs, or fetal death from hypoxia secondary to hypotension or other hemodynamic aberrations.

Toxicants may have minimal effect on the pregnant female but result in significant harm to the fetuses. Whether a toxicant has a direct effect on the fetuses will depend on several factors. Most importantly, in order for a toxicant circulating in the blood to directly impact the fetus, it will need to cross the placenta in sufficient quantities to cause fetal damage. Whether a toxicant can pass the placenta will depend on the physical and biochemical properties of the toxicant as well as the structure of the placenta, which varies according to species. Toxicants reaching the fetuses can result in fetal death, fetal malformation (teratogenesis), or functional abnormalities (e.g., behavioral abnormalities), depending on the toxicant,

species involved, and stage of gestation when the exposure occurs. Throughout gestation, there are peak times of susceptibility for organ malformation, generally coinciding with organogenesis. Organ-specific teratogens that are introduced prior to or after organogenesis may have little or no impact on the developing fetus (Rogers 2019). Toxicants administered during gestation may cause a wide range of fetal defects. For example, feeding carbaryl (a carbamate insecticide) to dogs during gestation resulted in abdominal-thoracic fissures, intestinal agenesis, brachygnathia, and a variety of appendicular skeletal abnormalities (Smalley et al. 1968).

Unfortunately, the potential effects of many toxicants on pregnant animals or their offspring are not known. When presented with a pregnant patient who has been exposed to a potential toxicant, it is always safest to err on the side of caution and attempt decontamination when it can be performed safely.

TOXICOKINETICS

Toxicokinetics refers to the movement of a toxicant through the body. The principles of toxicokinetics are the same as pharmacokinetics (the movement of drugs in the body) with the exception that the agent moving through the body is considered a toxicant rather than a therapeutic agent. The ultimate disposition of a toxicant in the body depends on the four components of toxicokinetics: absorption, distribution, metabolism (also called *biotransformation*), and elimination (Evans 2013). These components are often abbreviated as ADME for ease of use. The ADME characteristics will vary with the toxic agent, species, and individual.

Absorption

Other than caustic and corrosive agents that inflict their damage locally, most toxicants must enter the body to exert their effects (Evans 2013). *Absorption* is the process by which toxicants pass through the various barriers to enter the systemic circulation. The degree and extent to which a toxicant will be absorbed is dependent on the physical and chemical characteristics of the toxicant (molecular weight, pH, lipid solubility, etc.), the route of exposure, and species of animal. With the exception of intravenous injection, it is unlikely that 100% of a toxicant to which an animal is exposed will be absorbed. *Bioavailability* is a term that refers to the fraction of a toxicant that is actually absorbed.

The passage of toxicants into the body requires transport across cellular membranes to reach the general circulation; this transport can be passive (e.g., simple diffusion) or active, requiring energy to facilitate absorption (Evans 2013). Passive transport mechanisms do not require energy expenditure and include simple diffusion and filtration across membranes. Both of these processes require a concentration gradient for the toxicant to move along. The rate of toxicant movement is determined by the degree of difference in concentration between the two sides of the membrane, i.e., the larger the concentration differential, the faster the rate of movement. Simple diffusion is the primary means of toxicant passage across cell membranes, and it is most effective with small, lipid-soluble, nonionized molecules. Filtration is the movement of molecules through pores in cellular membranes and is dependent on the size of the pores and size of the toxicant molecule. Facilitated diffusion is mediated by carrier molecules, which assist in carrying molecules across membranes. Active transport processes are energy-dependent and do not depend on a concentration gradient; in fact, most active transport mechanisms work against concentration gradients (i.e., take a molecule from an area of low concentration to an area of high concentration). Examples of active transport "pumps" include the Na^+-K^+ ATPase transporter in nerve cell membranes and the P-glycoprotein-dependent multidrug-resistant "pumps" in the blood–brain barrier.

Absorption can be influenced by a variety of factors, including route of exposure and the chemical and physical properties of the toxicant. The route of exposure plays a major role in determining how and to what extent a toxicant will be absorbed. In the gastrointestinal tract, the majority of molecules are absorbed by passive diffusion or carrier-mediated processes (Slitt 2019). Gastrointestinal absorption is highly dependent on the pH of the toxicant, with weak acids being better absorbed in the stomach and weak bases being better absorbed in the proximal small intestine. Absorption of toxicants across the skin requires that the toxicant pass through the lipophilic stratum corneum (the major barrier to absorption of toxicants via the skin) and then through the hydrophilic dermis to reach the bloodstream. Solvents such as dimethyl sulfoxide (DMSO) greatly enhance absorption of topically applied agents by increasing the permeability of the stratum corneum. Absorption of toxicants (primarily gases, vapors, and aerosols) via the lungs is second only to intravenous injection in regard to the speed and efficiency of absorption. Toxicants reaching the alveoli have only a thin wall to pass through in order to reach the systemic circulation. Fortunately, the structure of the respiratory tract can filter out many toxicants and prevent them from reaching the alveoli.

Some toxicants undergo what is termed a *first-pass effect* whereby toxicants absorbed from the gastrointestinal tract are taken via portal circulation to the liver, where a fraction of toxicant is removed from the blood prior to reaching the systemic circulation. The first pass effect can dramatically decrease the bioavailability of toxicants. For example, a dog ingesting its owner's sublingual nitroglycerine tablets will be at low risk of toxicosis as long as the dog swallows all of the tablets. The nitroglycerine absorbed from the stomach will be largely removed by the liver and will not enter the systemic circulation. However, if the dog has one or more tablets that remain in the oral cavity (e.g., adhered to the oral mucosa), absorption across the oral mucosa will allow the nitroglycerine to enter the systemic circulation and the dog will develop signs of hypotension because compounds absorbed from the oral cavity do not enter the portal circulation.

Distribution

Once a toxicant enters the body it may remain within the systemic circulation, or it may distribute to organs and tissues. *Distribution* is the translocation of the toxicant to various organs and tissues throughout the body. The degree and extent to which a particular toxicant will distribute to tissues is dependent on a variety of toxicant properties, including lipid solubility, molecular weight, and the affinity of the toxicant for various tissues (Evans 2013; Slitt 2019). The body has several physiologic barriers that may limit the distribution of certain xenobiotics, such as the blood–brain barrier, which excludes a large number of molecules from the central nervous system. The distribution characteristics of a toxicant are important in determining the clinical effects that a toxicant will produce. For example, the herbicide paraquat selectively concentrates in the lungs, where it is converted into toxic metabolites that induce severe lung damage and fibrosis. A related compound, diquat, has a similar mechanism of action, but does not selectively locate to the lung and therefore does not cause the pulmonary lesions that are seen with paraquat.

The storage of some toxicants within the body can actually aid in decreasing the acute toxicity of the compound. Some common storage depots for toxicants include bone (e.g., lead, cadmium), fat (e.g., organochlorine pesticides such as DDT), liver (e.g., copper), and kidney (e.g., cadmium). The toxicants in these *storage depots* are in equilibrium with the plasma, but certain metabolic situations can sometimes disrupt the equilibrium. For example, in chronic, low-level exposure to lead, much of the lead is stored in the bones, which may protect the animal from manifestations of acute toxicosis; blood lead concentrations may be only slightly above the normal range in these cases. However, any condition that causes an increase in bone remodeling (e.g., lactation, fracture) may result in a sudden release of lead from the storage depot and precipitate acute lead toxicosis, even in a patient that is no longer exposed to lead from its environment.

Plasma proteins are a special storage depot for toxicants and are important in determining the toxicity of an agent. There are a large number of proteins in the blood that can bind toxicants, but albumin is the major protein responsible for the binding of xenobiotics (drugs and toxicants). Because only a free (unbound) toxicant can reach its site of action, plasma proteins essentially "bind up" the toxicant, preventing it from exerting its toxic effect. Toxicants that are highly protein-bound have a lower level of toxicity than similar toxicants, which have poor protein binding. Species differences in types and amounts of plasma proteins are one reason for species differences in toxicity of various toxicants. An important consideration when dealing with a highly protein-bound compound is the potential interaction that may occur with other highly protein-bound agents. For instance, a dog that is on carprofen (a highly protein-bound drug) for arthritis is exposed to a warfarin-based rodenticide. Because warfarin is also highly protein-bound, the two xenobiotics are in competition for plasma proteins, resulting in higher unbound concentrations of both, which may result in clinical signs of warfarin toxicosis at doses lower than those normally associated with warfarin. Additionally, there also might be increased risk of adverse effects from the carprofen (i.e., gastrointestinal upset or bleeding).

Metabolism

Metabolism refers to the fate of a toxicant within the body and is often used synonymously with the term *biotransformation*, which more correctly refers to the metabolic processes involved in creating a more water-soluble form of xenobiotics (Evans 2013). In order to prepare toxicants for elimination from the body, they must be converted into forms that are excretable. In most circumstances, this entails making the toxicant more water-soluble so that it can be eliminated by the kidneys; less commonly, compounds are made more lipid-soluble and eliminated via the bile into the feces. The body has a limited range of metabolic enzymes that can act on a wide range of substrates. These enzymes are present in most tissues but are most concentrated in

organs with highest exposure to xenobiotics, including the liver, gastrointestinal tract, kidneys, and lung.

There are two levels of biotransformation, termed *phase I* and *phase II* reactions, used to make toxicants more excretable. Not all toxicants undergo both reactions; some toxicants are eliminated with little or no metabolism, and others undergo one of the two reactions. Phase I reactions generally involve hydrolysis, oxidation, or reduction and are designed to make a compound more water-soluble and/or expose a functional group for a subsequent phase II reaction. Phase I reactions include the oxidation reactions mediated by cytochrome P450 enzymes, which are the basis for much of the individual variation in susceptibility to adverse drug reactions (Parkinson et al. 2019). Phase II reactions involve attachment (conjugation) of a functional group (sulfate, glucuronide, amino acid, glutathione, methyl group, acetyl group) to a parent compound or one of its metabolites that results in a compound that has greatly increased water solubility. Species differences in phase II reactions include the defective glucuronidation in cats that makes them sensitive to phenolic compounds such as acetaminophen.

Bioactivation

Although biotransformation is generally thought of as a detoxifying process, allowing the body to eliminate potential toxicants, in some instances reactions might result in a compound that is more toxic than the parent compound. This conversion of a low or nontoxic parent compound to a toxic metabolite is termed *bioactivation*. Examples include the conversion of ethylene glycol to metabolites that induce acidosis and renal failure, and the conversion of acetaminophen to a highly reactive intermediate that causes liver damage.

Elimination

Elimination is the process of removing toxicants and their metabolites from the body. As has been mentioned, most biotransformation reactions are geared toward making toxicants more water-soluble so that they can be excreted via the kidneys. Renal excretion is the most common means by which the body eliminates waste. Other elimination pathways include fecal (via bile), exhalation (via lungs), saliva, sweat, and milk. Toxicants and their metabolites can be eliminated by more than one route (e.g., fecal and urinary).

The elimination half-life of a toxicant is the amount of time it takes for the original absorbed dose to be reduced by one-half. Compounds with shorter half-lives will be eliminated from the body more quickly than those with longer half-lives. Two processes that can prolong the half-life of a toxicant include enterohepatic recirculation and saturation of metabolic enzymes. Enterohepatic recirculation is the repeated cycling of a toxicant between the liver and the gastrointestinal tract. The toxicant passes from the systemic circulation into the liver, where it is excreted via the bile duct into the small intestine, from where it is reabsorbed to reenter the systemic circulation. This continued cycling can greatly prolong the amount of time that a toxicant stays in circulation. For example, in dogs, the nonsteroidal anti-inflammatory drug naproxen undergoes extensive enterohepatic recirculation and has a half-life of 74 hours, whereas in humans naproxen does not undergo enterohepatic recirculation, is eliminated primarily via the urine, and has a half-life of only 6 hours (Frey and Rieh 1981; Lees 2018; Talcott and Gwaltney-Brant 2013).

Toxicants that must be metabolized through enzyme-mediated processes can have their half-lives increased if the dose of toxicant exceeds the capacity of the enzyme system to catalyze the conversion of toxicant to metabolite. In these situations, the toxicant "backs up" as the enzyme system becomes saturated with substrate. For toxicants that can be eliminated as parent compound as well as metabolites (e.g., ethanol), saturation may only mildly affect half-life, but for compounds that cannot be eliminated without first being converted to metabolites, the half-life can be significantly impacted. An example is aspirin, which requires glucuronidation for elimination. In cats, the half-life of aspirin ranges from 22 to 45 hours depending on the dose administered. As the dose increases, the half-life increases due to saturation of the cat's defective glucuronidation system. This is why the dosing interval of aspirin for cats is every 48–72 hours compared to every 8–12 hours for dogs.

CHAPTER 1 STUDY QUESTIONS

1. Banjo, a 2-year-old, 25-pound, neutered male dachshund mix ingested a 25-mg propranolol tablet that his owner accidentally dropped on the floor. When researching this drug, which of the following information would be LEAST helpful to you in determining whether Banjo is at risk for serious clinical effects?
   a. The minimum toxic dose for dogs
   b. The maximum tolerated dose for dogs
   c. The LD_{50} for dogs
   d. The minimum lethal dose for dogs
   e. The therapeutic index for dogs
2. Ranger, a 3-year-old golden retriever, was just prescribed phenobarbital to control his epilepsy. Ranger's owner called later that day to say that Ranger was acting groggy and wants to know whether this is expected with the phenobarbital. Ranger's veterinarian tells you to relay to the owner that this is an expected event and that Ranger should adapt to his medication after several days. A call back to the owner a week later finds that Ranger is no longer acting groggy after receiving his phenobarbital. Ranger's decreased sensitivity to the sedative effects of phenobarbital over time is an example of
   a. Potentiation
   b. Tolerance
   c. Synergism
   d. Antagonism
   e. Additivity
3. The fundamental principle of toxicology is "the dose makes the poison." When determining whether the dose of a particular compound poses a risk of toxicosis to an animal, which of the following must be taken into account?
   a. Physical properties of the compound (e.g., physical state, pH, reactivity, etc.)
   b. Species exposed to the compound
   c. Route of exposure
   d. Age, sex, and weight of the patient
   e. All of the above must be considered.
4. In general, the most rapid response to a toxicant will occur if it is administered
   a. Intravenously
   b. Intradermally
   c. Orally
   d. Intramuscularly
   e. Subcutaneously
5. The dose–response curve represents the characteristics of a xenobiotic within a _____, but _____ variation can result in increased or decreased response at a particular dose.
   a. Species, normal
   b. Population, individual
   c. Species, individual
   d. Population, normal
   e. Class, statistical
6. When compared to humans, the increased susceptibility of cats to acetaminophen toxicosis is related primarily to species differences in which of the following:
   a. Absorption of acetaminophen
   b. Distribution of acetaminophen
   c. Metabolism of acetaminophen
   d. Elimination of acetaminophen
   e. Bioavailability of acetaminophen
7. Some Doberman pinschers have an increased susceptibility to liver injury when they receive sulfonamide antibiotics at therapeutic doses. Because this susceptibility in Doberman pinschers is familial (i.e., runs in families), it is suspected that this trait is inherited. If so, this would be an example of
   a. Species difference
   b. Genetic polymorphism
   c. Age-related response
   d. Gender difference
   e. Fetal toxicity
8. In cats, organogenesis is complete in the first trimester (first 3 weeks) of pregnancy. At week 8 of pregnancy, a queen was exposed to a medication known to adversely affect fetuses. Which of the following would NOT be an expected outcome of this exposure?
   a. Anencephaly
   b. Abortion
   c. Stillborn kittens
   d. Mummified fetuses
   e. Premature parturition
9. The percentage of an ingested toxicant that is absorbed into the circulation is a measure of its
   a. Toxicity
   b. Distribution
   c. Metabolism
   d. Teratogenesis
   e. Bioavailability

Continued

10. Select the incorrect statement.
    a. Distribution refers to the movement of xenobiotics throughout the body and includes binding of xenobiotics to plasma proteins and storage of xenobiotics in various tissues, including the bone, liver, and kidney.
    b. The "first pass effect" refers to the inability of some toxicants to cross the gastrointestinal mucosal barrier and enter the systemic circulation.
    c. Metabolic activity that results in a metabolite that is more toxic than the parent compound is referred to as bioactivation.
    d. The predominant goal of metabolism is to make xenobiotics more water-soluble so that they can be more easily excreted via the urine.
    e. Enterohepatic recirculation of a xenobiotic can result in prolongation of the xenobiotic's half-life.

ANSWERS

1. c. The LD_{50} identifies the dose at which 50% of dogs will die but does not give an indication of the dose at which dogs can tolerate propranolol without showing clinical signs (maximum tolerated dose), the dose at which clinical signs may be expected to develop (minimum toxic dose), or the lowest dose at which death might be possible (minimum lethal dose). All of these parameters are far more helpful in determining the risk following an acute exposure than the LD_{50}.
2. b. Tolerance is the reduced responsiveness to a chemical due to prior exposure to that chemical (or a similar chemical). In the case of phenobarbital, the enzymes that metabolize the drug are induced in the liver, resulting in an increase in phenobarbital metabolism, lower blood levels, and decreased adverse effect.
3. e. All of these factors are important in determining the risk of toxicosis from a toxicant.
4. a. Intravenous administration will produce the most rapid distribution of a toxicant to its site of action in the body.
5. b. The dose–response curve represents the characteristics of a xenobiotic within a population, but individual variation can result in increased or decreased response at a particular dose.
6. c. Cats lack essential enzymes for metabolizing acetaminophen into nontoxic compounds and instead produce metabolites that are highly reactive, resulting in toxicosis at relatively low doses of acetaminophen.
7. b. Genetic polymorphisms are inherited traits that result in differences in response to xenobiotics.
8. a. Anencephaly (absence of brain) would not occur because the exposure occurred after the brain had formed (i.e., after completion of organogenesis).
9. e. Bioavailability
10. b. The first pass effect refers to the hepatic removal of a fraction of a xenobiotic that has been absorbed into the portal circulation before the xenobiotic can reach the systemic circulation.

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