General Toxicologic Principles for Clinicians

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- *Toxicology* is the science and study of how poisons affect organisms.
- Toxicology uses information extensively from medicine, pathology, chemistry, epidemiology, and statistics to reach the best diagnostic and therapeutic outcomes.
- Dosage is the most important factor that determines response to poisons.
- Toxicity is the quantitative amount of toxicant (dosage) required to produce a defined effect.
- Hazard or risk of poisoning depends on toxicity of the agent, characteristics of the animal's biology, and probability of exposure to the toxicant under conditions of use.
- Acute, subacute, and chronic toxicity are different chronological designations of chemical toxicity and are determined by relative dosage and the time and circumstances of exposure.
- LD_{50} values are useful for comparison of toxicity differences among chemicals but do not define the nature of toxicosis produced or the safe dosage for a majority of animals.
- The lowest known clinical toxic dosage is of greatest value for clinical toxicology.
- Many factors alter an animal's response to toxicants, including those inherent in the toxicant (chemical structure, solubility), the animal (metabolism, excretion), the environment (pollutants, natural toxins), and combinations of these major factors.
- Clinical toxicology evaluation depends heavily on determination of exposure, nature of clinical effects, and evidence for interacting factors that can alter toxicity.
- Determination of dosage and concentration are essential for thorough toxicologic evaluation and prognosis.

Dosage Makes the Poison

Toxicology is the study of poisons and their effects on living organisms. In veterinary medicine, this means understanding sources of poisons, circumstances of exposure, diagnosis of the type of poisoning, treatment, and use of management and educational strategies to prevent poisoning.[1-4]

Toxicology is based on the important principle of dose and response. There is a graded and possibly predictable response based on increasing exposure to the toxicant. In the words of Paracelsus, a physician-alchemist of the sixteenth century, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."[2,4] Paracelsus's principle of dosage and poisoning is still true and relevant in the

daily practice of nutrition, therapeutics, and toxicologic analysis. Today, with emphasis on synthetic drugs, natural or alternative therapies, and the rapidly growing fields of nutraceuticals and nanotoxicology, there is continuing interest in evaluating dosage and response principles for both beneficial and detrimental effects in the daily practice of veterinary medicine. Many toxicants discussed in this book provide examples of how dosage determines whether the agent is a nutrient, a remedy, or a poison.

Determinants of exposure that affect dosage may be more than simply the gross amount of material ingested or applied to the skin. Rather, the effective dosage at a susceptible receptor site determines the ultimate response. Thus species differences in metabolism, vehicle differences that promote skin penetration, specific drug or chemical interactions that potentiate response, and organ dysfunction that limits elimination can all influence the ultimate dosage.[2,3,5] Clinicians must consider all of these possibilities when working to diagnose a potential toxicosis or apply therapeutic agents to their patients.

Dosage Is Affected by Animal Systems for Absorption, Metabolism, and Elimination

Toxicology involves the knowledge of poisons, including their chemical properties, identification, and biologic effects, and the treatment of disease conditions caused by poisons. Toxicology shares many principles with pharmacology. The term *toxicokinetics* includes absorption, distribution, storage, metabolism, and elimination; another term, *toxicodynamics,* describes mechanisms of action and effects of poisons on the biochemistry and physiology of animals. These important concepts are more fully described in Chapter 2, "Toxicokinetics and Toxicodynamics."

Every specialty has its important characteristic terminology. Basic terminology is important when reading toxicology literature, reviewing laboratory reports, or describing effects to colleagues. The following are some of the more useful toxicologic terms.

A *poison* or *toxicant* is any solid, liquid, or gas that, when introduced into or applied to the body, can interfere with homeostasis of the organism or life processes of its cells by its own inherent qualities, without acting mechanically and irrespective of temperature. The term *toxin* is used to describe poisons that originate from biologic sources and are generally classified as *biotoxins.* Biotoxins are further classified according to origin as *zootoxins* (animal origin), *bacterial toxins* (both endotoxins and exotoxins), *phytotoxins* (plant origin), *phycotoxins* (from seaweed and algae), and *mycotoxins* (fungal origin).[2,3,5]

Poisons may be categorized as *organic, inorganic, metallic,* or *biologic* and may be synthetic or natural. Synthetic agents may have been designed specifically as toxicants or for other purposes that may have a very broad or very narrow range of toxicity (e.g., drugs for cancer chemotherapy) or may produce effects in very specific targets. Natural products used in nutrition, medicine, or commerce are sometimes believed to be less hazardous than synthetic products. However, natural products are not inherently more or less toxic than synthetic molecules. Indeed, some of the most toxic agents known (e.g., botulinum toxin, tetrodotoxin) are of natural origin. Knowledge of the chemical nature and specific effects of toxicants is the only certain way to assess hazard from exposure.

The terms *toxic, toxicity,* and *toxicosis* are often misunderstood or misused.[3,5] The word *toxic* describes the effects of a toxicant (e.g., the "toxic" effects of organophosphate insecticides are cholinesterase inhibition—lacrimation, salivation, vomiting, dyspnea, and diarrhea). However, *toxicity* is used to describe the quantitative amount or dosage of a poison that will produce a defined effect (e.g., the toxicity of ethylene glycol for cats is 2 to 5 mL/kg body weight). The toxic effects of ethylene glycol are acidosis and oxalate nephrosis; the result of being poisoned by ethylene glycol is ethylene glycol toxicosis. *Poisoning* and *toxicosis* mean essentially the same thing and either may be used.

Dosage Defines Exposure in an Accurate and Reliable Format

Dosage is the correct terminology for toxicity expressed as amount of toxicant per unit of body weight.[2,3,5] The commonly accepted dosage units for veterinary medicine are milligrams per kilogram (mg/kg) body weight. However, toxicity can also be expressed as moles

Table 1-1 Comparison of Body Weight to Surface Area for Animals of Representative Sizes

Body Weight (kg)	Body Surface (m^2)
0.5	0.06
1.0	0.10
5.0	0.29
10.0	0.46
20.0	0.74
40.0	1.17

or micromoles of agent per kilogram body weight. In some experimental studies, comparisons of large and small animals relate dosage to the body surface area, which is approximately equal to body weight.[2,3,5] The use of body surface area dosages is advocated by some as a more accurate way to account for very different body sizes in veterinary medicine. Examples in Table 1-1 show that as animals increase in weight, the body surface area increases proportionally less, and this may affect the rate of metabolism, excretion, and receptor interaction with toxicants.[3] For many toxicants, larger animals may be poisoned by relatively lower body weight dosages than smaller mammals.[5] However, other factors, such as species differences in metabolism, excretion, or receptor sites, can alter this generalization.

Dose is a term for the total amount of a drug or toxicant given to an individual organism. In veterinary medicine, the extreme ranges of body weight and surface area, even within species, generally make the term *dose* relatively inaccurate or imprecise.

Characteristics of the LD_{50}

A commonly used means to compare the toxicity of compounds with one another is the median lethal dosage, also known as the oral LD_{50} in a standard animal, such as the laboratory rat. The LD_{50} value is usually based on a single oral exposure with observation for 1 to 7 days after the chemical is administered to determine an end point for total deaths. The LD_{50} is a standardized toxicity test that depends on a quantal (i.e., all or none) response to a range of three or more regularly increasing dosages at logarithmic or geometric intervals. In some cases a multiple-dosage LD_{50} is used to show the acute effects (typically up to 7 days) produced by repeated dosages in the same animals. When cumulative deaths are plotted on linear graph paper, the dose-response curve is sigmoid, and the most predictable value is usually around either side of the LD_{50} (Figure 1-1).

The end point of an LD_{50} study is death, and the published LD_{50} value provides no information about severity or characteristics of clinical signs observed in the surviving animals.[2,3,5] Twenty or more animals may be used to arrive at an estimate of the LD_{50}, which may limit the use of LD_{50} trials in animals of economic significance. In some species, such as birds and fish, toxicity is often expressed on the basis of the concentration of the substance in air, feed, or water. The acute oral toxicity for birds might be expressed as the LC_{50} (i.e., the lethal concentration for 50% of animals exposed) and may be measured as

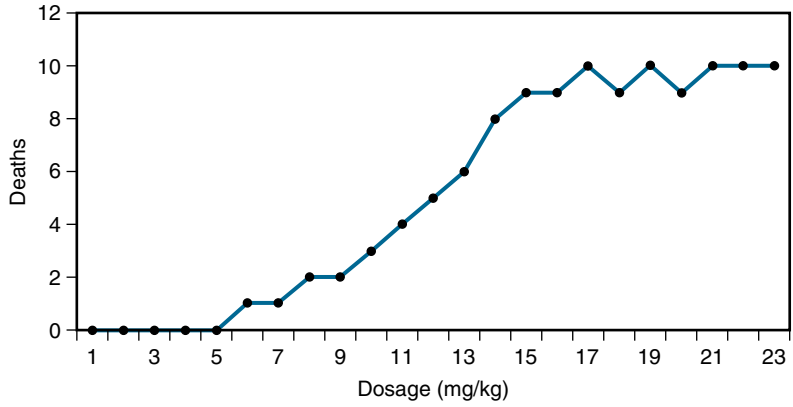

Figure 1-1 Dose-response curve for a typical LD_{50} study.

milligrams of compound per kilogram of the toxic medium (e.g., air, water, feed). For fish, the LC_{50} refers to a concentration of toxicant in the water.

Definition of Response to Toxicant Exposures

Other terms are used in some circumstances (e.g., *safety testing*) to define toxicity of compounds. The highest nontoxic dose, also known as the *no observed adverse effect level,* is the largest dose that does not result in hematologic, chemical, clinical, or pathologic drug-induced alterations. The toxic dose low or the lowest observed adverse effect level is the lowest dose to produce toxicant-induced alterations. The lethal dose low is the lowest dose that causes toxicant-induced deaths in any animal during the period of observation. Various percentages can be attached to the LD value to indicate doses required to kill: 1% (LD_1), 50% (LD_{50}), or 100% (LD_{100}) of the test animals. Another acronym occasionally used is *MTD.* It has been used to note the *maximum tolerated dose* in some situations or *minimal toxic dose.* Thus one should read such abbreviations carefully and look for the specific term defined.

Time Relationships of Poisoning

Acute toxicity is a term usually reserved to mean the effects of a single dose or multiple doses measured during a 24-hour period. If toxic effects become apparent over a period of up to 7 days, it may be considered an acute effect. *Subacute toxicity* may refer to any effects seen between 1 week and 1 month of exposure, whereas *chronic* often refers to effects produced by prolonged exposure of 3 months or longer. The interval between 30 days and 90 days postexposure may be called *subchronic.*

Toxicant Characteristics Can Define Acute or Chronic Response

Duration of exposure to specific toxicants can greatly affect the toxicity. One way to define the effects is the chronicity factor. Chronicity factor is determined by acute LD_{50}/90 day LD_{50}. For warfarin in rats the acute LD_{50} is 1.6 mg/kg, and the 90-day LD_{50} is 0.077 mg/kg, resulting in a ratio of 1.6/0.077, which is a chronicity factor of 21. On the other hand, the single-dose LD_{50} for caffeine in rats is 192 mg/kg and the 90-day LD_{50} is slightly lower at 150 mg/kg, giving an acute to 90-day ratio of 192/150 or 1.3. This demonstrates the chronic or cumulative nature of warfarin versus caffeine.

Animals may also develop tolerance for a compound such that repeated exposure serves to increase the dosage required to produce lethality. The single-dose LD_{50} of potassium cyanide in rats is 10 mg/kg, whereas rats given potassium cyanide for 90 days are able to tolerate a dosage of 250 mg/kg without mortality. Thus cyanide has a very low chronicity factor as a result of tolerance developed with time.

Toxicity Is Different from Risk or Hazard

The concept of *risk* or *hazard* is important to clinical toxicology. Although toxicity defines the amount of a toxicant that produces specific effects at a known dosage, hazard or risk is the probability of poisoning under the conditions of expected exposure or usage. Compounds of high toxicity may still present low hazard or risk if animals are never exposed to the toxicant. For example, ethylene glycol antifreeze is defined as low toxicity (2 to 5 mL/kg body weight), but because it is often readily available in homes, is voluntarily consumed by cats, and is difficult to reverse once clinical signs have developed, it is seen as a high-risk or high-hazard toxicant. By comparison, potassium cyanide is a recognized, very potent poison, but is virtually unavailable in most homes, so risk is low because it is generally not available to pets.

Another way to define risk is to compare the ratio of the lowest toxic or lethal dosage (e.g., the LD_1) with the highest effective dosage, which could be defined as the ED_{99}. The ratio of LD_1/ED_{99} is defined as the standard safety margin, and it is useful for comparing the relative risk of therapeutic drugs, insecticides, anthelmintics, and other agents applied to animals for their beneficial effects.[2,5] For a therapeutic drug or animal insecticide, if the LD_1 is 10 mg/kg and the ED_{99} is 1 mg/kg, then the safety margin is 10 and the likely lethal effect is much higher than the probable use level.

If all animals in an LD_{50} study were the same, then the LD_{50} would actually be a standard toxic dosage for all animals. However, at the same LD_{50} dosage, not exactly 50% of animals will die each time. This biologic variation can be due to many factors, and veterinary clinicians must exercise judgment about the response of animals to a given toxicant.

Even more variability is expected because of the differences in species, age, body size, route of exposure, inherent differences in metabolism, and pregnancy and lactation effects. Remember also that the slope of the LD_{50} curve is important and is not revealed from the LD_{50} value alone. An LD_{50} with a very steep dose-response slope indicates a toxicant or drug has a very narrow margin between no effects and maximal lethal effects.[3,5] Although such compounds may be dangerous to use as therapeutics, they could be very effective pesticides because of lower probability of survival of target animals.

Factors That Influence Toxicity

Many factors inherent in the toxicant, the animal, or the environment can alter a toxicity value determined under defined experimental conditions. The toxicity of a compound varies with the route of exposure. Usual routes of exposure are oral, dermal, nasal, intravenous, intraperitoneal, and subcutaneous. In addition, the most potent routes of exposure are usually the intravenous, intrapulmonary, and intraperitoneal routes. In clinical veterinary toxicology oral and dermal routes of exposure are the most common, and these routes generally delay the absorption and diffuse exposure over a longer period. A daily dosage of toxicant mixed in food and consumed over a 24-hour period may cause much less effect than that same dosage given as a bolus at one specific time. However, retention in the gastrointestinal tract, including enterohepatic cycling, and dermal or hair retention of poisons can significantly prolong the exposure or exposures.[2,3,5] Another factor that can accentuate the toxic effects of a compound is concurrent organ damage as a result of other causes. This is most important for diseases that alter liver or kidney function, leaving the animal with insufficient resources to metabolize and excrete toxicants. Chapter 2 deals with the important aspects of biotransformation, excretion, and toxicodynamics that greatly influence toxicity of many chemicals.

Species and breed differences exert important influences on toxicity. The familiar example of cats and their intolerance to phenolic compounds results directly from their limited glucuronyl transferase activity, which is necessary to produce glucuronides for the excretion of phenolic metabolites. A common example is acetaminophen, which is quite toxic to cats partly as a result of ineffective excretion of the toxic metabolite. In addition, the amino acid and sulfhydryl content of feline hemoglobin and a relative lack of methemoglobin reductase in erythrocytes makes it more susceptible to oxidant damage caused by the acetaminophen metabolite. As a result, the cat is more likely to be poisoned by agents that induce methemoglobinemia.[5] Occasional differences within a species can increase the probability of toxicosis. The anthelmintic ivermectin provides an example of breed susceptibility differences, with collies and individuals in other herding breeds being genetically more susceptible than most other breeds.

Many environmental and physiologic factors can influence the toxicity of compounds, and one should remember that such factors, or possibly other unknown factors, can substantially influence an individual's response to toxicants. Entire publications are devoted to drug and chemical interactions, and the reader is encouraged to be aware of toxicologic interactions that are illustrated throughout this text. Some examples of factors that alter response to toxicants are presented in Table 1-2.

Biologic Variation and Toxicity Data in Veterinary Practice

Biologic variation is a significant factor in interpretation of clinical and diagnostic data used in toxicology. A single toxicity figure will not define the range of toxicity and effects in a given population. Because LD_{50} or other values are usually defined in very similar animals (e.g., laboratory rats and laboratory beagles), the laboratory toxicity figure does not reflect the biologic variation and differences in toxicity that may occur in a diverse group of breeds within the canine or any other species. For animals of veterinary importance, there

Table 1-2 Factors That May Alter Response to Toxicants

Alteration or Change	Mechanism or Example
Impurities or contaminants	Recently melamine and cyanuric acid contaminants in cat food caused renal failure. For dogs, aflatoxin contaminated corn in dog foods has caused bleeding and liver failure.
Changes in chemical composition or salts of inorganic agents	Toxicity of metals may be altered by valence state. Trivalent arsenicals are much more toxic than pentavalent arsenic. Specific salts also alter toxicity (e.g., barium carbonate is cardiotoxic, whereas barium sulfate is insoluble and nearly nontoxic).
Instability or decomposition of chemical	Some organophosphate insecticides under adverse storage conditions can decompose to form more toxic degradation products. Zinc phosphide rodenticide decomposes rapidly to release highly toxic phosphine gas.
Ionization	Generally, dependent on pH and pKa, compounds that are highly ionized in the stomach (e.g., strychnine) are poorly absorbed and thus less toxic.
Vehicle effects	Nonpolar and lipid-soluble vehicles usually increase toxicity of toxicants by promoting absorption and membrane penetration. Examples are petroleum products and highly volatile hydrocarbons.
Protein binding	Binding to serum albumin is common for many drugs and toxicants, limiting the bioavailability of the agent and reducing toxicity. Agents displaced from protein binding (e.g., vitamin K responsive anticoagulants) enhance toxicity by allowing more freely available toxicants.
Chemical or drug interactions	Chemicals may directly bind, inactivate, or potentiate one another. One chemical may also induce microsomal enzymes to influence the metabolism of another. Barbiturate drugs stimulate metabolic activation of many toxicants to a more toxic metabolite.
Biotransformation*	Prior exposure to the same or similar chemical may induce increased metabolic activity of microsomal MFOs. Foreign compounds activated by MFOs can then be conjugated by phase II metabolism and be excreted. If toxicants are activated by MFO activity, toxicity may be increased. Liver disease, very young or very old animals, and specific breeds or strains of animal can be factors that lead to altered ability of MFO to begin metabolism followed by phase II detoxification of foreign compounds.
Liver disease	Reduced synthesis of glutathione, metallothionein, and coagulation factors may alter response to acetaminophen, cadmium, and anticoagulant rodenticides, respectively.
Nutrition and diet	Natural dietary compounds, such as calcium and zinc, may affect absorption and response to lead. Vitamin C and vitamin E can aid in scavenging of free radicals and repair of cellular protective mechanisms.

MFO, Mixed function oxidase.
*See Chapter 2 for details on biotransformation.

is usually insufficient information on the variability of effects from low or moderate exposures. Furthermore, individual environmental and husbandry conditions vary widely and can affect the severity of response in any particular group of animals for a specific toxicant and dosage. Therefore thorough clinical and environmental investigation and good laboratory diagnostic procedures are essential to toxicologic evaluation in a suspected exposure.

Calculations for Toxicology

As indicated earlier, the basis for toxicologic effects is the dosage versus response relationship. In a practical clinical situation, the dosage is often not defined. Rather, an animal is ill with clinical signs that suggest toxicosis, and there is potential exposure to a known or suspected amount of poison that is probably at some concentration less than 100% in a commercial product or natural source. Alternatively, the animal owner may have seen an exposure, such as an animal consuming some tablets or a potential toxicant such as chocolate. Sometimes animals with subacute or chronic signs are suspected of consuming some toxicant in the food. Analysis of a food may reveal a concentration in parts per million (ppm), mg/kg, mcg/g, or percentage, and the concentration in the food must be related to a known toxicity based on milligrams per kilogram of body weight. In all these circumstances, the veterinary clinician must first relate a probable amount of toxicant to a body weight dosage and then decide if detoxification therapy or antidotal treatment is necessary. If dosage is low, careful observation with no treatment may be a valid option. Thus the clinician should investigate the probable dosage as part of the decision process for whether therapy or observation is more appropriate.

The ability to accurately convert numbers relating to concentration and dosage and to convert different expressions of exposure or concentration is essential to the practice of medicine, and is equally important in clinical toxicology. The principles of dosage and calculations practiced in pharmacology and therapeutics are similar to those used in toxicology. Of particular importance in toxicology is the need to differentiate between and convert different expressions of concentration as stated on labels or obtained from laboratory analysis. The toxicologist is further challenged to correlate the level of contamination in food, water, or baits to the clinical signs observed in a suspected poisoning. The following examples are intended to clarify some of these calculations and to show how they are used in clinical toxicology.

Table 1-3 Common Comparative and Equivalent Values in Veterinary Toxicology

Expression or Measurement	Equivalent Value
1 ppm	1 mg/kg or 1 mg/L
1 ppm	1 µg/g or 1 µg/mL or 1 mcg/g or 1 mcg/mL
1 ppm	0.0001%
1 ppm	1000 ppb
1 ppm	1,000,000 ppt
1 ppb	0.000001%
1 ppb	1 ng/g
1 ppb	1 µg/kg or 1 mcg/kg
1%	10,000 ppm
(Convert % to ppm by moving decimal point four places to the right)	
1 mg/dL	10 ppm or 10 mg/L
1 ounce	28.35 g
1 pound	453.6 g
1 kg	2.205 lb
1 liter	0.908 qt
1 gallon	3.785 L
1 teaspoon	5 mL
1 tablespoon	15 mL
1 cup	8 oz or 227 mL
1 quart	32 oz or 946 mL

Concentration and Dosage in Veterinary Toxicology

The amount of a toxic agent in feed, water, baits, and solutions is often expressed as a weight/weight relationship (e.g., g/ton, mg/kg, mcg/g), as a weight/volume relationship (e.g., mg/mL, mg/dL, mg/L), or as a proportion of the toxicant to the total medium in which it is held, such as percentage, ppm, parts per billion (ppb), and parts per trillion (ppt). For correct toxicologic evaluation, one must understand the relationships among these expressions. Relationships and equivalencies of common expressions of concentration useful in calculations and interpretation for veterinary toxicology are shown in Table 1-3.

In addition, the clinician may find toxicity data expressed as milligrams per kilogram body weight of animal (dosage), but may receive a label or statement of analysis that expresses the feed, water, or bait concentration as proportional or as

weight/weight relationships (concentration). The accurate assessment of toxicologic risk depends on the ability to convert different toxicologic expressions to an equivalent common denominator.

One common clinical situation is the need to convert a feed or bait concentration to body weight basis toxicity. The following clinical problem illustrates this calculation.

Clinical Problem 1 **Is This a Toxic Exposure?** If the acute toxicity of cholecalciferol rodenticide is 2000 mcg/kg of body weight and the bait concentration is 0.075%, is a 1-oz package of bait likely to be toxic to a 70-lb German shepherd that consumes the entire package at one time?

Solution

To evaluate this risk, one must know or assume the following:

- Amount of food or bait consumed (1 oz)
- Weight of the animal at risk (70 lb)
- Concentration of toxicant in the food or bait (0.75%)

In this case, first convert as much as possible to the metric system:

- 70-lb dog/(2.2 lb/kg) = 31.8 kg
- 0.075% is 750 mg cholecalciferol/kg or 0.75 mg cholecalciferol/g of bait
- One ounce of bait × 28.35 g/oz = 28.35 g bait

Thus total consumption of cholecalciferol is expressed as:

- 28.35 g bait × (0.75 mg cholecalciferol/g bait) = 21.26 mg cholecalciferol consumed
- 21.26 mg cholecalciferol/31.8-kg dog = 0.67 mg/kg or 670 mcg/kg body weight

Thus toxic dosage is not consumed.

From the calculations, it is apparent that this exposure would cause a low risk of toxicosis from cholecalciferol.

If the concentration of vitamin D in a complete pet food is known or assumed, one may also need to calculate the potential for toxicosis based on feed contamination.

Clinical Problem 2 **Is There a Cumulative Toxic Exposure?** Continuing cholecalciferol to another example, assume that vitamin D at 2000 IU/kg body weight/day for 1 to 2 weeks can cause subacute toxicosis to dogs. If a dog food were accidentally fortified with a concentration of 1000 IU/lb, would long-term consumption likely result in toxicosis in a 35-lb dog?

Solution

In this case, the needed information is expanded from Clinical Problem 1, because we do not know the amount of contaminated material consumed. Also, convert components to the same system (metric units).

- From current knowledge: food intake for a 35-lb dog is 2.5% of body weight.
- Convert a 35-lb dog to kg (i.e., 35 lb ÷ [2.2 lb/kg]) = 15.9 kg; 15.9 kg × 0.025 = 0.3975 kg [amount ingested].
- Vitamin D in feed at 1000 IU/lb: 1000 IU/lb × 2.2 lb/kg = 2200 IU/kg of feed.
- Daily total vitamin D intake = 0.3975 kg/day × (2200 IU/kg feed) = 874.5 IU/day.
- Dosage to the 15.9-kg dog = 874.5 IU/day/15.9 kg = 55 IU/kg/day: Body weight dosage.

Daily body weight dosage at 55 IU/kg is far below the toxic dosage of 2000 IU/kg body weight/day.

In this clinical example, the daily dosage of 55 IU/kg on a body weight basis is approximately twice the recommended requirement but far below the known toxicity of 2000 IU/kg.

Small animal toxicants may sometimes be expressed in blood or body fluids by different units. Most common are ppm, milligrams per deciliter (mg/dL), and milliequivalents per liter (mEq/L). If laboratory results are given in one of these units, but toxicity information is available to the clinician in different units, the ability to convert to comparable units is essential to interpretation. Clinical Problem 3 illustrates this conversion.

Clinical Problem 3 **Converting Laboratory Values from ppm to mEq/L** In a dog exhibiting neurologic signs and a suspected salt toxicosis, toxicology laboratory results are returned indicating a serum sodium value of 4320 ppm. Expected normal values in your practice are 135 to 145 mEq/L. Is the laboratory analysis indicative of hypernatremia suggesting salt toxicosis?

Solution

In this case, it is necessary to convert the laboratory analysis results to mEq/L for interpretation. There is a common formula for converting mg/dL to mEq/L. To use this formula, do the following:

- Convert ppm to mg/dL.
- Because 1 ppm = 1 mg/L, and 1 mg/dL = 10 mg/L, then dividing ppm by 10 = mg/dL (4320 ppm divided by 10 = 432 mg/dL).
- mEq/L = mg/dL × valence × 10/atomic weight = 432 × 1 × 10/23 = 187.8 mEq/L.

Result provides laboratory confirmation of hypernatremia.

Clinical Problem 3 illustrates the tenfold difference between ppm and mg/dL (1 mg/dL = 10 ppm) and shows that to convert from mg/dL to mEq/L one must know the valence and atomic weight of specific toxicants or metals.

Toxicoses, although difficult clinical problems, can best be managed by using basic principles and calculations to estimate probable exposure to toxicants and the factors that may alter those responses. Adding to this knowledge of the systemic and medical effects of toxicants and the principles of antidotal and detoxification therapy should result in the best possible outcome in response to small animal toxicoses.

Clinical Problem 4 **Owners Suspect Acute Aflatoxicosis—Is It Likely?** A reported LD_{50} for aflatoxin in dogs is 0.80 mg/kg of body weight. If a beagle dog is exposed to aflatoxin at 200 ppb on a continuing basis, will the toxic dosage be exceeded?

Solution

In this scenario, the toxic body weight dosage must be compared against risk from a known or presumed concentration in the diet. The body weight dosage must be converted to a dietary concentration. In addition, remember the principle that dietary dosage is affected by the amount of food consumed. No weight was given for the dog, but it is a beagle, so one can assume a weight of 22 lb for purposes of calculation.

- First, convert all weights to the metric system. A 22-lb beagle can reasonably be assumed to weigh 10 kg (22 lb/2.2 kg).
- Next, estimate the food intake of the beagle. As in Clinical Problem 2, a reasonable intake is 2.5% of body weight daily.
- Calculate food ingested daily: 10 kg × 0.025 = 0.25 kg food.
- Calculate the amount of aflatoxin in 0.25 kg food: 200 ppb = 200 mg/kg = 0.2 mg/kg or 0.2 ppm; at 0.2 mg/kg × 0.25 kg the food consumed contains 0.05 mg aflatoxin.

- Calculate the dosage of aflatoxin in mg/kg of body weight: 0.05 mg/10 kg body weight = 0.005 mg/kg.
- Alternatively, a formula to convert ppm to mg/kg of body weight is:

$$\text{mg/kg BW} = \frac{\text{ppm in feed} \times \text{kg feed eaten}}{\text{body wt in kg}}$$

$$\text{mg/kg BW} = \frac{0.20 \text{ mg/kg} \times 0.25 \text{ kg}}{10 \text{ kg}} = 0.005 \text{ mg/kg BW}$$

Conclusion: 200 ppb (0.2 ppm) dietary aflatoxin is not an LD_{50} dosage of aflatoxin.

Clinical Problem 5 Express the following concentrations in ppm and in percent

Combination Mixture	Concentration (%)	Concentration (ppm)
a. 17 ounces in 12 liters	4.19	41990
b. 0.25 quarts in 56 gallons	0.1116	1116
c. 9.27 grams in 1 kilogram	0.927	9270
d. 30 lb premix in 2 tons of dog food	0.75	750
e. 34 ounces in 200 gallons	0.1328	1328
f. 54 mg caffeine in 12 oz Mountain Dew	0.0152	152

Solutions

a. Convert to percentage by making a ratio in the same units. (Note: There are 33.81 ounces/L.) Then convert ratio to % and % to ppm (moving decimal 4 places right):

$$\frac{17 \text{ oz}}{12 \text{ L} \times 33.81 \text{ oz/L}} = \frac{17 \text{ oz}}{405 \text{ oz}} = \underset{\text{Ratio}}{0.0419 \text{ ratio}} = \underset{\%}{4.19\%} = \underset{\text{ppm}}{41{,}990 \text{ ppm}}$$

b. Create ratio in same units (e.g., quarts, then use [ratio × 100 = %] and [% × 4 decimals right]:

$$\frac{0.25 \text{ qt}}{56 \text{ gal} \times 4 \text{ qt/gal}} = \frac{0.25 \text{ qt}}{224 \text{ qt}} = 0.001116 = 0.1116\% = 1116 \text{ ppm}$$

c. 9.27 g in 1 kg (first convert both terms to grams):

$$\frac{9.27 \text{ g}}{1 \text{ kg} \times 1000 \text{ g/kg}} = \frac{9.27}{1000} = 0.00927 = 0.927\% = 9270 \text{ ppm}$$

d. 30 lb of premix in 2 tons of dog food (first convert all terms to pounds, and then calculate ratio, percent, and ppm):

$$\frac{30 \text{ lb premix}}{2 \text{ tons dog food}} = \frac{30 \text{ lb premix}}{4000 \text{ lb food}} = 0.0075 = 0.75\% = 750 \text{ ppm}$$

e. 34 ounces in 200 gallons:

$$\frac{34 \text{ oz}}{200 \text{ gal} \times 128 \text{ oz/gal}} = \frac{34}{25,600} = 0.001328 = 0.1328\% = 1328 \text{ ppm}$$

f. 54 mg caffeine in 12 oz soda (convert ounces to milliliters, then grams, then milligrams):

$$\frac{54\text{ mg}}{12\text{ oz}\times 29.6\text{ mL/oz}}=\frac{54\text{ mg}}{355.2\text{ mL}\times 1\text{ g/mL}}=\frac{54\text{ mg}}{355.2\text{ g}\times 1000\text{ mg/g}}=\frac{54\text{ mg}}{355{,}200\text{ mg}}$$
$$=\text{ratio of }0.000152113=0.0152\%=152\text{ ppm}$$

• **Quick Guide** Figure 1-2 provides a range of body weight dosages and food consumption for quick reference in estimating equivalent ppm concentrations in the diet without using calculations. Remember that as a higher proportion of food is consumed relative to body weight, then the same dietary concentration will cause increasing dosage of the toxicant per unit of body weight.

	ppm toxicant in diet					
% BW Consumed	**1**	**10**	**50**	**100**	**500**	**1000**
1	0.01	0.1	0.5	1	5	10
2	0.02	0.2	1	2	10	20
3	0.03	0.3	1.5	3	15	30
4	0.04	0.4	2	4	20	40
5	0.05	0.5	2.5	5	25	50
10	0.1	1	5	10	50	100

Equivalent body weight dosage (mg/kg)

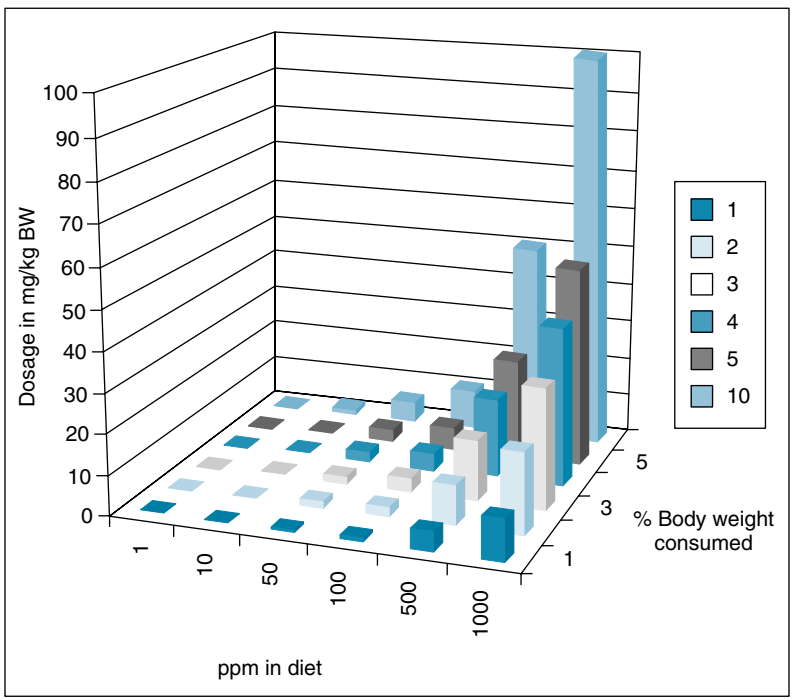

Figure 1-2 Relationships of food intake and body weight dosage.

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